

CAHIER DES PRÉSENTATIONS

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PRÉSENTATIONS ORALES – 12 MINUTES

RÉSUMÉ 21 - Le récepteur d'acide gras à longue chaîne FFA4 stimule la sécrétion d'insuline par inhibition de la libération de somatostatine par les cellules δ

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Le récepteur aux acides gras FFA4 est exprimé dans les îlots pancréatiques, mais ses mécanismes d'action restent inconnus. Nos études précédentes suggèrent que FFA4 régule la sécrétion de somatostatine (SST) dans les cellules δ.

Hypothèse: Les agonistes de FFA4 stimulent indirectement la sécrétion d'insuline par inhibition de la sécrétion de SST.

Méthodes: Les lignées de souris suivantes ont été utilisées : SST-knockout (SSTKO), avec ablation des cellules δ (SST-iDTR) et Gα(z)-knockout. La sécrétion d'hormones a été évaluée dans des incubations statiques d'1 heure d'îlots isolés ou de cellules EndoCβH5 (lignée cellulaire de cellules β humaines) en réponse à 2,8 ou 16,7mM de glucose +/- les agonistes de FFA4 : CpdA (20-50 µM) ou AZ13581837 (10 µM).

Résultats: Dans les îlots témoins (WT), le CpdA potentialise la sécrétion d'insuline stimulée par le glucose (SISG) (204±28 %, n=8, p<0,05) et diminue la sécrétion de SST (34±5 vs. 58±8 pM, n=8, p<0,01). Le CpdA n'a aucun effet sur la SISG dans les îlots de souris SSTKO ou SST-iDTR (140±25 % et 126±27 % respectivement, n=6, NS). Le CpdA n'inhibe pas la sécrétion de SST dans les îlots de de souris GnazKO (35±8 vs. 47±5 pM, n=8, NS). Comme l'expression de FFAR4 est élevée dans les cellules β humaines, nous avons étudié l'activation de FFA4 dans les cellules EndoCβH5. AZ13581837 potentialise la SISG (186±13 %, n=5-6, P<0,01), suggérant une action directe sur les cellules β humaines.

Conclusion: Les agonistes de FFA4 stimulent la sécrétion d'insuline chez les rongeurs indirectement en inhibant la sécrétion de SST via la protéine Gα(z). Ce mécanisme semble différent dans les îlots humains avec une action directe sur la cellule β.

RÉSUMÉ 76 - Identification des caractéristiques phénotypiques des cellules réservoirs du VIH

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Le principal obstacle à l'éradication du VIH est la persistance de cellules infectées de manière latente, malgré les thérapies antirétrovirales (TAR). Ces réservoirs viraux provoquant inéluctablement un rebond viral à l'interruption des traitements, le développement de stratégies visant à les éliminer est capital et nécessite l'identification des mécanismes contribuant à leur persistance. Dans cette étude exploratoire, nous avons testé plusieurs hypothèses pouvant expliquer cette persistance : la capacité à demeurer quiescente, l'auto-renouvellement, et la capacité à échapper à la pression immunitaire.

Nous avons analysé phénotypiquement les cellules hébergeant des provirus inductibles (cellules p24+) dans des échantillons longitudinaux (3-24 ans de TAR) de 10 participants.

Le phénotype de 395 cellules portant un provirus inductible a été déterminé à partir de 390 millions de cellules T CD4+. Comparativement aux cellules p24-, les cellules p24+ montrent plusieurs caractéristiques suggérant leur capacité à échapper à la réponse immunitaire : des niveaux plus faibles de HLA-ABC ($p=0,026$, 1,4 fois moins), ainsi qu'une expression plus fréquente de la protéine anti-apoptotique Bcl-2 ($p=0,006$, 1,1 fois plus) et des granzymes A et B ($p<0,0001$, 6,2 fois plus et $p=0,02$, 6,8 fois plus). Les molécules de points de contrôle immunitaire PD-1 et TIGIT, montrées comme favorisant le maintien de la latence, sont exprimées à des niveaux plus élevés dans les cellules p24+ ($p<0,0001$, 1,8 fois plus et $p<0,0001$, 3,4, fois plus, respectivement). De même, CD127, récepteur de l'IL-7 (qui permet le maintien de la survie et la prolifération homéostatique) est exprimé à des niveaux plus élevés dans les cellules p24+ ($p<0,0001$, 2,4 fois plus).

Nos données suggèrent un potentiel accru des cellules p24+ pour la survie, la cytotoxicité et le maintien de la latence. Certains de ces marqueurs étant associés à la sénescence, nous prévoyons d'évaluer l'impact d'agents sénolytiques utilisés en cancer sur la persistance des réservoirs du VIH.

Bourse FRQS

RÉSUMÉ 116 - Intracellular Cell Adhesion Molecule 1 on T cells promotes chronic neuroinflammation by regulating microglia function during MS

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Introduction: Neuroinflammatory processes cause acute and chronic neuroglial injury and impair repair mechanisms in the central nervous system (CNS) of people with Multiple Sclerosis (pwMS). CNS-infiltrating pro-inflammatory T cells are present at the edges of chronic active lesions; however, the mechanisms by which they contribute to neuroglial injury and to the lesion environment are poorly understood. Though Intracellular Cell Adhesion Molecule 1 (ICAM-1) on T cells has been previously implicated in T cell activation and tissue retention, its role during MS progression has yet to be explored.

Methods: Expression of ICAM-1 on T cells from healthy controls and pwMS in the cerebrospinal fluid, blood and human rapid autopsy ex-vivo brain tissue was characterized by multiparametric flow cytometry analysis. CD4cre:ICAM-$1^{fl/fl}$ mice were induced with active MOG_{35-55} EAE to assess the impact of ICAM-1 ablation in T cells on the clinical course, neuroinflammatory processes and CNS histopathology. Anti-ICAM-1 treated human primary T cells were co-cultured with primary microglia to assess contact behavior (live imaging) and cell activation.

Results: T cells from the peripheral blood of pwMS express higher levels of ICAM-1 compared to controls. Pro-inflammatory ICAM-1+ T cells are also enriched in the CSF and CNS and microglia express high levels of LFA-1, the corresponding ligand, during MS and EAE. Ablation of ICAM-1 on T cells in mice resulted in a marked improvement of EAE clinical scores, accompanied by fewer numbers of infiltrating immune cells, reduced microglia/myeloid cell activation, reduced axonal injury, and increased myelination in the CNS. Blocking ICAM-1 on T cells prior to co-culture with microglia resulted in altered T cell contact behavior and reduced microglia activation.

Conclusion: ICAM-1 on T cells promotes deleterious neuroinflammatory processes associated with chronic EAE progression and neuroglial injury in vitro and in vivo.

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RÉSUMÉ 136 - Single-Cell Profiling of Peripheral Immune Cells in Parkinson's Disease

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Although Parkinson's disease (PD) research has unsurprisingly focused on the neurodegeneration happening in the brain, mounting evidence suggests the immune system plays an important role in pathogenesis. With multiple studies pointing to peripheral immune dysregulation as a key contributor to PD progression, identifying specific signatures from blood samples could offer significant insights into patient prognosis classification. Therefore, we aimed to perform the first comprehensive analysis of the complete peripheral blood mononuclear cells (PBMC) compartment in PD patients utilizing the resolution of single-cell sequencing. PBMC were isolated from 14 blood samples from individuals with PD diagnosis, and 10 healthy age-matched control samples. Single-cell libraries were obtained with standard 10X Genomics protocols, with each pool of libraries (5-plex samples) being split into two prior to sequencing. Transcriptomic and T cell receptor (TCR) sequencing were run in parallel on the pools to enable the comparison of transcriptomic and immunologic profiles from single cells. Thorough bioinformatics processing and annotations were performed with standard tools such as Seurat. Broad cluster analysis showed a general increase in activation signaling in PD samples, with the latter exhibiting a slight trend of increased monocytes and decreased lymphocytes. Further analysis of myeloid cells revealed an activated $CD14^{+}/CD83^{+}$ monocyte subpopulation, for which differentially expressed genes suggested a heightened inflammatory state in PD. Lymphoid cells analysis also showed increased pro-inflammatory NK56hi cells in PD samples. TCR clonotyping identified PD-specific sequences, with multiple motifs shared across multiple samples, but none were linked to known causative sequences in current annotation databases. Overall, we present the first comprehensive single-cell atlas of the PBMC compartment, and provide insights into the peripheral immune mechanisms at play in PD pathogenesis. We believe these data could lead to the definition of prognosis gene signatures, and the identification of new therapeutic targets.

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RÉSUMÉ 139 - Preliminary Evaluation of the Feasibility of Transbronchial Cryoablation. An Ex-Vivo Human Lung Model.

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With the emergence of robotic bronchoscopy, transbronchial ablation - namely using cryo -, may present as a future alternative to surgical resection. However, no commercially available transbronchial cryocatheters have been developed and there is no evidence to suggest the use of existing probes for this purpose.

This study aims to evaluate the potential of existing and in-development cryoprobes for transbronchial cryoablation by testing using an ex-vivo human lung model.

Explanted lungs from transplant recipients (n=26) were placed in an EVLP set-up. All cryoprobes (Boston Scientific IcePearl 2.1, IceSeed 1.5 and IceForce [argon gas], ERBE 2.4mm single-use cryoprobe [CO_2] and an in-development cryoablation probe by Endocision [biphasic nitrogen]) were subjected to three cycles of 10-minute freeze and 15-minute passive thaw. Thermocouples were placed at probe tip, 1cm and 2cm away to record temperature. Ice ball size was measured after each freeze using a caliper.

10 specimens were sent for pathological assessment.

16 ablations were included in the analysis. 10 were excluded due to excessive tissue damage. IceForce reached the lowest temperature at probe tip in the first cycle, followed by Endocision, IceSeed, IcePearl and ERBE. Endocision was the most consistent throughout subsequent cycles. IcePearl and IceForce were better able to maintain a plateau at their lowest temperatures and thus generate larger ice balls. ERBE did not consistently reach minimal ablation temperatures.

Pathological analysis was inconclusive.

Cryo demonstrates great potential for lung ablation; targeting tissues with higher water content (tumour) and sparing surrounding structures.

Translating this technology for use in navigational bronchoscopy would require adequate isolation along a flexible, radiopaque shaft adapted in size for subsegmental bronchi.

An in-vivo survival study is in the works to determine the safety and feasibility of transbronchial cryoablation, establish proper freezing protocols and compare the intervention to transthoracic percutaneous cryoablation.

Chaire Marcel et Rolande Gosselin de Chirurgie Thoracique

RÉSUMÉ 146 - Does physical activity in social contexts mitigate the adverse effect of screen time on mental health in early adults?

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Introduction: Screens can have adverse effects on mental health. Physical activity (PA) in social contexts (team sports and informal group PA) has numerous mental health benefits. Whether they could mitigate or reduce the association between screen time (ST) and mental health remains unknown. This project estimates the associations between occupational and recreational ST and positive mental health (PMH) in adults and tests for effect modification by team sports and informal group PA.

Methods: Data from the NDIT Study are used (n = 623, mean (SD) age = 35.2 (0.6) years). The mean hours/day of ST was measured for occupational and recreational contexts. PMH was measured six months later using the Mental Health Continuum-Short Form. The monthly frequency of team sports or informal group PA participation was measured using a 6-point Likert scale. Multivariable linear regressions were fit, adjusting for sex, age, education level, and PA volume. We test for effect moderation by adding an interaction term (ex.: ST*team sports) and stratified analyses to compare frequent and infrequent subgroups for team sports and informal group PA.

Results: Both occupational ST (B[95%CI] = -0.3[-0.6, -0.0]) and recreational ST (-1.1[-1.6, -0.7]) ST were negatively associated with PMH. Stratified analyses suggest that recreational ST was negatively associated PMH among those reporting infrequent informal group PA (-1.2[-1.7; -0.6]); this negative association was no longer present in those participating in frequent informal group PA (-0,8 [-1.7; 0.2]). A similar pattern was observed for team sports. Neither team sport nor informal group PA moderated the association between occupational ST and PMH.

Conclusion: Recreational and occupation ST are inversely associated with PMH in adults. The moderating effect of PA in social contexts provides a promising avenue for intervention. Further investigations using longitudinal study designs with larger samples are needed.

Funding : RRSPQ



PRÉSENTATIONS ORALES – 5 MINUTES

RÉSUMÉ 1 - Impact of miRNAs on G3BP1 mRNA stability and their implication in TDP-43 associated amyotrophic lateral sclerosis.

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Introduction: Our lab has shown that a reduction in nuclear TDP-43 causes a downregulation of G3BP1, a key stress granule component. We have identified a pair of miRNAs whose binding sites partially overlap with its conserved element. These miRNAs exhibit different expression profiles, where one is enriched in the human brain. Given that RBPs and miRNAs are known to engage in competitive binding to regulate transcripts stability, we hypothesize that G3BP1 mRNA stabilization is governed by competition between the identified miRNAs and TDP-43. This work aims to investigate the involvement of miRNAs in this stabilization mechanism in humans.

Methods: We assessed the levels of G3BP1 after the use of miRNA inhibitors in human cells. *In vitro* assays evaluated the competitive binding of TDP-43 and these miRNAs for the relevant sequence. We used FISH to assess the expression of the miRNAs in different nervous tissues. Then, we evaluated the role of TDP-43 on the stability of the G3BP1 transcript.

Results: Analysis of miRNA expression levels in different human cell types identified a higher expression of one particular miRNA in SH-SY5Y cells compared to HeLa cells. This miRNA visualized by FISH in human cortex was found to be enriched in motor neurons. In an EMSA assay, the miRNA was capable of displacing the TDP-43 RNA binding domain from the G3BP1 3'UTR, confirming that they compete for the conserved element. An mRNA stability assay demonstrates that TDP-43 stabilizes G3BP1 mRNA and thus prevents miRNA mediated mRNA degradation.

Discussion: Our data provide a molecular insight of the mechanism by which G3BP1 is regulated by TDP-43. This work may be informative to future strategies to stabilize G3BP1 and improve neuronal survival.

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RÉSUMÉ 12 - Single-cell transcriptomic analysis reveals IL-32-expressing effector-like CD8 T cells during spontaneous resolution of HCV reinfection

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Introduction: The development of a successful vaccine against hepatitis C virus (HCV) requires identification of signature pathways of protection. Expansion of HCV-specific CD8 T cells with high polyfunctionality has been associated with protection upon reinfection. However, the molecular mechanisms underlying protection remain understudied. Here, we performed single-cell RNA-sequencing (scRNA-seq) of virus-specific CD8 T cells during HCV reinfection from individuals who either resolved two consecutive HCV episodes (SR/SR) or developed a chronic infection despite clearing a previous one (SR/CI).

Methods: We used activation-induced markers assay following stimulation with HCV peptide pools to identify and sort HCV-specific CD8 T cells from PBMCs of SR/SR (n=4), and SR/CI (n=2) at key time points post-reinfection. Sorted HCV-specific CD8 T cells were subjected to scRNA-seq along with TCR typing using 10X Genomics.

Results: At early acute reinfection (< 3 months), SR/SR showed enrichment of effector ($P < 0.01$) and effector memory ($P < 0.01$) HCV-specific CD8 T cells and a lower percentage of exhausted virus-specific CD8 T cells ($P < 0.01$) compared to SR/CI. This was associated with higher levels of IFNg, TNFa, IL-2, and IL-18 in the supernatant of stimulated cells. *IL32* was significantly upregulated ($P < 0.05$) in multiple clusters of virus-specific CD8 T cells from SR/SR. Two populations of effector-like CD8 T cells were identified both in SR/SR and SR/CI. However, within these clusters, *IL32*, *TNF* and the cytotoxic molecules *GZMB*, *GZMH*, and *GZMK* were upregulated ($P < 0.05$) in SR/SR compared to SR/CI. TCR analysis revealed that the most expanded virus-specific CD8 clonotypes in SR/CI were enriched within exhausted cells. Finally, spontaneous resolvers displayed a higher frequency of MAIT cells ($P < 0.01$).

Conclusions: Spontaneous resolvers of HCV reinfection exhibit virus-specific IL-32-expressing effector-like CD8 T cells with greater cytotoxic capacity than chronic patients.

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RÉSUMÉ 27 - Regulation of adipogenesis by 14-3-3zeta scaffold protein occurs via modulation of chromatin accessibility in the initial phases of adipocyte differentiation

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Introduction: Key adipogenic transcription factors (ATFs) like C/EBP-β, C/EBP-δ, C/EBP-α, and PPARγ drive formation and expansion of adipose tissue. The molecular adaptors coordinating their nuclear entry and activity remain unknown. Previous evidence suggests 14-3-3ζ, a scaffold protein strictly required for adipocyte differentiation, may regulate these transcriptional complexes. This study explores whether 14-3-3ζ drive nuclear translocation of ATFs and whether targeting 14-3-3ζ could help reduce adiposity.

Methods: CRISPR-Cas9 editing was used to generate TAP (FLAG-HA)-tagged 14-3-3z-expressing 3T3-L1 pre-adipocytes to analyze the nuclear 14-3-3ζ interactome during adipogenesis. HDAC and DNMT activities were measured in nuclear fractions of control or 14-3-3ζ siRNA-transfected 3T3-L1 cells at 0, 24, and 48h of differentiation. ATAC-Seq assessed 14-3-3ζ's role in chromatin remodeling during 3T3-L1 differentiation.

To further examine the specific roles of 14-3-3z in adipogenesis, *Adipoq*-Cre:14-3-3ζKO and *Pdgfra*-Cre:14-3-3ζKO mice were generated to knock out 14-3-3ζ in either mature adipocytes (MAs) or adipocyte progenitor cells (APCs), respectively, before chow or high-fat diet (HFD) feeding and subsequent assessment of body weight (BW) and adiposity.

Results: At 24h and 48h post-differentiation, the TAP-14-3-3ζ nuclear interactome was enriched with proteins regulating chromatin accessibility, such as DNMT1/3a and HDAC1. Depletion of 14-3-3ζ decreased activities of these enzymes. Combining ATAC-seq results with previous transcriptomic analysis (GSE60745) revealed that 14-3-3ζ is required for accessibility and expression of key adipogenic genes (*i.e.*, *Fapb4* and *Retn*).

In animal experiments, male and female Adipoq-Cre-14-3-3ζKO mice exhibited no significant differences in BW, total fat, or fat mass, regardless of diet, compared to WT mice. However, while these parameters were reduced in male Pdgfra-Cre-14-3-3ζKO mice, they were significantly potentiated in female Pdgfra-Cre-14-3-3ζKO. Finally, male Pdgfra-Cre-14-3-3ζKO mice were protected from HFD-induced obesity.

Conclusion: The adipogenic effects of 14-3-3ζ are specific to APCs and rely on the modulation of key effectors of chromatin accessibility during the early stage of adipogenesis.

RÉSUMÉ 35 - ACIDE URIQUE ET COMPLICATIONS COGNITIVES DE LA CIRRHOSE DU FOIE : CONCLUSIONS TIRÉES D'UN MODÈLE MURIN

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Introduction: Environ 40% des patients cirrhotiques présentent des troubles cognitifs associés à une diminution de la détoxification hépatique de l'ammoniaque. Toutefois, les concentrations circulantes d'ammoniaque ne sont pas toujours corrélées avec la sévérité des symptômes cognitifs. Un autre médiateur circulant, l'acide urique (AU), est reconnu pour son effet délétère sur le cerveau et son implication dans la progression de la maladie hépatique chronique. Cette étude vise à explorer les altérations comportementales et lésions cérébrales dans un modèle murin de cirrhose et hyperuricémie.

Méthodes: Nos animaux sont divisés en 4 groupes combinant la cirrhose (S (contrôle) ou B (ligature de la voie biliaire)) et l'hyperuricémie (R (diète régulière) ou H (diète 3% AU)). Des prélèvements sanguins au jour 7 et 28 permettent de mesurer l'AU plasmatique avant l'évaluation de la mémoire et de l'anxiété. Au jour 33, les foies sont inclus en paraffine pour évaluer la sévérité des lésions hépatiques. Le cortex frontal, l'amygdale et l'hippocampe sont également isolés pour analyser la perte neuronale en évaluant l'apoptose par l'activité enzymatique de la caspase-3 ainsi que par Western Blot et immunohistochimie (NeuN et SMI311).

Résultats: Aucune altération de la sévérité des lésions hépatiques n'est constatée entre les groupes BR et BH. Une augmentation de l'AU circulant aux jours 7 et 28 est détectée dans le groupe BH. Au jour 14, la mémoire à court terme diminue et l'anxiété augmente chez les BH. Associé à ces altérations comportementales, une augmentation de l'apoptose et une diminution des marqueurs neuronaux dans les trois régions cérébrales étudiées est observé chez les animaux BH.

Conclusion: Chez les animaux cirrhotiques, l'hyperuricémie entraîne des altérations précoces au niveau de l'anxiété et de la mémoire associées à une augmentation de l'apoptose et de la perte neuronale dans le système limbique.

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RÉSUMÉ 69 - Longitudinal study of the involvement of IgG subclasses in immune responses against SARS-CoV-2 after vaccination

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Introduction: Since the emergence of SARS-CoV-2 in December 2019 and despite the rapid development of mRNA vaccines, many variants have emerged, including Omicron. The neutralizing and Fc-effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), play a key role in protection against SARS-CoV-2. IgG plays a key role in humoral responses, but few studies have investigated the implication of its different IgG subclasses in immune responses against SARS-CoV-2, as well as their evolution after multiple vaccinations.

Methods: In this longitudinal study, we measured the neutralizing and Fc-effector functions of antibodies against SARS-CoV-2 against the D614G mutation and the Omicron subvariant BA.4/5 in vaccinated CHUM healthcare workers. We also measured the binding capacity of IgG and its subclasses (IgG1, IgG2, IgG3, and IgG4) after each dose of vaccine against the same spikes.

Results: Our study demonstrates that vaccination allows the induction of IgG and its subclasses with ascending levels after each dose for total IgG, IgG1 and IgG4. Effector responses are maintained over time against D614G, and ADCC increases against BA.4/5, while the neutralizing response increases against both spikes. Finally, we observe an induction of IgG4 after the 3rd dose of vaccine only, and ascending levels after each immunization. This correlates negatively with Fc-effector responses after the 3rd, 4th and 5th doses of vaccine.

Discussion/Conclusion: These results suggest that repeated vaccination allows the maintenance of total IgG and IgG1, as well as immune responses against the Omicron BA.4/5 subvariant. However, our results show a marked increase in IgG4 levels from the 3rd vaccine dose. This is interesting because this subclass seems to have an impact on the ADCC response. This study expands our knowledge on the involvement of Fc-effector responses against SARS-CoV-2 and the role of IgG subclasses in these responses.

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RÉSUMÉ 82 - ATP released by Ultrasound Targeted Microbubble Cavitation Induces Vascular Inflammation and Improves Immune Checkpoint Blockade Efficacy

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Introduction: Extracellular ATP (eATP) is a potent immune stimulant that functions as a damage-associated molecular pattern. The regulation of eATP is primarily mediated by cell surface ecto-nucleotidases (CD39 and CD73) which hydrolyze ATP into adenosine, a potent immune suppressor. CD39 and CD73 are upregulated in most cancers. Therapeutic strategies aimed at increasing ATP release in the tumor microenvironment or inhibiting adenosine activity are active areas of research in immuno-oncology. Ultrasound-Targeted Microbubble Cavitation (UTMC) is an externally applied, spatially targeted approach that has demonstrated synergy with immune checkpoint blockade (ICB) in solid tumors. However, the underlying mechanisms and optimal therapeutic combinations remain under investigation. We hypothesized that modulating purinergic signaling by UTMC could further leverage ICB efficacy.

Methodologies: Here, we investigated non-ablative and flow-preserving UTMC to enhance ATP release and induce inflammatory responses in a murine syngeneic colorectal tumor model (MC38) with and without CD39 inhibition. We compared two UTMC pressures (400 and 850 kPa), evaluating their impact on tumor blood flow by contrast perfusion imaging, their ability to release ATP using bioluminescence, their effect on vascular inflammation and cancer cell death through histological analysis, and their synergy with aPDL1 to improve ICB efficacy.

Results: UTMC at 850 kPa and in CD39 knockout model released higher eATP concentrations, which correlated with increased vascular inflammation, enhanced cancer cell death, and reduced cancer cell proliferation. The combination of aPDL1 with UTMC and CD39 blockade significantly reduced tumor growth.

Conclusion: Our findings support that purinergic signaling can be leveraged in combination with UTMC to improve ICB therapy.

RÉSUMÉ 89 - Methionine intake restriction: a dietary approach to shape gut microbiota and regulate neuroinflammatory processes in MS

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Background: Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS). The gut microbiota is altered in MS and can exacerbate the course in its animal model, experimental autoimmune encephalomyelitis (EAE). Western diet, rich in methionine, is associated with gut dysbiosis and worsens MS course. Dietary methionine restriction (MR) is an anti-aging intervention reducing inflammation. Our team previously found that MR delays EAE onset and limits proliferation of pro-inflammatory immune cells and their infiltration in the CNS. We now aim to investigate the mechanisms mediating the benefits of MR such as the gut microbiota and gut-associated lymphocyte tissue (GALT) in EAE and gut microbiota and immune cell/inflammatory/metabolic profile in humans.

Methods: We use active MOG-induced EAE and spontaneous EAE in transgenic TCR1640/SJL mice. Mice are assigned to experimental diets (80% reduction, 40% reduction vs control diet) and are monitored for EAE symptoms. Flow cytometry, immunofluorescence and 16S rRNA sequencing (feces) will be used to characterize the gut microbiota profile, gut-associated immune cell populations and the state of the intestinal barrier at different stages of EAE. Furthermore, we perform a pilot clinical study using an MR diet with methionine supplementation (add-back) versus placebo in healthy controls.

Results: Our team had previously found that 80% MR significantly influences the composition of the gut microbiota compared to control in a sex-biased manner in active and spontaneous EAE. We have optimized protocols to characterize by flow cytometry immune cells from the mesenteric lymph nodes, Peyer's patches, intraepithelial lymphocytes and lamina propria. We are currently testing 40% MR vs. 80% MR and control diet in active and spontaneous EAE and will present preliminary results. The study in human healthy control is ongoing.

Conclusions: Our preliminary data show that MR impacts gut bacteria which could in turn influence GALT, immune cell profile and EAE onset.

Funding: MSCanada

RÉSUMÉ 107 - Investigating the mechanisms by which HIV induces cellular release of the proinflammatory cytokine IL-32 in people with HIV

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Background: Identifying biomarkers and mediators of increased risk of cardiovascular disease (CVD), represents a research priority for People with HIV (PWH). We have recently shown that the proinflammatory cytokine IL-32 is upregulated in PWH and is associated with coronary artery and carotid artery subclinical atherosclerosis. However, mechanisms by which IL-32 (a protein lacking the signal peptide) is released from the producing cells are yet to be identified, although extracellular vesicles (EVs) were previously suggested as the carrier vesicles for IL-32. Therefore, we hypothesize that HIV infection is associated with increased release of IL-32-containing EVs and that these vesicles are higher in individuals with chronic inflammation and CVD.

Methods: We employed two methods for the isolation of EVs from plasma collected from PWH; multi-step centrifugation and size exclusion chromatography (SEC). Isolated EVs were then characterized by flow cytometry analyzers optimized for the analysis of nanoparticles (CytoFlex) to detect EV-specific tetraspanin proteins (CD9, CD63, and CD81) and Western blotting to detect IL-32.

Results: We first established that extracellular vesicles isolated with either methods; SEC or multi-step centrifugation, were detectable by CytoFlex. The majority of these vesicles expressed the tetraspanin marker CD9 together with the amines-binding stain Cell-Trace (a marker for viable cells/vesicles). Furthermore, Western blotting using anti-CD9 antibodies demonstrated that the SEC method allows EV isolation at the expected column's fraction. Finally, the presence of IL-32 in these vesicles (isolated from both PWH and controls) were then confirmed by Western blotting using IL-32-specific antibodies recognizing the total IL-32 proteins.

Conclusions: Our data show that the proinflammatory cytokine IL-32 is readily detectable in EVs isolated from human plasma, which suggests EVs as a cellular pathway for IL-32 secretion. Work is ongoing to isolate these vesicles from PWH with/without CVD to study the potential of these IL-32-containing vesicles as biomarkers of disease and potential targets for therapy.

Funding: NIH

RÉSUMÉ 124 - Volonté d'utiliser la prophylaxie préexposition contre le VIH chez les personnes utilisatrices de drogues à Montréal participant à la Cohorte HEPCO

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Introduction: L'infection par le VIH continue d'affecter disproportionnellement les personnes utilisatrices de drogues par injection (PUDI). La prophylaxie préexposition (PrEP), une médication orale, est utilisée avec succès en prévention chez d'autres groupes à risque, mais peu dans cette population.

Méthodes: Analyses descriptives sur les questions portant sur la PrEP dans la HEPatitis COhort (HEPCO), une cohorte de PUDI recrutés dans la communauté, à leur première visite entre 2017 et 2022. Nous avons comparé les participants (perceptions, variables sociodémographiques et comportements) en fonction de leur volonté d'utiliser la PrEP, utilisant des tests de khi-carrés et de Fischer.

Résultats: Parmi 465 participants (82% d'hommes, âge moyen de 43 ans) le taux de volonté d'utiliser la PrEP était de 48% (220/465). Les PUDI disposées à utiliser la PrEP avaient une perception plus positive de la PrEP et étaient davantage en accord avec des énoncés décrivant son utilité potentielle. L'âge, l'anglais comme langue principale, et l'instabilité du logement étaient associés à la volonté d'utiliser la PrEP. Pour les facteurs de risque de VIH, seule l'injection de cocaïne était significative, avec 64% (141/220) des PUDI volontaires contre 54% (129/241) chez leur contrepartie. L'incarcération et le partage de matériel d'injection n'avaient toutefois pas d'association significative.

Discussion / Conclusion: La moitié des PUDI étaient disposés à utiliser la PrEP et cette disposition était associée au souhait d'éviter l'infection par le VIH si prise de risque. Cependant, la prise rapportée de risque n'était pas associée à cette volonté d'utiliser la PrEP. Ces résultats renforcent un passage vers une approche de prescription de la PrEP plus large, basée sur la demande des PUDI plutôt que la recherche de facteurs de risque spécifiques par les prescripteur.e.s.

Ce projet est financé par une Bourse d'études supérieures du Canada (BESC-M) des IRSC et la cohorte HEPCO est financée par les IRSC (PJT-175233)

RÉSUMÉ 127 - Fate mapping demonstrates that γδ T cells are the earliest and predominant IL-17A-producing cells during mouse acute liver injury

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Background: The IL-17A cytokine plays an important role in the development of acute liver injury (ALI) by promoting immune cell infiltration, liver damage, and inflammation. While various cell types are identified as IL-17A producers, kinetics of their recruitment and functionality are not well understood.

Methods: We used an IL-17A-CreEYFP reporter mouse in the carbon tetrachloride (CCl_4)-induced ALI model to undertake *in vivo* fate mapping of IL-17-producing cells. Liver damage was assessed by serum ALT/AST and H&E staining. Flow cytometry on intrahepatic leukocytes was used to determine the frequency and fate of IL-17-producing cells.

Results: Tissue damage peaked at 24h and 48h post-CCl_4, and was temporally associated with high IL-17A hepatic expression. Among myeloid cells, neutrophils were the first to show massive infiltration in the liver at 12h and 24h post-CCl_4, followed by monocytes at 48h. At 72h, we observed a second wave of infiltrating neutrophils accompanied by eosinophils. None of the myeloid cells expressed either IL-17A nor YFP. In contrast, IL-17A was significantly expressed in four populations of lymphoid cells, the γδ T, $CD3^-$ $NK1.1^-$ (ILC3), $CD3^+$ $CD4^-$ $CD8^-$ γδTCR$^-$ and $CD3^+$ $CD4^+$ Th17 cells. γδ T cells were the earliest and predominant producers of IL-17A, peaking at 24h and 48 h. They also showed the highest proportion of cells actively producing IL17A (IL-$17A^+YFP^+$) and ex-producers of the cytokine (IL-$17A^-YFP^+$). In contrast, ILC3 and Th17 cells exhibited the highest frequency of IL-17A-low producers (IL-$17A^+YFP^-$), that suggests their inability to achieve full effector functions. By 72 h, IL-17A and eYFP expression returned to baseline levels.

Conclusion: We determined the kinetics of infiltrating IL-17A-producing cells during ALI, and demonstrated that γδ T cells exhibit the earliest and highest expression of IL-17 and the greatest capacity for activation. Thus, γδ T cells emerge as key therapeutic targets in IL-17-associated pathologies.

RÉSUMÉ132 - Reconstruction 3D pulmonaire depuis des simulations radiographiques biplans

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Introduction: Le système d'imagerie radiographique biplan basse dose EOS est actuellement dédié aux pathologies orthopédiques. Ce projet vise à étendre son utilisation à la prise en charge de pathologies pulmonaires en développant une méthode de reconstruction 3D des poumons.

Méthode: Une approche récente a permis de modéliser simultanément les structures osseuses du genou en 3D basée sur le réseau de neurones V-Net à partir de simulations radiographiques (DRR) biplans. En s'inspirant de la solution proposée précédemment, nous avons entraîné un réseau prenant en entrée des DRR biplans thoracique et en sortie les labélisations 3D des poumons droit et gauche. La base de données de DRR à été construite à l'aide des scanners thoraciques de la base publique LIDC-IDRI avec une résolution ≤2mm. Les reconstructions 3D pulmonaires de référence ont été générées avec des réseaux préentraînés publics. Au total, 441 scanners ont été retenus pour simuler les DRR puis répartis en ensembles d'entraînement (80%) et de test (20%).

Résultats: Nous avons évalué la précision volumique (Dice), le chevauchement volumique (Jaccard), la moyenne des distances maximales surfaciques (distance de Hausdorff) et la distance moyenne surfacique (distance de Chamfer).Sur la base de test, le modèle obtient un Dice moyen de 95%, un Jaccard de 91%, une distance de Chamfer de 4mm une distance de Hausdorff de 37mm.Nous avons extrait chaque lobe des reconstructions 3D et l'évaluation par lobe révèle que tous affichent un Dice supérieur à 94 %.

Discussion / Conclusion: Les résultats démontrent que le V-Net génère une bonne modélisation 3D des poumons à partir de deux images radiographiques simulées. Une étude sur la localisation des erreurs est en cours pour pouvoir envisager une application clinique. Pour le moment, l'étude utilise des données simulées simplifiées qui ne considèrent pas la géométrie réelle du système d'imagerie EOS.

Subvention: Medteq-EOSImaging

RÉSUMÉ 156 - Investigating the molecular function of THAP12, a novel gene associated with a rare epileptic encephalopathy

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Lennox-Gastaut Syndrome (LGS), a severe form of epileptic encephalopathy developing in childhood, presents significant challenges in both diagnosis and treatment. Since the etiology of LGS in about 30% of patients is unknown, there is a dire need to understand the pathogenic mechanisms of this disease. This study aims to investigate the molecular mechanisms which contribute to the pathogenicity of LGS in two symptomatically diagnosed siblings. Whole genome sequencing performed on both siblings revealed a compound heterozygous mutation in *THAP12*, a novel gene never previously associated with neurodevelopmental disorders. Interestingly, THAP12 contains a zinc-finger domain which has been predicted to enable DNA binding. This leads us to believe that THAP12 acts as a transcription factor regulating the expression of key genes involved in cell signalling and proliferation, and that mutations in this gene may lead to epileptic encephalopathy. To unravel the molecular mechanisms of THAP12, we employed a comprehensive approach utilizing both in-vitro and in-vivo models. Fibroblasts obtained from our patients allow for examination of the cellular responses to the mutation. The development of *THAP12*-KO HEK293FT cells will allow us to identify potential chromatin binding sites through ChIP-seq. We also created a stable line of *thap12*-KO zebrafish to validate findings from our fibroblasts and to examine how neurodevelopmental processes may be impacted by a loss of *thap12*. Analysis of patient fibroblasts revealed a loss of THAP12 at the protein level and altered growth and morphology. Our zebrafish models showed expression of THAP12 in the developing brain, and severe neurodevelopmental defects were observed when *thap12* was knocked out. Overall, our preliminary results indicate *THAP12* may play a significant role in the development of epileptic encephalopathy. By unravelling the pathogenic mechanisms of mutations in *THAP12*, our work has the potential to unveil actionable molecular targets, needed for the development of non-canonical therapeutic strategies.



PRÉSENTATIONS PAR AFFICHE

RÉSUMÉ 2 - Approche thérapeutique novatrice utilisant des lactonases pour contrer les effets nocifs de Pseudomonas aeruginosa sur la réparation de l'épithélium des voies aériennes

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Introduction: Chez les patients atteints de fibrose kystique (FK), causée par des mutations du canal CFTR, les infections bactériennes chroniques, notamment à *Pseudomonas aeruginosa* (PA), entraînent des dommages de l'épithélium des voies aériennes (VA). Nos travaux ont montré que les facteurs de virulence (VirF, dont l'élastase) secrétés par PA compromettent l'intégrité épithéliale, réduisent la capacité de réparation des lésions, déjà insuffisante en FK, et affectent l'efficacité des traitements avec les modulateurs de CFTR. Notre objectif est d'identifier des stratégies permettant de diminuer la virulence bactérienne, via des enzymes (lactonases) et de promouvoir la réparation de l'épithélium des VA.

Méthodologie: Des cultures primaires de cellules épithéliales des VA provenant de donneurs sains ou de patients FK ont été exposées à des filtrats bactériens (VirF) de PA (cultivée en présence ou non de lactonases) ainsi qu'aux modulateurs de CFTR (Trikafta, pour les cultures FK) avant d'évaluer les processus de réparation suite à des lésions.

Résultats: Nous avons d'abord confirmé l'effet délétère de l'exposition aux VirF de PA sur la migration guidée, la prolifération cellulaire et la vitesse de réparation de l'épithélium des VA. Nos résultats indiquent que le traitement de PAO1 aux lactonases diminue drastiquement les niveaux d'élastases produits, comparé aux cultures de PAO1 non traitées ou traitées à une lactonase inactive. Grâce aux lactonases actives, l'effet néfaste des VirF de PA sur les processus de réparation épithéliale est aboli dans les cultures des VA non-FK, FK et FK traitées au Trikafta.

Discussion: Nos résultats montrent que l'effet délétère de PAO1 est contrecarré par les lactonases actives en réduisant drastiquement la production de VirF et en préservant la capacité de réparation de l'épithélium des VA FK et de donneurs sains. Notre projet présente un potentiel thérapeutique afin de préserver l'intégrité épithéliale des patients infectés.

Remerciements: IRSC/RSRQ/CRCHUM/Université de Montréal

RÉSUMÉ 3 - Role of DNA Methylation on 15-lipoxygenase-1 Gene Expression in Osteoarthritis

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Objective and design: Osteoarthritis (OA) is the most prevalent type of arthritis and a major contributor to physical impairment with a significant financial impact. OA. Pain, stiffness, and a restricted range of motion are the primary signs and symptoms of OA. Genetics, age, obesity, joint damage, and knee malalignment are risk factors for OA. Numerous anti-inflammatory and immunomodulatory lipid mediators are produced by 15-lipoxygenase-1 (15-LOX-1), which has been shown to have protective effects against a number of inflammatory diseases, including OA. The purpose of this study was to assess the expression of 15-LOX-1 in the cartilage of OA patients and normal donors, as well as to ascertain whether DNA methylation controls this expression.

Methods: Cartilage samples were collected from both OA-affected at the time of total knee replacement surgery, and normal knee joints during autopsy. Real-time polymerase chain reaction (PCR) was used to assess the expression of 15-LOX-1. Using 5-Aza-2'-desoxycytidine (5-Aza-dC), a DNA methyltransferase inhibitor, the significance of DNA methylation in 15-LOX-1 expression was evaluated. Using a CpG-free luciferase vector, the impact of CpG methylation on the activity of the 15-LOX-1 promoter was assessed. Pyrosequencing was used to ascertain the 15-LOX-1 promoter's DNA methylation status.

Results: Compared to healthy cartilage, OA showed increased expression of 15-LOX-1. 15-LOX-1 mRNA levels were upregulated in chondrocytes treated with 5-Aza-dc, and 15-LOX-1 promoter activity was downregulated in vitro through methylation. The methylation status of the 15-LOX-1 gene promoter did not differ between cartilage from normal and OA cartilage. **Conclusion**. In OA cartilage, there was an increased expression level of 15-LOX-1, which might be related to a healing process. The methylation status of 15-LOX-1's promoter was not linked to its upregulation in OA cartilage, indicating that alternative mechanisms may be at play.

RÉSUMÉ 4 - Utilisation du virus oncolytique VSVΔ51-IL2 comme adjuvant dans un contexte de vaccination anticancéreuse // Oncolytic virus VSVΔ51-IL2 as an adjuvant for anticancer vaccination

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Introduction: Les virus oncolytiques sont caractérisés par leur capacité à préférentiellement cibler et tuer les cellules cancéreuses, ainsi que d'induire une forte réponse immunitaire tout en épargnant les tissus sains. Notre groupe a récemment pu démontrer que leur co-administration avec des peptides tumoraux peut induire une forte réponse dirigée contre les cellules cancéreuses et donc servir d'adjuvant de vaccination. Nous avons précédemment généré une souche oncolytique du virus de la stomatite vésiculaire encodant l'interleukine 2 (VSVΔ51-IL2), une cytokine importante pour l'activation lymphocytaire et l'induction d'une forte réponse mémoire. Avec ce projet, nous cherchons à déterminer si VSVΔ51-Il2 exhibe un potentiel vaccinal accru, comparé à sa souche parentale.

Méthodes: L'adjuvanticité vaccinale des deux souches virales ont a été caractérisées in vivo sur des souris vaccinées avec des peptides cibles coadministrés avec VSVΔ51-Il2 ou sa souche parentale (VSVΔ51-YFP). La réponse immunitaire spécifique à l'antigène ciblé induite par ces vaccins a été évaluée systématiquement (sang et rate) par cytométrie en flux. La protection thérapeutique induite par ces traitements a également été étudiée en vaccinant des souris portant des mélanomes (B16F10) sous-cutanés et en suivant la progression tumorale.

Résultats: Suite à une vaccination contre l'antigène modèle ovalbumine (Ova), nous avons pu constater que VSVΔ51-IL2 permet la génération d'une plus grande proportion de cellules T CD8 antigène-spécifiques ainsi qu'une transition accrue de cette population vers un phénotype mémoire. Utilisé dans un contexte thérapeutique VSVΔ51-Il2 permet également un meilleur contrôle de la progression de mélanomes encodant l'antigène cible (B16F10-Ova).

Discussion / Conclusions: De manière générale, ce projet a le potentiel d'approfondir notre compréhension de la capacité adjuvante des virus oncolytiques et ainsi, de faciliter le développement de nouveaux vaccins anticancéreux.

RÉSUMÉ 5 - Virothérapie du cancer ovarian par le virus de la stomatite vésiculaire

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Introduction: Le cancer ovarien est la 1ère cause de mortalité parmi les femmes atteintes de cancers gynécologiques. En clinique, plus de 70% des patientes sont diagnostiquées avec un stade avancé, associé à une survie à 5 ans de 17%. Plus de 80% d'entre elles vont rechuter après les traitements de première ligne, d'où l'urgence de trouver de nouvelles options thérapeutiques.

Les immunothérapies telles que les virus oncolytiques (VO) sont de puissants outils anticancéreux. Les VO se répliquent sélectivement dans les cellules tumorales, grâce aux défauts acquis au cours de leur transformation maligne. Un VO prometteur est le virus de la stomatite vésiculaire (VSV), plus spécifiquement son variant oncolytique VSVΔ51, un présentant une mutation dans sa protéine de matrice qui rend le virus sensible aux voies antivirales souvent défectueuses dans le cancer.

Méthodes: Nous avons évalué le potentiel de VSV seul ou en combinaison avec divers médicaments anticancéreux contre le cancer ovarien en utilisant un panel de 33 lignées cellulaires de cancer ovarien dérivées de patientes et des modèles de xénogreffes.

Résultats: Nous avons constaté que la majorité des lignées cellulaires sont sensibles à VSV. Afin d'améliorer son efficacité, VSV a été combiné à diverses drogues. Bien qu'aucune des combinaisons de VSV avec les molécules utilisées dans le cadre du cancer ovarien n'ait amélioré l'infection virale, sa combinaison à des inhibiteurs de JAK a promu l'infection virale *in vitro* et *ex vivo*, améliorant également l'efficacité du traitement dans les xénogreffes du cancer ovarien humain.

Discussion/Conclusion: Nous montrons que VSV, seul ou combiné avec des inhibiteurs de JAK, pourrait être efficace comme option thérapeutique pour les patientes atteintes de cancer ovarien. Étant donné que les inhibiteurs de JAK testés sont approuvés par les autorités de santé, notre approche a le potentiel d'être rapidement transposée en clinique.

Funding agencies: FRQS, CRCHUM, ICM

RÉSUMÉ 6 - Role of epigenetic regulation and Sp1 transcription factor on DP1 receptor expression in Osteoarthritis

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Objective: Epigenetic changes particularly DNA methylation plays an essential role in the regulation of gene expression. Numerous genes implicated in the pathophysiology of Osteoarthritis (OA), including those encoding pro-inflammatory mediators and enzymes that break down cartilage, have been shown to be expressed in a manner regulated by DNA methylation. The prostaglandin D2 receptor, D prostanoid receptor 1 (DP1), is essential for modulating inflammation and cartilage metabolism. Our previous findings demonstrated that DP1 signalling is protective against OA in mice and down-regulates catabolic responses in cultured chondrocytes. Nonetheless, little is known about the DP1 transcriptional regulation mechanisms in cartilage. The aim of this study was to characterize the human DP1 promoter and investigate how DNA methylation affects DP1 expression in chondrocytes. Furthermore, we assessed the methylation state and expression level of the DP1 gene promoter in both normal and OA cartilage.

Methods: A minimal promoter region (-250/-120) containing three binding sites for specificity protein 1 (Sp1) was identified by deletion and site-directed mutagenesis analyses. Electrophoretic mobility shift assays (EMSA) and chromatin immunoprecipitation (ChIP) were used to confirm the binding of Sp1 to the DP1 promoter.

Results: Both DP1 mRNA expression and DP1 promoter activity were reduced by treatment with the Sp1 inhibitor mithramycin A. Treatment with DNA methylation inhibitor, 5-Aza-2'-deoxycytidine, up-regulated DP1 expression, and the DP1 promoter activity was reduced in the in vitro methylation. There was no difference in the methylation status of the DP1 promoter or the level of DP1 expression between normal and OA cartilage.

Summary: DNA methylation and the transcription factor Sp1 are important determinants of DP1 transcription regulation. Furthermore, they suggest that OA cartilage does not exhibit changes in the methylation status or expression level of DP1. These results will advance our knowledge of the DP1 transcription regulatory mechanisms.

RÉSUMÉ 7 - Umbilical Cord Mesenchymal Stromal/Stem Cells Interplay with Th-17 Cell Response Pathway

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Umbilical cord derived mesenchymal stromal/stem cells (UC-MSCs) were assessed, as an immunomodulatory therapeutics, for their dynamic interaction with the Th-17 immune response pathway. UC-MSCs were able to modulate lymphocyte response by promoting a Th-17-like profile. Such modulation depended on the cell ratio of the co-cultures as well as the presence of an inflammatory setting. UC-MSCs significantly increased the expression of IL-17A and RORγt but differentially modulated IL-23R expression by T cells. In parallel, the secretion profile of the fifteen factors (1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-22, IL-21, IL-23, IL-25, IL-31, IL-33, INF-γ, sCD40, and TNF-α) involved in the Th-17 immune response pathway was substantially altered during these co-cultures. Upregulation of cytokines and regulatory mediators demonstrates the capacity of UC-MSCs to sense and actively respond to tissue challenges. Protein network and functional enrichment analysis indicated that several biological processes, molecular functions and cellular components linked to distinct Th-17 signaling interactions are involved in several trophic, inflammatory and immune network responses. These immunological changes and interactions with the Th-17 pathway are likely critical to tissue healing and may help to identify molecular targets that will improve therapeutic strategies involving UC-MSCs.

RÉSUMÉ 8 - Cibler la glycolyse afin d'améliorer la thérapie par virus oncolytiques

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Les virus oncolytiques (OV) sont des virus capables d'infecter et tuer préférentiellement les cellules cancéreuses. Cependant, tous les patients ne répondent pas de manière égale au traitement, par conséquent, il est essentiel de comprendre pourquoi certaines tumeurs sont sensibles à ce traitement alors que d'autres sont réfractaires.

Bien que la réponse antivirale de l'hôte soit un déterminant majeur de la susceptibilité à l'infection par les virus oncolytiques, le métabolisme cellulaire est une autre caractéristique des tumeurs qui joue un rôle important dans la détermination de la susceptibilité aux virus oncolytiques.

En effet, les virus utilisent la machinerie cellulaire de leur hôte cellulaire pour fournir les éléments de base à leur réplication. Cependant, l'interaction entre l'immunité antivirale et le métabolisme tumoral, particulièrement dans le contexte de la thérapie par virus oncolytiques, demeure mal comprise.

Nos données préliminaires suggèrent que la glycolyse est accrue dans les cellules tumorales infectées par le virus de la stomatite vésiculaire (VSV).

Puisqu'il a été démontré que l'inhibition de la glycolyse empêche l'expression des cytokines avec l'activité antivirale (comprenant TNFα, IFNγ), nous émettons l'hypothèse que la glycolyse régule négativement la réplication de VSV, et que l'inhibition de la glycolyse devrait améliorer cette thérapie.

Nous avons pour objectifs de déterminer l'impact de la glycolyse sur la réplication de VSV, et de cibler la glycolyse pour améliorer l'efficacité des OV et l'immunité antitumorale.

Pour ce faire, nous traitons des cellules avec les molécules inhibitrices de la glycolyse puis infectons avec VSV, les titres viraux sont ensuite quantifiés par plaque assay, nous effectuons aussi des qPCR et ELISA afin de mesurer les cytokines produites. Nous investiguons aussi l'effet in-vivo.

Cette approche est particulièrement attrayante, car cibler le métabolisme tumoral peut avoir des effets anticancéreux seul et, par conséquent, la combinaison avec les virus oncolytiques engendrerait une action synergique intensifiée.

RÉSUMÉ 9 - Cibler la production de l'itaconate afin d'améliorer la virothérapie oncolytique.

Jessica Meunier[1, 2], Dominic Roy[1, 2]

[1]Université de Montréal, [2]CRCHUM

La virothérapie oncolytique est une thérapie moderne contre le cancer utilisant des virus oncolytiques, c'est-à-dire des virus capables de se répliquer dans les cellules cancéreuses afin de les infecter et de les tuer. Malgré des résultats d'essais cliniques prometteurs, ce ne sont pas tous les patients qui répondent au traitement puisque la sensibilité des tumeurs face aux virus oncolytiques est variable. Cette variabilité serait en partie menée par le métabolisme des tumeurs, qui lui est encore mal compris.

Nous savons qu'infecter des cellules tumorales avec le virus oncolytique VSVΔ51 induit fortement l'expression du gène Irg1, qui est responsable de la production de l'itaconate. Sachant que le gène Irg1 est induit par l'interféron et que VSV est sensible à l'activité antivirale des interférons, nous pensons que Irg1 et l'itaconate possèdent une activité antivirale contre VSV, limitant l'efficacité de la virothérapie oncolytique.

Pour découvrir l'impact de l'itaconate sur le métabolisme des tumeurs et sur l'immunité antivirale, nous utiliserons plusieurs lignées cellulaires murines et humaines. Nous allons «knockout (KO)» Irg1 via la méthode CRISPR, puis évaluer l'efficacité du traitement in vitro en mesurant la réplication virale par «plaque assay». Afin de mieux comprendre comment la production d'itaconate module la réplication du virus, nous allons étudier la voie JAK-STAT1, une voie antivirale clé contre VSV, puisqu'il a été suggéré qu'elle serait inhibée par l'itaconate. Nous mesurerons l'expression de l'IFN-β par qPCR dans des cellules de type sauvage (WT) et KO pour Irg1. Nous ferons aussi des Western Blots afin d'examiner l'activation et la phosphorylation de la voie JAK-STAT1 dans des cellules WT et KO pour Irg1.

Ces travaux pourraient mener à l'amélioration de la virothérapie oncolytique ainsi qu'au développement d'une thérapie qui combinerait les virus oncolytiques et l'inhibition de l'itaconate.

Bourses: Canderel (ICM), Bourse de formation (CRCHUM)

Subvention: CIHR

RÉSUMÉ 10 - Understanding the role of proline metabolism in supporting T cell function

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T cells play a crucial role in the immune system and when activated rapidly proliferate and release cytokines to mount an immune response. The switch from quiescent to active state requires the engagement of metabolic pathways. While many metabolites are known to be important for T cell function, the significance of many amino acids, particularly non-essential amino acids, remains unclear. Our objective is to further our understanding of proline metabolism in T cells.

To determine the impact proline availability has on T cells *in vitro* we use media lacking proline or supplemented with low, medium, or high concentrations of proline. To study proline metabolism, *in vitro* and *in vivo* we use retroviral vectors encoding shRNAs to knockdown relevant genes in proline metabolism. Additionally, for *in vivo* experiments we use an adoptive transfer model with OT-I T cells. Methods used to study proline metabolism and its effects include RT-qPCR, western blotting, and stable isotope tracer analysis (SITA). Methods used to study T cells include growth curves and flow cytometry.

Results revealed that activated T cells have increased proline metabolism when compared to naïve T cells. *In vitro*, shRNA knockdown of P5CS, an enzyme involved in proline synthesis, revealed decreased proline synthesis and as a result impaired T cell growth and decreased protein synthesis. *In vivo*, P5CS KD resulted in reduction of T cell proliferation and cytokine production.

Our results suggest that proline synthesis is required for optimal T cell proliferation and function. To further understand proline metabolism in T cells we want to continue characterizing proline dynamics, determine the impact modulating proline availability has on Teff cells and explore the roles of proline metabolism in Teff cells.

Scholarships: Bourse d'Excellence en Recherche CRCHUM, Canada Graduate Scholarship-Master's CIHR, Bourse Canderel de l'Institut du cancer de Montréal

RÉSUMÉ 11 - HCV-Specific CD4+ T-Cells are Targeted by HIV-1 for Infection and Viral Reservoir Persistence

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Introduction: Hepatitis C virus (HCV) infection is a serious comorbidity in people with HIV (PWH). Antiretroviral therapy (ART) reduces HIV replication to undetectable levels but does not eliminate HIV reservoirs, which persist in CD4+ T-cells of various antigenic specificities. Herein, we aimed to investigate whether HCV-specific CD4+ T-cells are permissive to HIV infection and carry HIV reservoirs during ART, before and after spontaneous HCV clearance.

Methods: Memory CD4+ T-cells from chronic HCV+ participants and HCV-negative controls (n=20/group) were infected with CCR5-tropic $HIV_{NL4.3BaL}$ *in vitro*. HIV integration and replication were measured by real-time PCR and HIV-p24 flow-cytometry and ELISA, respectively. CFSE-based T-cell proliferation combined with intracellular HIV-p24 staining was used to examine the susceptibility of HCV-specific T-cells to $HIV_{NL4.3BaL}$ infection in HCV resolvers (n=8) and HCV chronic (n=2) participants. In one ART-treated PWH who underwent three subsequent HCV infections, Activation Induced Marker (AIM) assay was used to phenotype HCV-specific T-cells. Integrated HIV-DNA was measured in sorted HCV-specific T-cells. A monocyte-derived dendritic cell-based viral outgrowth assay (MDDC-based VOA) was used to detect replication-competent HIV reservoirs.

Results and Discussion: CD4+T-cells from HCV+ chronics were more susceptible to $HIV_{NL4.3BaL}$ infection *in vitro than* controls, as demonstrated by intracellular ($p=0.0344$) and soluble HIV-p24 expression ($p=0.0298$). A fraction of HCV-specific T-cell proliferation in response to HCV-NS3 highly supported productive HIV infection *in vitro*. In the one ART-treated PWH acutely infected with HCV, the MDDC-based VOA demonstrated that HCV-specific T-cells exhibit a Tfh phenotype and carry replication-competent HIV reservoirs, following spontaneous HCV clearance that population shifted from Tfh toward Th17 and increased integrated HIV-DNA.

Conclusion: Our results provide evidence that HCV-specific CD4+ T-cells are susceptible to HIV infection and may represent long-lived HIV reservoirs that could be largely remodeled by HCV spontaneous resolution in ART-treated PWH.

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RÉSUMÉ 13 - Comparative Outcomes of Repetitive Versus Deep Transcranial Magnetic Stimulation in Major Depression: A Pilot Randomized Trial

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Introduction: Transcranial magnetic stimulation (TMS) is a proven treatment for individuals with treatment-resistant depression (TRD). The two main types of TMS are repetitive TMS (rTMS) and deep TMS (dTMS). dTMS generates a broader magnetic field, which minimizes coil positioning errors and increases the likelihood of optimal cortical stimulation. A previous RCT comparing these modalities demonstrated a greater reduction in depression scores and higher response/remission rates with dTMS, though it narrowly missed significance for remission rates (the primary outcome). Limitations of this RCT included an insufficient number of treatment sessions and inadequate statistical power, potentially masking true differences between the modalities. Establishing the superiority of one TMS type over another could significantly improve outcomes for TRD patients, who face a chronic and debilitating condition. Additionally, research into predictive biomarkers is essential, as it could speed up remission and prevent unnecessary treatments.

Objectives: This study aims to evaluate the comparative efficacy of dTMS versus rTMS in TRD and to explore the predictive potential of scalable candidate biomarkers.

Methods: This pilot randomized controlled trial will include 50 TRD participants, randomly assigned to receive either rTMS (n=25) or dTMS (n=25). Outcomes will be assessed using the 17-item Hamilton Depression Rating Scale, with response defined as a ≥50% reduction in score from baseline and remission defined as a score ≤7. Furthermore, baseline biomarker assessments, including EEG-based reward positivity, electrocardiography, and pupillometry, will be performed to assess their predictive value for TMS efficacy.

Conclusion: This study aims to compare the clinical outcomes of rTMS and dTMS in TRD as a preparatory step for a larger, more comprehensive trial. Additionally, identifying predictors of TMS response prior to treatment initiation could hasten remission, reduce unnecessary interventions, and optimize the use of clinical resources, ultimately improving treatment efficiency and patient care.

Fond Instituts de recherche en santé du Canada

RÉSUMÉ 14 - Delineating the role of type I IFN in the efficacy of oncolytic virotherapy against breast cancer

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[1]Université de Montréal

Our group has previously shown in mice that oncolytic virotherapy in the neoadjuvant setting is a promising avenue for TNBC therapy. Furthermore, we found that oncolytic viruses (OVs), in addition to directly killing cancer cells, can be used to induce anti-tumour immunity and sensitize the tumour microenvironment to immunotherapies, such as PD-L1 blockade. In response to OV treatment, there is an influx of type I interferons (IFN-I) within the tumour niche. While IFNs are antiviral cytokines, they are also master stimulators of innate and adaptive immunity such, they antagonize OVs but potentiate anti-tumour immunity. Delineating the importance of IFNs for the therapeutic efficacy of OVs against triple-negative breast cancer (TNBC) is important as it could contribute to improved therapies. The importance of the IFN-I response in the context of anti-tumour immunity remains to be fully characterized. The objective of the project is to characterize the role of IFN-I in secondary tumour challenge and whether anti-tumour immunity requires functional IFN-I. Using syngeneic models of Stage IV TNBC, IFN-I KO vs WT tumour cell lines will be treated with OVs to determine immune activation and identify surface markers, quantify cytokines and monitor changes in anti-tumour gene expression. The WT vs KO tumours will also be infected before surgery, and then rechallenged to determine if virus treatment prevents relapse even in the absence of IFN-I or its receptor. This will also be repeated in IFN-I KO mice to determine the importance of IFN-I produced by non-tumour cells, as well as in the complete absence of IFN-I using IFN-I KO tumour cells in these mice. Results from this project will support further translational research using patient-derived xenografts to further investigate the important role of IFN OV-mediated oncolysis in clinically relevant samples.

RÉSUMÉ 15 - Study of the immunological environment predicting a strong anti-tumoral immunity following oncolytic virotherapy

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[1]UDEM

Introduction: Despite the current advances in medicine, one in four Canadians are estimated to die from cancer, and those who survive are faced with therapies that take a heavy toll on their quality of life. Our group proposes the use of oncolytic viruses (OVs) as a cancer therapy, given their high efficiency and low toxicity. Indeed, these viruses are able to preferentially target, infect and kill cancer cells while sparing healthy cells. We have recently shown that, in mice, treatment with OVs induce a powerful anti-tumoral immunity against primary breast cancer tumours, and that this powerful immunity protects mice against tumour rechallenge. Indeed, 20% of the treated mice were completely resistant to this rechallenge, and the other animals had a slower tumoral growth than their untreated counterparts, suggesting that OV treatment modulated the immune system of these mice, preventing or dampening tumor growth. While the importance of the immune system is well known, the mechanisms involved in this anti-tumoural immunity, including the differences between the challenge resistant and the non-resistant mice, are not well understood.

Methods and Results: Thus, our goal is to characterise the immune populations modulated by OV therapy by using single-cell RNA sequencing of surgically removed tumours in these animals. We hypothetise that multiple immune cell types in the tumours are modulated and/or activated following OV therapy and that they differ between resistant and non-resistant mice.

Conclusions: Understanding these modulations will be important to develop viruses able to better induce these important cell types, improving OV therapy efficiency.

RÉSUMÉ 16 - Investigating the role of the immunoproteasome for the efficacy of oncolytic virotherapy against breast cancer

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Oncolytic viruses are a novel form of cancer immunotherapy. The viruses confer therapeutic benefits by directly infecting and killing cancer cells, while triggering a powerful immune response against cancer. In previous work, we found that vesicular stomatitis virus (VSV) is notably effective against breast cancer (BC). We demonstrated that while inducing a type I interferons dependent antitumor immunity, VSV also induces the major histocompatibility complex (MHC) class I antigen presentation pathway, including the immunoproteasome. The immunoproteasome is a key organelle, induced by inflammation, that mediates the cleavage of peptides with high affinity for the MHC-I peptide-binding groove. After investigation, we found that high immunoproteasome expression correlated with good prognosis in 2 different patient cohorts, at RNA and protein level. Therefore, we hypothesize that VSV induces the immunoproteasome through local inflammation, which modifies the peptide repertoire of cancer cells and generates antitumor immunity. Immunoproteasome induction upon VSV infection was further demonstrated at protein level in 13 BC cell lines, and in 3D models using immunofluorescence on BC spheroids. Additionally, immunoproteasome knockout (KO) clones were generated in 4T1 and EO771 murine BC cell lines using CRISPR-Cas9, in order to evaluate the immunoproteasome importance for antitumor immunity in immunocompetent mice. Finally, we aim to study changes in the peptide repertoire upon VSV therapy. Preliminary results indicate about 40 potentially immunogenic peptides upregulated in infected cancer cells, as well as 10 unknown viral peptides. Further peptide experiments will also be conducted on immunoproteasome KO clones. The project presents a novel therapeutic avenue that is still little explored. It creates new opportunities for patients and participates in the research of new, effective, minimally invasive, and less toxic treatments for BC.

Special thanks to the CRS for the funding, and to the University of Montreal, ICM, and CHUM for the various scholarships.

RÉSUMÉ 17 - Apoptotic exosome-like vesicles and their specific sets of nucleic acids shape endothelial function.

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Introduction: Rarefaction of peritubular capillaries (PTC) is a key determinant of progressive chronic kidney disease following ischemia-reperfusion injury (IRI). Renal IRI induces apoptosis of PTCs, leading to the release of apoptotic exosomes (ApoExos), a distinct type of extracellular vesicle. These ApoExos carry mRNA coding for PCSK5, a serine protease from the proprotein convertase family. In turn, neighboring endothelial cells (EC), take up ApoExos which induces increased expression of PCSK5. The purpose of the following experiments was to determine the impact of ApoExos and their cargoed PCSK5 mRNA on endothelial function, specifically regarding proteolysis, migration, and angiogenesis.

Methods: ApoExos were isolated by ultracentrifugation from serum-free media conditioned by primary human EC. EC were transfected with pLX302-PCSK5 plasmid and PCSK5 siRNA to respectively increase and inhibit PCSK5 expression. Apoptosis, wound closure and angiogenic activity were monitored by in vitro caspase-3/7 activity, scratch and tube formation assays respectively. Unilateral hind limb ischemia, a model of persistent vascular injury, was surgically induced by femoral arteriectomy. Mice were injected intravenously with ApoExos or intramuscularly with PCSK5 plasmid. Blood flow recovery and capillary density were assessed by laser Doppler and CD34 immunohistochemistry respectively.

Results: Both ApoExos and PCSK5 inhibited apoptosis of EC and promoted endothelial wound closure and tube formation. Silencing of PCSK5 expression in endothelial cells in vitro decreased angiogenic activity while showing no impact on cell migration. Both ApoExo- and PCSK5-injected mice exhibited enhanced blood flow recovery. Capillary density was increased in the ApoExo-injected group.

Discussion / Conclusion: These results suggest that PCSK5, the predominant mRNA found in endothelial ApoExos, may play a crucial role in facilitating the recovery of the microvasculature after severe vascular injury. These findings offer new insights into microvascular restoration mechanisms of potential use for preventing microvascular rarefaction.

IRSC Fondation J-L Lévesque Chaire Shire en néphrologie, transplantation et régénération rénales

RÉSUMÉ 18 - étude de la thérapie virale des cancers du sein résistants aux thérapies endocriniennes

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Introduction: Le cancer du sein, constitue la 2e cause de décès, par cancer chez les femmes. Il existe plusieurs types de cancers du sein et les pronostiques varient. Les formes hormonosensibles sont moins agressives et plus facilement traitables à l'aide de thérapies ciblées (endocriniennes), certains cancers du sein sont intrinsèquement résistants à ces traitements. Au laboratoire, nous étudions l'utilisation de virus oncolytiques pour le traitement du cancer du sein. De manière intéressante, les cancers résistants aux thérapies endocriniennes ont souvent une voie de signalisation des estrogènes constitutivement active et notre équipe a découvert que l'estrogène sensibilise le cancer aux virus oncolytiques. Nous pensons donc que les virus oncolytiques seraient particulièrement efficaces contre les formes de cancer du sein résistantes aux thérapies endocriniennes. De ce fait, l'objectif de mon projet est de tester l'efficacité de la thérapie virale du cancer du sein hormono résistants.

Méthodes : le tamoxifène (l'hormonothérapie la plus utilisée) est un anti-œstrogène qui bloque la prolifération des cellules tumorales. Nous possédons 4 paires de lignées cellulaires de cancer du sein humaines sensibles et résistantes au Tamoxifène. De plus, les résistances aux thérapies endocriniennes sont souvent le résultat de mutations du récepteur de l'estrogène. Nous avons obtenu trois lignées MCF7 modifiées pour incorporer les mutations Y537S, L536R et D538G fréquemment observées chez les patientes résistantes aux traitements. Nous évaluerons la quantité de particules virales produites par essaie de plaque, ainsi que la mort des cellules tumorales après infection.

Résultats: L'œstrogène améliore la sensibilité virale dans les cancers résistants aux traitements endocriniens. Tandis que le tamoxifène limite l'infection. Ainsi, les cellules ayant la voie des œstrogènes constitutivement active présentent une excellente sensibilité au virus.

Conclusion et discussion: L'approfondissement de ces connaissances générées sur le projet permettrait de contribuer au bon développement d'un traitement prometteur pour les cancers résistants aux thérapies endocrines.

RÉSUMÉ 19 - Hemopexin treatment alleviates colitis severity in the absence of IL-22RA1 signaling in mice

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Introduction: Inflammatory bowel disease (IBD) is often defined by persistent intestinal epithelial inflammation, bleeding, and pain. IBD's pathogenesis is fundamentally characterized by the release of free luminal heme. Interleukin 22 (IL-22) is produced in the gut by immune cells, and it is known to induce a protective response mediated by hemopexin, a plasma heme scavenger produced in the liver that limits the availability of heme iron to microbes and suppresses bacterial growth. We evaluated the protective role of IL-22 by stimulation of hemopexin in a mouse model of acute colitis.

Methods: To assess the effect of IL-22 on colitis, *Il22ra1*$^{-/-}$ and wild-type (Wt) mice on a C57BL/6 background received 2.5% dextran sodium sulphate (DSS) in drinking water for 12 days to induce colitis. To reverse colitis severity, three groups of mice received 2.5% DSS in drinking water for 12 days. The treatment group (*Il22ra1*$^{-/-}$) received 15 mg/kg BW hemopexin injection intraperitoneally on day 7 of the DSS treatment, while the other groups, Wt and *Il22ra1*$^{-/-}$, received the vehicle (PBS).

Results: *Il22ra1*$^{-/-}$ mice had significantly greater weight loss, higher disease activity index (DAI) score and shorter colon length on day 12 (endpoint) compared to the Wt mice. Significant increases in inflammatory markers such as lipocalin-2 (lcn-2), TNF-α and IL-6 were observed in *Il22ra1*$^{-/-}$ mice, contributing to their condition. Decreased fecal hemopexin and increased free luminal heme were observed in *Il22ra1*$^{-/-}$ mice compared to the Wt mice. Hemopexin administration reversed inflammatory markers, increased fecal hemopexin and reduced luminal heme in the *Il22ra1*$^{-/-}$ mice.

Conclusion: Hemopexin is present in the gut during colitis. The absence of Il-22ra1 enhances free luminal heme production, reduces hemopexin concentration in the gut, and aggravates colitis in mice. Hemopexin administration reduces free luminal heme in the gut, enhances hemopexin availability and alleviates colitis severity in mice.

RÉSUMÉ 20 - Exploiter du blocage de la voie de signalisation NF-κB pour améliorer la thérapie virale oncolytique du cancer du sein

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Introduction: Le cancer du sein triple négatif (CSTN) représente 15-20% des cancers du sein, il s'agit d'un sous-type de cancer du sein très agressif caractérisé par l'absence d'expression de récepteurs hormonaux ce qui les rend réfractaires aux traitements habituels. Les patientes souffrant de CSTN ont plus que jamais besoin de thérapies alternatives.

On sait que les cellules cancéreuses présentent des défauts dans la réponse à l'interféron, ce qui peut être exploité par les virus oncolytiques (VO), une classe d'immunothérapie tuant spécifiquement les cellules tumorales. Notre équipe a démontré que l'estrogène peut bloquer la voie de signalisation NF-κB, ayant des effets antiviraux, ce qui sensibilise les cellules cancéreuses exprimant le récepteur de l'estrogène à l'infection par VSVΔ51, un VO largement étudié comme immunothérapie anticancer.

Hypothèse: On pense donc que bloquer de la voie NF-κB préalablement à l'infection par VSVΔ51 pourrait représenter un traitement amélioré dans le cadre du CSTN.

Méthodes: Nous déterminerons l'importance de NF-κB sur différentes lignées de cellules CSTN en mesurant l'activation de la voie après infection par VSVΔ51 par des techniques d'immunofluorescence et d'immunobuvardage de type Western. Puis, nous évaluerons l'efficacité d'inhiber NF-κB en combinaison avec notre VO dans le contexte du CSTN, soit par l'utilisation de drogues bloquant NF-κB ou en modélisant un virus encodant un dominant négatif de IKBα, une molécule inhibitrice qui maintient NF-κB inactif.

Résultats: Jusqu'à maintenant, nos résultats soutiennent que VSVΔ51 tue spécifiquement les cellules du cancer du sein, et montrent que son infection prolongée permet l'activation de la voie NF-κB dans des cellules CSTN.

Conclusion: Si nos travaux sont concluants, les traitements développés pourraient constituer une alternative thérapeutique efficace pour les patientes atteintes de CSTN ainsi que pour tous les types de cancer, qu'ils expriment ou non le récepteur de l'estrogène.

Financement : Instituts de recherche en santé du Canada (IRSC)

RÉSUMÉ 22 - Co-développement d'une nouvelle offre de service en ergothérapie au Centre de gestion de la douleur du CHUM: analyse rapide du point de vue des partenaires

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Introduction: Une étude en cours vise à adapter une intervention danoise en complémentarité avec les soins actuellement offerts au Centre de gestion de la douleur du CHUM. La co-construction de la version préliminaire de cette intervention s'effectue en partenariat avec des patients, cliniciens, gestionnaires et auteurs de l'intervention originale. Il s'agit d'abord de recueillir leurs points de vue au sujet du contenu et du format de l'intervention, ainsi que de son éventuelle implantation.

Méthodes: La première des deux phases de cette recherche-action participative utilisant un devis multiméthodes consiste en une série de groupes de discussion (n=5) et d'entretiens individuels (n=3) avec des individus vivant avec de la douleur chronique, des cliniciens et des gestionnaires (n=27) en utilisant un guide d'entrevue basé sur le modèle d'implantation de Proctor. Une analyse rapide est en cours. Trois membres de l'équipe de recherche ont créé, testé et bonifié un canevas ayant ensuite été utilisé pour résumer les trois premiers verbatims de façon indépendante. Une matrice sera ensuite utilisée pour synthétiser les résultats par catégorie de participants et ainsi mettre en évidence les aspects satisfaisants et les pistes d'amélioration.

Résultats: L'analyse préliminaire des données suggère que 1) trois séances de groupe et six séances individuelles serait une intensité de traitement adéquate ; 2) l'utilisation d'un journal de bord quotidien facile à compléter supporterait le processus d'adaptation occupationnelle des patients ; et 3) l'usage de la téléréadaptation pourrait compenser le fait que l'ergothérapeute de l'hôpital ne puisse pas effectuer de visite à domicile pour le moment.

Discussion / Conclusion: Cette première phase de l'étude s'appuie sur une méthodologie rigoureuse pour déployer une offre de service en ergothérapie qui réponde aux besoins des patients tout en considérant les contraintes du milieu. Elle permettra de générer la première version du manuel d'intervention qui sera ensuite testée et bonifiée.

RÉSUMÉ 23 - Contribution of the immunoproteasome to the efficacy of a leukemia infected cell vaccine

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Introduction: Leukemia treatments rely on aggressive approaches which are associated with severe side-effects. There is therefore a need to develop less toxic therapies. Our proposal is a vaccine of leukemia cells infected with an oncolytic virus (**OV**) - viruses that selectively kill cancer cells. This leukemia infected cell vaccine (**LICV**) was shown to protect mice in the L1210 model, yet its mechanism remains unknown. It is conversely known that prompting anti-tumor immunity relies on proteasomal degradation of cancer antigens, allowing for their presentation on MHC-I. The immunoproteasome (**ImP**), an alternative proteasome, produces peptides with increased MHC-I affinity. Interestingly, interferons, known ImP inducers, are produced upon viral infection. Consequently, **we hypothesize** that the ImP is important for LICV efficacy. Our objective is to elucidate the LICV's mechanisms.

Methods: LICVs will be made by infecting hematological cancer cell lines with oncolytic vesicular stomatitis virus, and administered to syngeneic mice, which will then be challenged with corresponding cancer cells. To assess the role of the ImP, mice will be vaccinated with ImP-WT or ImP-KO LICVs prior to challenge. Induction and incorporation of ImP subunits will be assessed by Western blot. In parallel, the immunopeptidome will be analyzed by mass spectrometry. Finally, we will improve the LICV by testing VSV variants for their ImP-stimulating abilities.

Results: We have shown ImP subunit induction, mediated by type I interferons produced upon OV infection. Additionally, we have shown that induced subunits are incorporated into functional ImP. *In vivo*, we have shown that LICVs expressing higher ImP levels better protect mice from leukemia.

Discussion/conclusion: Our proposal will elucidate the effects of OV treatment on ImP levels, and its importance for OV-based vaccination platforms. If successful, it could translate into a novel leukemia treatment.

Funded by: FRQS, Cole Foundation, Institut du cancer de Montréal, Faculté de médecine de l'Université de Montréal

RÉSUMÉ 24 - Mechanistic Insights into STAT1 Regulation: Implications for Rare Immune Deficiency Disorders

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Introduction: IFNg is a key proinflammatory cytokine with a critical role in driving inflammation and immunoregulatory responses. STAT1, the primary transcription factor in the IFNg signaling pathway controls the expression of Interferon Stimulated Genes. Dysregulation or mutation of STAT1 can lead to severe immune deficiency disorders or autoimmune diseases. This is underscored by Single Nucleotide Polymorphisms in the *STAT1* gene, which are linked to rare diseases such as Chronic Mucocutaneous Candidiasis Disease (CMCD). The regulation of STAT1 through different post-translational modifications is well-documented. In this study we explore the role of reversible oxidative post-translational modifications in the fine-tuning of STAT1 activity.

Methods: To investigate the functional significance of cysteine redox modifications on STAT1 activation, we employed advanced redox labeling techniques and STAT1-deficient cells reconstituted with cysteine-mutated STAT1 variants. We assessed STAT1 phosphorylation and dephosphorylation using biochemical methods, monitored cytoplasmic-nuclear shuttling via indirect immunofluorescence, and conducted RNASeq analysis to determine the impact on the transcriptome.

Results and Discussion: Our results demonstrate that IFNγ induces reversible oxidative post-translational modifications on STAT1. We identified three critical cysteines within two functional domains which are associated with GOF phenotypes when mutated to prevent the oxidation. The oxidation of these specific residues differentially correlates with reduced activating phosphorylation, diminished nuclear accumulation and enhanced dephosphorylation. Modifications of these specific cysteine residues selectively affect the expression of distinct subsets of STAT1 target genes. Notably, two of the identified cysteine are linked to SNPs associated with CMCD.

Conclusion: Our findings support a model in which reversible oxidation of STAT1 cysteine residues attenuates STAT1 activation in response to IFNγ. Additional studies are ongoing to decipher the molecular mechanism controlling STAT1 activity through redox modifications. These insights advance our understanding of STAT1-mediated cytokine signaling and shed light on mechanism underlying GOF associated with CMCD.

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RÉSUMÉ 25 - Characterizing the heterogeneity of neuropsychiatric symptoms across neurodegenerative disorders

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Introduction: Neuropsychiatric symptoms (NPS) in neurodegenerative disorders are clinically heterogeneous, with variability in presentations and prognoses. While prevalent over the course of these disorders, predicting NPS trajectories over time remains a challenge. Identification of predictive factors for emergence and persistence of NPS across neurodegenerative disorders, such as Alzheimer's disease (AD), Lewy body dementias (LBD, i.e., Parkinson's disease dementia [PDD] and dementia with Lewy bodies [DLB]), and frontotemporal dementias (FTD), would have critical clinical utility. Our objectives are to characterize NPS features across neurodegenerative disorders (i.e., AD, LBD, and FTD) and to identify potential predictive factors.

Methods: This study consists of the baseline results of a longitudinal study following older adults (aged ³60 years) with a neurodegenerative disorder and their caregivers recruited from the cognition clinic at the CHUM. NPS were captured using the Neuropsychiatric Inventory (NPI), a questionnaire evaluating frequency and severity of 12 NPS. Potential predictive factors explored included age, sex, clinical stage (Clinical Dementia Rating [CDR]), comorbidities, neurocognitive diagnosis, and cerebral vascular changes.

Results: A total of 99 individuals were recruited (37% AD-noVasc, 31% AD-Vasc, 21% DLB and 10% FTD). Mean ages were 81.7 (6.9) for AD, 79.9 (6.4) for LBD and 75.9 (7.6) for FTD. Total NPI scores were significantly lower in AD than in LBD (p=0.04) and FTD (p=0.04). We detected less anxiety in AD compared to LBD (p=0.02); more hallucinations in LBD compared to AD (p=0.01) and FTD (p=0.01), and less sleep manifestations in AD compared to LBD (p=0.03) and FTD (p=0.03). We detected, in AD, concomitant cerebral vascular changes as a significant predictor of NPS, and comorbidities in AD-Vasc as a significant predictor of behavioural manifestations.

Conclusion: Our baseline data show potential predictive factors of NPS presentation in neurodegenerative disorders, which could be integrated in future personalized therapeutic interventions.

RÉSUMÉ 26 - Exploration de l'hétérogénéité fonctionnelle au sein de populations de cellules sénescentes

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En réponse à divers facteurs de stress/dommages génomiques, les cellules en prolifération peuvent entrer en phase de senescence enclenchant un arrêt permanent de leur cycle cellulaire avec la formation d'un phénotype pro inflammatoire dit SASP (phénotype sécrétoire associé à la sénescence).de façon intéressante, dans une population de cellules sénescentes pas toutes les cellules présentent le même phénotype au niveau individuel. Cette hétérogénéité a également été observée lorsque les cellules sénescentes présentaient divers degrés de sensibilité aux sénolytiques suggérant que ce ne sont pas toutes les cellules sénescentes qui seraient éliminées. Nous proposons de caractériser des marqueurs spécifiques de sénescence dans des groupes hétérogènes de cellules de cancer de l'ovaire ayant subi un double traitement d'irradiation et sénolytique selon le principe de la thérapie "one-two punch". Nous émettons l'hypothèse que l'hétérogénéité de la population de cellules sénescentes pourrait révéler des caractéristiques liées à la résistance/sensibilité à ce traitement. En ayant recours à l'immunofluorescence multiplexe permettant l'évaluation quantitative de 40 marqueurs de sénescence, il s'agira d'évaluer la variation des phénotypes de senescence à l'échelle unicellulaire suite à des traitements séolytiques (perte/gain de certaines sous populations de cellules). Nous nous attendons à déterminer de nouvelles caractéristiques de sénescence spécifiques à chaque sous-groupe de cellules étudié afin d'évaluer la sensibilité des populations de cellules sénescentes aux sénolytiques actuels et dans un contexte plus poussé concevoir de nouveaux sénolytiques basés sur l'hétérogénéité pour cibler de façon plus spécifique les cellules sénescentes et améliorer le potentiel translationnel de ces traitements en clinique.

RÉSUMÉ 28 - Exploration des perceptions des infirmières des soins intensifs concernant l'acceptabilité des nouvelles technologies et de l'utilisation des données des pompes volumétriques

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Introduction: Les soins intensifs (USI) sont reconnus pour l'émergence de nouveaux outils d'aide à la prise de décision alimentés par des données médicales (c.-à-d. *clinical decision support systems* [CDSS]). Cependant, peu de ces outils utilisent les données des pompes volumétriques. Ces pompes sont pourtant l'un des outils de travail principaux des infirmières de l'USI. Ceci pourrait être l'influencé par la complexité de ces données et par notre compréhension limitée de l'acceptabilité des CDSS, et de l'utilisation des données des pompes volumétriques.

Objectifs: Nos objectifs sont de décrire les perceptions des infirmières concernant : 1) l'acceptabilité de développer et d'implanter de nouvelles technologies (c.-à-d. CDSS) aux USI; et 2) de décrire leurs perceptions quant à l'acceptabilité d'utiliser les données des pompes volumétriques.

Méthodes: Dans le cadre d'une étude mixte, nous avons mené une étude qualitative descriptive. Nous avons réalisé des entrevues semi-dirigées de 30 minutes entre janvier et mars 2024 auprès de 10 infirmières d'USI du Québec. Nous avons utilisé une analyse de contenu inductive pour identifier les catégories principales émanant des perspectives des infirmières recrutées.

Résultats: Le développement et l'implantation de CDSS et l'utilisation des données des pompes était perçue comme acceptable. La discordance entre le développement rapide de technologies avec des capacités computationnelles avancées et les délais observés en pratique clinique dans l'informatisation des soins influençait négativement les perceptions quant aux CDSS. Les données des pompes volumétriques étaient considérées comme utiles pour améliorer les pratiques cliniques. L'acceptabilité de leur utilisation était motivée par la perception que les données des pompes devraient concorder avec ce qui est documenté manuellement dans les dossiers médicaux.

Conclusion: Les CDSS et l'utilisation des données des pompes volumétriques sont jugés comme acceptable par les infirmières de notre échantillon. Nos résultats offrent des perspectives pour l'éventuelle implantation de nouvelles technologies aux USI.

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RÉSUMÉ 29 - Self-reported Burden and Health-related Quality of Life in Acute Kidney Injury Survivors compared to Patients living with Advanced Chronic Kidney Disease

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Background: Survivors of severe acute kidney injury (AKI) are at risk of increased morbidity. However, little is known about the quality of life (QOL) of patients having recently suffered from an AKI episode. The purpose of this study was to explore the health-related QOL of severe AKI survivors when compared to patients living with advanced chronic kidney disease (CKD).

Methods: A prospective observational cohort study of severe AKI survivors who attended follow-up in a specialized post-AKI clinic was compared to a cohort of patients with advanced stage 4 or 5 CKD followed in a dedicated nephrology clinic. Self-reported health-related QOL was determined with the Treatment Burden Questionnaire (TBQ) and compared between both groups.

Results: A total of 100 participants were included in the analysis. As opposed to CKD patients, AKI survivors were younger (median age: 63 [52-72] vs. 72 [62-79]), had lower comorbidities (median Charlson index: 5 [2-7] vs. 8 [6-9]) and higher eGFR at follow-up (median: 60 [40-82] vs. 15 [12-20]). The overall QOL reported by AKI survivors was not statistically different from advanced CKD patients (median TBQ score: 19.0 [6.5-43.6] vs. 25 [12.8-43.0]), p=0.45). The only domain where a significant difference was observed between the two cohorts was dietary restrictions (p=0.037). A negative correlation between age and TBQ score was observed (Spearman's rank: -0.23 [p=0.02]) especially in CKD patients (-0.51 [p=0.001]). No correlation was observed for hospital length of stay, burden of medication or follow-up duration since hospital discharge.

Conclusions: Health-related QOL of patients recently discharged from a severe AKI episode is comparable to the low QOL reported by patients living with advanced CKD. The findings of this study suggest that healthcare providers should consider QOL as part of a patient-centred approach when discussing and managing patients after an episode of AKI.

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RÉSUMÉ 30 - Comparison of clinical phenotypes of people living with latent autoimmune diabetes in adults (LADA) and type 1 diabetes (T1D) in the Canadian BETTER registry

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Introduction: Latent Autoimmune Diabetes in Adults (LADA) is known for a slow progression of autoimmune destruction of beta-cells that span a spectrum between classic type 1 diabetes (T1D) and type 2 diabetes phenotypes. To date, lacking a good understanding of LADA has prohibited the release of clinical practice guidelines and optimal management. Objectives: The study aims at: 1) clinically describing a cohort of patients diagnosed with LADA in the BETTER registry; 2) comparing patient-reported outcomes (demographics, treatment and complications) in LADA participants to those with classic T1D.

Methods: Cross-sectional analysis of online clinical questionnaires in the Canadian BETTER registry; 2877 participants, of which 266 (9.25%) reported LADA and 2611 (90.75%) T1D.

Results: LADA vs T1D were 50 ± 13 y.o. vs 40 ± 16 y.o ($p<0.001$); 67% vs. 64% females ($p=0.430$) and had a diabetes duration of 10 ± 9 years vs. 22 ± 15 years ($p<0.001$). LADA patients were older than T1D patients at diagnosis (41 ± 13 vs. 18 ± 12 years old; $p<0.001$), only half started insulin in first year of diagnosis (54% vs. 97%; $p<0.001$), more often reported a family history of T1D (42% vs. 31%; $p<0.001$). Percentage of participants who reached glycemic goal of HbA1c <7% was comparable (39% vs. 35%, $p=0.087$). Fewer LADA patients reported at least an episode of level II hypoglycemia (<3.0mmol/L) in last month (61% vs. 75%; $p<0.001$), and severe hypoglycemia (8% vs. 12%, $p=0.037$). Diabetes related hospitalizations were higher in LADA (8% vs 6%) without reaching statistical significance. Insulin pumps and glucagon were less used in LADA.

Conclusion: Some differences emerged between the two groups which might be related to dissimilarities in pathophysiology in LADA compared to classic T1D cases. These results set the stage for building a prospective Canadian cohort of LADA to undergo phenotyping, genotyping and interventional trials to optimize diabetes management in LADA.

RÉSUMÉ 31 - Early-life stress induces persistent astrocyte dysfunction resulting in fear generalisation

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Exposure to adverse environmental factors during infancy is a major risk factor for the latter development of psychiatric pathologies. In our laboratory, we are particularly interested in studying the long-term effects early life stress (ELS). Using an ELS model based on maternal separation and limited nesting resources, we have recently shown that stress during infancy has a profound effect on fear memory formation in adults. ELS mice loose the capacity to discriminate between neutral and aversive environmental cues, displaying generalised fear responses. ELS mice also display decreased long-term-potentiation evoked in the lateral amygdala, a key region for fear learning. The impact of ELS on fear memory formation and synaptic plasticity seems to be partly dependent on a dysfunction of lateral amygdala astrocytes. Astrocytes are known to modulate energetic supply to neurons, recycling and clearance of neurotransmitters and synaptic plasticity. Through these functions, astrocytes readily modulate learning and memory in different contexts, such as ELS. By virally inducing a dysfunction in lateral amygdala astrocytes, we fully reproduced the impacts of ELS on fear memory formation and synaptic plasticity in non-stressed animals. Interestingly, we have found that following learning, both ELS and lateral amygdala astrocyte dysfunction lead to the formation of larger fear engrams, a type of neuronal ensemble supporting memory. To our knowledge, this is the first report of astrocyte dysfunction leading to the formation of larger engrams. Our results also directly implicate astrocytes in the process of engram-size regulation and memory specificity. Interestingly, we report an inverse correlation between engram size and the specificity of memory, with larger engrams leading to less precise memories. The relationship between engram size and memory specificity seems to take place in other brain regions such as the hippocampus and could be a general principle in engram biology.

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RÉSUMÉ 32 - Développement et utilisation de la base de données IndiQ-AVC portant sur la prise en charge en phase aiguë de l'AVC ischémique : principaux défis et solutions

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Introduction: L'accident vasculaire cérébral (AVC) entraîne plus de 50 000 hospitalisations annuelles au Canada. Pour garantir des soins de qualité, il est indispensable d'évaluer rétrospectivement les pratiques dans les dossiers de santé. Bien que plusieurs registres en AVC existent, peu se concentrent sur les soins aigus. Au Québec, les études descriptives en AVC exposent quelques défis liés à la qualité des données, mais fournissent peu d'information quant à leur définition, codification et utilisation. Nous présentons le développement de la base de données clinico-administrative IndiQ-AVC portant sur des indicateurs prioritaires en phase aiguë de l'AVC et discutons des principaux défis rencontrés lors de son utilisation.

Méthodologie: Les indicateurs de qualité, identifiés dans un examen de la portée, ont été sélectionnés selon leur pertinence, validité et faisabilité avec un processus Delphi composé d'experts interdisciplinaires en AVC et un patient partenaire. La base de données IndiQ-AVC, conçue pour répondre à une question de recherche, comprend 142 variables couvrant l'entièreté de la phase aiguë du continuum de soins en AVC ainsi qu'un dictionnaire de données avec le codage associé.

Résultat: La base de données IndiQ-AVC a été utilisée auprès d'un échantillon aléatoire de 132 dossiers de santé provenant de trois centres au Québec (primaire, secondaire et tertiaire), avec des admissions entre le 1 décembre 2021 et le 31 mai 2022. Les principaux défis rencontrés concernaient la disponibilité, la définition et l'intégrité des données ainsi que la gestion des données manquantes.

Conclusion: La base de données IndiQ-AVC est la première au Québec à intégrer l'ensemble de la pratique interdisciplinaire en phase aiguë de l'AVC. Son utilisation a permis de suggérer des solutions pour l'amélioration continue de la qualité des soins au bénéfice des personnes touchées. Ce projet est soutenu par des bourses d'études doctorales (MES-Universités/OIIQ et FRQS) et financé par la Fondation Santé de Trois-Rivières.

RÉSUMÉ 33 - Factors Associated with the Well-Being of Family Physicians in Quebec: A Cross-Sectional Observational Study

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Context: According to the Canadian Medical Association, over 50% of family physicians are experiencing professional burnout. The lack of well-being among family physicians has significant impacts at both the individual and healthcare system levels. Studies that have looked at associations with well-being have only focused on professional burnout, which is a key element of well-being. However, there is still no conclusive data on the overall concept of well-being among family physicians.

Objectives: Describe the level of well-being among family physicians in Quebec, and to examine the association between demographic and organizational characteristics of family physicians and their level of well-being**.**

Study design: This is a cross-sectional study based on a survey that was distributed to all practicing family physicians in Quebec (approximately 10,000) in November 2023. Survey questions will be described using descriptive statistics and graphical representations to facilitate knowledge transfer. Regression models will be conducted to examine the association between family physicians' well-being and their demographic characteristics (age, gender, years of practice, etc.) and organizational characteristics (primary practice setting, type of practice, environment). The questionnaire was developed in close collaboration with representatives from the Ministry of Health and Social Services, based on validated questionnaires, and included questions about their demographic characteristics and organizational characteristics, job satisfaction, and level of well-being as measured by the Physician Well-Being Index.

The results: will be represented by adjusted means and their respective 95% confidence intervals. This study will shed light on the current state of well-being among family physicians and inform current and future policies aimed at promoting family medicine and improving the well-being of family physicians in Quebec.

Expected Outcomes: We expect to see a significant lack of well-being among family physicians, with variations in the level of well-being depending on demographic and organizational characteristics.

RÉSUMÉ 34 - Interventions intersectorielles pour améliorer la trajectoire de vie des personnes vivant avec l'obésité: Résultats préliminaires d'un scan environnemental

Thameya Balasingam[1], Anne Schweitzer[2], Sopie Marielle Yapi[2], Laurence Berthelet[3], Megane Pierre[2], Alexandre Tremblay[2], Nadia Sourial[1, 2], Antoine Boivin[2], Maxime Sasseville [4, 5], Jean-Baptiste Gartner[4], André Coté[4], Frédérique Bergeron[4], Lily Lessard[3], Brigitte Vachon[1], Géraldine Layani[1, 2]

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Introduction: Vivre avec l'obésité est un problème de santé complexe et multifactoriel. Le système de santé ne contribue qu'à 20% des facteurs affectant la santé d'une personne vivant avec l'obésité (PVO) et à lui seul est insuffisant pour répondre aux besoins des PVO. L'objectif de cette étude est d'identifier les interventions de santé intersectorielles développées dans la communauté et en soins primaires pour améliorer la santé et le bien-être des PVO.

Méthodes: Une équipe composée de chercheurs, cliniciens, gestionnaires et une usagère-partenaire ont effectué une analyse environnementale de la littérature académique et de la littérature grise sur MEDLINE, Web of Science, CINAHL et des sites spécialisés. Pour être inclue, la citation devait décrire ou évaluer une intervention intersectorielle développée en soins primaires et/ou dans la communauté pour les PVO. Deux personnes ont révisé indépendamment la littérature éligible basée sur le titre et l'abstract, ont complété une revue du texte complet et ont extrait les données de toutes les citations inclues. Les discordances étaient résolues par consensus.

Résultats: Les résultats sont rapportés dans un diagramme PRISMA et dans un tableau. En date de juillet 2024, nous avons révisé 1020 abstracts et 149 textes complets pour identifier 6 interventions. Les résultats préliminaires démontrent que la majorité des interventions implique une coopération ou une collaboration entre le secteur communautaire et celui de la santé à travers des conseillers en santé. Les secteurs de l'agriculture, des affaires et de la religion sont également mobilisés pour influencer les déterminants sociaux de la santé tels que les facteurs socioéconomiques à travers un soutien social et les comportements sains par la diète et l'exercice.

Conclusion: Cette revue permettra de cartographier les interventions intersectorielles disponibles et de contribuer à la co-construction d'une communauté de pratique intersectorielle pour mieux répondre aux besoins des PVO.

Financement: Bourse PREMIER

RÉSUMÉ 36 - Deciphering the non-classical functions of depdc5 in zebrafish brain development

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Epilepsy is one of the most common brain disorders, affecting more than 70 million people, worldwide. Despite the availability of 28 classical antiepileptic drugs, approximately 1/3rd fail to effectively control the recurring seizures. *depdc5* (Dishevelled, Egl-10 and Pleckstrin (DEP)-domain containing 5), an epilepsy-associated gene, is responsible for 12-37% cases of focal seizures. It encodes for an inhibitor protein, which regulates mTOR signaling. Using zebrafish as a model, our lab previously unravelled an unknown function of *depdc5* in regulating the development of GABAergic synapses in the brain. The data also suggests that this activity is mediated through non-canonical mechanisms involving axon guidance cues. Now, we are investigating the molecular and cellular basis of the non-classical functions of *depdc5*. We are analyzing whether *depdc5* is required for the establishment of the GABAergic synapses and/or for their survival after initial development. In addition, we are also determining which domain of Depdc5 protein is mediating the non-canonical functions by developing zebrafish lines with in-frame deletion of a few conserved amino acids from each domain. Using Bio-ID assay, we are also delving in to identify the novel interaction partners of Depdc5. Altogether, our study will enhance the understanding about the functioning of a significant genetic player involved not only in epilepsy but in various other neurological disorders and ultimately pave the way for the development of novel therapeutic targets for the patients suffering from these debilitating disorders.

This study is supported by a CIHR grant to Dr. Eric Samarut

RÉSUMÉ 37 - The induction of nucleolar stress associated senescence through a knockdown of RSL1D1

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Dans le cadre de la lutte contre le cancer et soumis à un vieillissement de la population qui prévient les interventions chirurgicales, nous avons besoins de nouvelles stratégies. L'une d'elle consisterait à cibler le processus de la ribogénèse, qui est dérégulé dans les processus cancérigènes. Cependant, il existe peu de médicaments sur le marché qui peuvent réaliser cet exploit avec peu d'effets indésirables. En étudiant la sénescence induite par un stress nucléolaire, nous avons découvert qu'une diminution de la protéine nucléolaire RSL1D1, en plus de causer la senescence, s'accompagne d'une diminution de la fibrillarine, un signe de stress nucléolaire. Cependant, RSL1D1 n'est pas reconnue comme un agent de stabilité du nucléole. La question est comment la diminution de RSL1D1 provoque le stress nucléolaire? Pour y répondre, nous avons observé les effets de la diminution de l'expression de RSL1D1 via un etechnologie shRNA dans des cellules C2C12 de souris et dans un modèle transgénique inductible, le modèle RickDo, qui a été éprouvé avec succès en 2023. Les résultats préliminaires in vitro nous permettent d'affirmer que la diminution de RSL1D1 s'accompagne d'un accroissement de la senescence avec une augmentation de l'autophagie, une diminution de la vitesse de croissance et une diminution de l'expression des gènes de croissance. De futures expériences pourront éclairer plus en détail les modifications dans ces cellules. Le modèle in vivo est actuellement en cours pour des expériences de longévité et des études métaboliques. Les premiers résultats devraient arriver prochainement. En première conclusion, nos recherches permettront de mieux comprendre le rôle du nucléole dans la régulation cellulaire ainsi que d'offrir une potentielle cible thérapeutique.

RÉSUMÉ 38 - DUOX2 promotes the extracellular release of apoptotic caspases to protect respiratory epithelial cells from respiratory syncytial virus-induced cell death

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Introduction: The Dual Oxidase 2 (DUOX2) enzyme catalyzes the production of extracellular hydrogen peroxide. DUOX2 expression is upregulated in respiratory epithelial cells (ECs) upon infection with various respiratory viruses, including respiratory syncytial virus (RSV), influenza A virus, and SARS-CoV-2. Prior studies, including our own, have highlighted the critical role of DUOX2 in orchestrating the interferon-mediated antiviral response and promoting the secretion of proinflammatory cytokines that drive neutrophilia during respiratory virus infections. Programmed cell death is a fundamental process in the host-virus interactions, significantly shaping the outcome of infection. RSV is associated with high rate of morbidity and mortality in infants, children and elderly, but also adults of all ages with a compromised immune system, cardiopulmonary diseases or patients who have undergone transplantation. In this study, we investigate the role of DUOX2 in the regulation of RSV-induced epithelial cell death.

Methods: Using Crispr-Cas9 generated A549 alveolar ECs deficient in DUOX2, and control cells, we compared RSV-induced cell death using SYTOX staining and lactate dehydrogenase (LDH) release assay. Additionally, we analyzed the cleavage and activity of proapoptotic caspases by immunoblot and substrate cleavage assays.

Results: Our findings revealed an increase in RSV-induced cell death in the absence of DUOX2, which was associated with enhanced cleavage of intracellular caspase-3/-7 and -8 along with PARP. Notably, we observed a marked increase in extracellular caspase-3/-7/-8 activity following RSV infection, which was significantly decreased in the absence of DUOX2.

Conclusion: Our findings reveal a novel and critical role for the hydrogen peroxide-producing enzyme DUOX2 in regulating the release of activated caspases during RSV infection, a mechanism that appears to protect ECs from apoptosis. This adds a new dimension to our understanding of how DUOX2 may modulate the cellular response to viral infections.

Project funded by NSERC, FRQNT, Réseau Santé Respiratoire and CIHR

RÉSUMÉ 39 - Lack of protective immunity against hepatitis C virus reinfection post antiviral therapy

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Introduction: HCV infection spontaneously resolves in ~30% of acutely infected subjects with long-lived immune memory responses that are protective upon reinfection. Persistent HCV infection is characterized by dysfunctional immune responses that can be restored by direct-acting antivirals (DAA) although they remain functionally impaired. Whether this restored immunity is protective upon reinfection/vaccination in high-risk individuals like people who inject drugs (PWID) is unclear. We aimed to determine if recovered antibody and T-cell responses are protective against HCV reinfection in DAA and interferon (IFN)-cured PWID.

Methods: We assessed the proportion of participants from the Montreal Hepatitis C cohort who spontaneously cleared an HCV reinfection episode (n=75) following spontaneous resolution (SR), DAA- or IFN-cure of a prior infection. We examined longitudinally immune responses in a subset of PWID reinfected after DAA- (n=6) or IFN-cure (n=15). We evaluated antibodies by ELISA and neutralization assays (HCVpp), and T-cell response by IFNg-ELISpot against overlapping peptide pools of HCV polyprotein.

Results: Individuals who previously resolved an HCV infection were more likely to clear a reinfection episode (25 of 37), as opposed to those cured with IFN (7 of 26) or DAA (1 of 12). Prior to reinfection (<2 years), HCV antibodies in DAA-cured individuals were significantly higher (P=0.004) and exhibited broader plasma neutralization activity (P=0.0015) than IFN-cured. However, pre-existing antibodies were not associated with the prevention of HCV reinfection. Subjects who became persistently reinfected after DAA-cure showed no significant change in the antibody response during reinfection, while antibodies in those reinfected after IFN-cure were boosted although with limited neutralization capacity. We found that reduced early T cell response was associated with a chronic outcome upon reinfection post-IFN, but not post-DAA.

Discussion / Conclusion: Our results suggest that restored memory immune responses by antiviral therapy may not prevent chronicity upon re-exposure underscoring the need for tailored vaccination strategies.

RÉSUMÉ 40 - THAP12 regulates brain development and mutations are associated with epileptic encephalopathy

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Children with epilepsy often develop additional seizure disorders, such as Lennox-Gastaut syndrome (LGS), characterized by severe, drug-resistant seizures. Unfortunately, 25% of LGS cases are idiopathic, highlighting the need to uncover novel genetic factors underlying severe infantile epilepsies for a comprehensive understanding of their pathophysiology. Recently, our collaborators identified two novel variants in the THAP12 gene in previously undiagnosed LGS patients. Remarkably, THAP12, unlike other epilepsy-associated genes, lacks known functional annotations or associations with neurological diseases, rendering it a compelling target for further investigation.Utilizing patient fibroblasts, we demonstrated that patients' mutations result in the loss of THAP12 protein expression, suggesting a pathogenic loss-of-function mechanism. Additionally, we confirmed the pathogenicity of our patients' mutations in mice, which led to early embryonic lethality, underscoring the essential role of THAP12 in development. To circumvent this lethality, we established a zebrafish thap12-KO model, where mutant larvae exhibited reduced survival, loss of posture, diminished brain size, spontaneous motor seizure-like behavior in darkness, and oversensitivity to pro-convulsants. Single-cell RNA sequencing data revealed that thap12 is expressed in cell clusters associated with cycling progenitors in the brain, implying a critical role in early neuronal development. Consistently, we observed defects in the establishment of an inhibitory neuronal population in thap12-KO zebrafish larvae.Collectively, our findings substantiate the causative role of these novel THAP12 mutations in LGS and advocate for further exploration into THAP12's function during neurodevelopment, spanning molecular mechanisms to brain circuitry. This research endeavors to uncover novel actionable targets for epileptic encephalopathies like LGS, offering promising avenues for future therapeutic developments. Through multidisciplinary approaches encompassing cellular, animal, and genomic studies, we aim to uncover the intricate mechanisms underlying the function of THAP12 in brain development and epileptic syndromes.

RÉSUMÉ 41 - Effet du renversement de la transition épithélio-mésenchymateuse sur la reconnaissance immunitaire du cancer colorectal métastatique

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[1]First Author, [2]Primary Investigator, [3]Co-director

Le cancer colorectal (CCR) métastatique constitue la deuxième cause de mortalité par cancer et est résistant aux nouvelles immunothérapies pourtant efficaces dans d'autres types de cancers communs. Nous émettons l'hypothèse qu'un des mécanismes de résistance du CCR métastatique est la transition épithélio-mésenchymateuse (EMT), qui rend les cellules cancéreuses moins visibles et plus résistantes aux lymphocytes T infiltrant (TIL) en diminuant l'expression des molécules de CMH-I et en augmentant l'expression de ligands immunosuppresseurs comme PD- L1.

Notre objectif général est d'évaluer si un nouvel inhibiteur de l'EMT, qui bloque la clusterine sécrétée par les cellules cancéreuses, redonne un phénotype plus épithélial aux cellules cancéreuses de métastases hépatiques du CCR et les rend plus susceptibles à la destruction par les TIL.

Pour ce faire, nous allons mesurer l'impact de l'anti-clusterine sur l'expression de marqueurs d'EMT, du CMH_I et du PD-L1, sur des lignées cancéreuses déjà établies et sur des organoïdes que nous obtenons de métastases hépatiques de CCR fraîchement opérées. Ensuite, nous évaluerons si cette modulation affecte la capacité des lymphocytes T et de TIL autologues à lyser ces cellules cancéreuses, pré-exposées ou non à l'anti-clusterine.

De plus, à partir des métastases de patients ayant reçu l'anti-culsterine avant d'être opérés (étude clinique CHUM), nous caractériserons le phénotype EMT des cellules cancéreuses, l'abondance et le phénotype des TIL et leur capacité à reconnaître les organoïdes dérivés des métastases, en comparaisons aux métastases de patients non exposés à l'anti-clusterine.

Améliorer la reconnaissance immune du CCR métastatique pourrait augmenter l'efficacité des immunothérapies pour ce cancer léthal.

RÉSUMÉ 42 - Dynamique temporelle des niveaux de gp120 soluble chez les personnes vivant avec le VIH-1

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Introduction: Malgré la prise de traitements antirétroviraux (ART) permettant d'atteindre une virémie indétectable, des signes d'inflammation chronique et de dysfonctions immunitaires persistent chez certaines personnes vivant avec le VIH (PVVIH). Dans le cadre d'une étude transversale avec des participants avirémiques sous ART, nous avons détecté de la gp120 soluble (sgp120) et celle-ci était associée à certains marqueurs inflammatoires. Toutefois, les fluctuations de la sgp120 avant et après l'initiation d'ART et son association avec des marqueurs inflammatoires et de dysfonctions immunitaires reste à déterminer.

Méthodes: Afin d'évaluer les modulations temporelles de la gp120 soluble avant et après ART, nous avons mesuré dans 151 échantillons longitudinaux, provenant de 23 PVVIH, les niveaux de gp120 soluble ainsi que plusieurs classes d'anticorps ciblant la gp120, dont les anticorps ciblant le site de liaison au récepteur CD4 (CD4bs). Nous avons aussi mesuré des marqueurs inflammatoires associés à l'infection au VIH. Des analyses uni- et multivariées ont été effectué entre ces différents paramètres.

Résultats: Chez certains participants, la sgp120 est détectée malgré une charge virale indétectable suite à la prise d'ART, et celle-ci est inversement associée aux comptes de lymphocytes CD4. De façon intéressante, la présence d'anticorps ciblant le site d'interaction de CD4 de la gp120 (CD4bs) semble moduler l'effet délétère associé à la présence de sgp120.

Conclusion: Les effets immunomodulateurs associés à la gp120 soluble pourraient être expliqués par la capacité de sgp120 d'interagir avec le récepteur cellulaire CD4. Ainsi, les anticorps anti-CD4bs, en bloquant l'interaction entre la sgp120 et CD4, pourraient avoir un effet bénéfique chez les PVVIH ayant de la sgp120 détectable. Nos résultats démontrent la nécessité d'étudier davantage le rôle immunomodulateur de la sgp120, ce qui pourrait ouvrir la voie à de nouvelles approches thérapeutiques chez les PVVIH.

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RÉSUMÉ 43 - Evaluation of the oxygenating potential of marine worm haemoglobin to improve tumour biobank conservation protocols

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[1]CRCHUM, [2]UdeM, [3]CHUM

Used for several decades, biobanking samples play a crucial role in biomedical research for understanding the mechanisms underlying oncogenesis and therapeutic resistances, while reproducing the diversity and heterogeneity observed within a population. Numerous methods have been developed to minimise the degradation of tumour samples. However, their quality can be compromised by ischemia-hypoxia conditions, affecting tissue integrity, representativeness, and viability. These alterations can distort research results and limit their relevance for subsequent studies. Hemarina, a pharmaceutical laboratory, investigates oxygenating properties of hemoglobin from a marine worm. This extracellular hemoglobin (M101) can transport substantial oxygen and is 250 times smaller than human red blood cells.

This project aims to use M101 in order to characterize and minimize ischemia-hypoxia while improving biobank preservation, viability, and functionality.

In the first objective immunofluorescence, WB and ELISA techniques will be used to detect hypoxic, inflammatory, and genomic markers while developing optimal hypoxic cultures conditions in vitro. M101 will be added to the culture and cell fates will be compared. The second objective aims to compare tissue preservation and viability with M101, analyzing hypoxic, necrotic, and structural markers using IF/RTqPCR/WB.

Adding M101 into the hypoxic cell culture decreased significantly hypoxic marker expression and inflammatory markers. Conservation of PC3 xenograft samples into the M101 supplemented solution reduced expression of HIF-1a by 90% compared to the controls. CA-IX expression does not appear to change due to its long half-life (36h).

M101 reduces hypoxic state in vitro, allowing us to now investigate cell fate under hypoxia and M101 potential in reversing/improving these later. Moreover, M101 seems to reduce hypoxic set-up during tumor tissue assessment, thus improving its quality for future analyses. Further analysis will be done on tissue necrosis and metabolism.

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RÉSUMÉ 44 - Cryoablation Algorithms for Lung Tumors: a systematic review and meta-analysis of proposed mechanisms for non-operative pulmonary cryosurgery

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Background: Cryoablation offers a minimally invasive alternative to surgical resection for lung tumors, particularly beneficial for inoperable cases. However, optimal protocols lack robust scientific evidence, and the adaptability of cryoablation cycles to various tumor characteristics remains largely unexplored.

Methods: We conducted a systematic review and meta-analysis of studies reporting on cryoablation for lung tumors. PubMed-MEDLINE and EMBASE databases were searched for articles published between January 1, 2000, and July 7, 2024. The primary outcome was local tumor control at 1 year. Secondary outcomes included factors affecting local control and complication rates. Data were combined using a random-effects model, and factors affecting success rates were analyzed through multivariable meta-regression.

Results: Nineteen studies comprising 786 patients with 1048 lung tumors were included. The pooled estimate for local tumor control at 1 year was 90.5% (95% CI, 85.1%-94.1%). Factors significantly associated with improved local control included smaller tumor size, use of three freeze-thaw cycles, shorter first freeze duration, longer final freeze duration, and the presence of a final thaw phase. The incidence of serious adverse events was 4.9% (95% CI: 2.9% - 6.9%), with pneumothorax being the most common complication.

Conclusion: Percutaneous cryoablation demonstrates high efficacy for lung tumor control, with optimal results achieved using a triple freeze-thaw cycle protocol and specific cycle parameters. Patient and tumor characteristics significantly influence outcomes, suggesting that cryoablation protocols can be tailored to these factors. Further research is needed to establish long-term efficacy and develop personalized protocols. Future studies should explore cryoablation strategies via endoscopic approaches to minimize pleural complications. Additionally, randomized controlled trials comparing cryoablation to other treatment modalities are essential to solidify its place in lung tumor management and refine patient selection criteria.

RÉSUMÉ 45 - Deficiency of Hedgehog Interacting Protein (Hhip) in Endothelial Cells Prevents Renal Ischemia Reperfusion-Mediated Renal Tubular Cell Senescence

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Background/aim: Acute kidney injury (AKI) caused by renal ischemia/reperfusion (R I/R) injury is a major clinical issue lacking viable therapies, and with incompletely delineated underlying mechanisms. Given the important roles of hedgehog interacting protein (Hhip) in glomerular endothelial cells (ECs), we asked whether Hhip knockout (KO) in ECs prevents R I/R-induced kidney injury *in vivo* and *in vitro*.

Methods: Both male $Hhip^{EC}$ KO and control $Hhip^{fl/fl}$ mice at 10-weeks of age were subjected to 45 minutes of unilateral R I/R or sham surgery along with contralateral nephrectomy in both groups. The time course of AKI was followed at Days 1, 3 and 7. We also studied naïve renal proximal tubular cells (IRPTCs) exposed to the conditioned media harvested from mouse endothelial cell (mECs) with or without Hhip (siRNA) ± cisplatin (2μM) treatment.

Results: In line with the AKI time course, $Hhip^{fl/fl}$-R I/R mice had higher mortality with significant kidney apoptosis documented by IVISense™ Annexin-V 750 fluorescent imaging probe; increased urinary albumin-to-creatinine ratio; and displayed renal dysmorphology with enhanced kidney injury molecule-1 expression in their kidneys. Notably, renal tubular cell senescence was significantly increased in $Hhip^{fl/fl}$-R I/R mice. In contrast, those changes were significantly ameliorated in the kidneys of $Hhip^{EC}$ KO -R I/R mice. *In vitro*, naïve IRPTCs exposed to the conditioned media harvested from mECs treated with cisplatin exhibited higher cellular senescent activity. It was largely prevented in naïve IRPTCs exposed to the conditioned media harvested from Hhip KO mECs treated with cisplatin.

Conclusion: Our data suggest that Hhip KO in ECs prevented or ameliorated AKI-induced renal tubular injury. This potential protection may be mediated, at least in part, by the inhibition of Hhip-mediated tubular cell senescence.

RÉSUMÉ 46 - Lipid droplets in the brain regulate glycerolipid metabolism and energy homeostasis

Danie Majeur[1, 2], Romane Manceau[1, 2], Josephine Robb[1], Demetra Rodaros[1], Khalil Bouyakdan[1], Frederick Boisjoly[1, 2], Ciaran Murphy-Royal[1, 2], Stephanie Fulton[1, 2], Thierry Alquier[1, 2]

[1]CRCHUM, [2]UdeM

Introduction: Fatty acids (FA) are the main building-blocks for lipid synthesis in the brain and act as central signals regulating energy homeostasis. Our group has shown that in hypothalamic neurons and astrocytes FA are esterified in triglycerides (TG) that are stored in lipid droplets (LD). We have previously shown that disruption of acyl-CoA pools in hypothalamic astrocytes modulates energy homeostasis which in turn increases the activity of hypothalamic POMC neuron that are essential for energy homeostasis. However, whether FA released from LD play a role in energy balance remains unknown.

Methods: To test this, we studied the role of Adipose Triglyceride Lipase (ATGL), the enzyme responsible for the first step of TG breakdown, in POMC neurons and astrocytes.

Results: We show that hypothalamic neurons and astrocytes express ATGL and accumulate LD in response to its inhibition. Furthermore, using a genetic approach to knock-out ATGL in melanocortin neurons (POMC-Cre x ATGL-fl) or astrocytes (GLAST-CreER x ATGL-fl) we show that ATGL is required to maintain energy homeostasis under cold and fasting conditions respectively. Furthermore, using a viral approach (AAV5-GFAP-Cre-GFP) in chow-fed male mice we show that the loss of ATGL specifically in medial basal hypothalamic astrocytes reduces body weight and alters feeding behavior.

Conclusion: Our data shows an unprecedented role for TG metabolism in hypothalamic astrocytes and POMC neurons in energy homeostasis.

Funding: ClHR, FRQS, NSERC, UdeM, CRCHUM, Db Qc

RÉSUMÉ 47 - Dynamics of lipid droplets in microglia regulates neuroinflammatory responses to LPS

Frederick Boisjoly[1], Josephine Robb[1], Danie Majeur[1], Romane Manceau[1], Demetra Rodaros[1], Khalil Bouyakdan[1], Stephanie Fulton[1], Thierry Alquier[1]

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Introduction: Lipid droplets (LD) are organelles that store neutral lipids such as triglycerides (TG). While LD are primarily known to generate fatty acids (FA) acting as energy substrates, they also play a role in inflammation by sequestering or releasing FA that are precursors for the synthesis of lipid signals of inflammation. Accumulation of LD has been observed in microglia and macrophages in response to pro-inflammatory stimuli. Recent studies suggest that adipose triglyceride lipase (ATGL), the enzyme catalyzing the first step of TG lipolysis in LD, is a key regulator of inflammatory responses in different cell types. Thus, we aimed to establish the role of LD accumulation in microglia on inflammatory responses to acute pro-inflammatory insult.

Methods: Mouse primary microglial cultures were treated with the ATGL inhibitor Atglistatin and/or lipopolysaccharide (LPS) to assess the role of ATGL in lipid droplet accumulation, inflammatory gene expression and secretion, as well as in the lipidome, using LC-MS/MS. Furthermore, a novel mouse model with specific ATGL loss in microglia was used to study the role of microglial ATGL on inflammation *in vivo.* To model neuroinflammation, animals were administered with LPS.

Results: First, lipolysis inhibition in mouse primary microglia led to LD accumulation and blunted the expression and secretion of pro-inflammatory cytokines induced by LPS. Targeted and untargeted lipidomic studies revealed that ATGL inhibition reduced the production of pro-inflammatory prostanoids induced by LPS. Finally, specific ATGL deletion in microglia reduced LPS-induced of IL-6, IL-1β and microglial density.

Conclusion: Our findings demonstrate that ATGL inhibition reduces LPS-induced inflammation and suggest that inhibiting LD lipolysis may play a beneficial role in neuroinflammation. Ongoing studies are aimed at testing the role of LD formation in inflammatory responses by targeting the main esterification enzyme (DGAT1) in microglia.

RÉSUMÉ 48 - Le rôle du système du complément dans les dommages microvasculaires associés à l'ischémie-reperfusion rénale.

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Background: Renal ischemia-reperfusion injury (IRI) during kidney transplantation leads to acute kidney injury (AKI) and contributes to long-term renal dysfunction. Peritubular capillary (PTC) rarefaction is crucial in the progression from AKI to chronic kidney disease (CKD). Endothelial cell apoptosis, whether during IRI or after transplantation, triggers the release of immunogenic apoptotic exosome-like vesicles (ApoExo), promoting the production of anti-LG3 autoantibodies targeting the C-terminal motif of perlecan and activating the complement system. The dynamics of complement activation in PTCs during the transition from AKI to CKD remain to be fully characterized. Our objective is to elucidate the interactions between ApoExos, anti-LG3 antibodies, and complement activation within the kidney following IRI.

Methods: Unilateral renal artery clamping with contralateral nephrectomy was performed in wild-type (C57Bl/6J) and complement C3-/- (C3KO) female mice. PBS or ApoExo purified were injected every other day, with endpoints assessed 21 days post-IRI. Kidney function was evaluated using BUN levels. Microvascular congestion and rarefaction were assessed through hematoxylin-eosin sections and CD34 immunohistochemistry, respectively. Anti-LG3 titers were measured by ELISA. Splenic follicular helper T and germinal center B cells were measured by FACS.

Results: All groups exhibited reduced renal function following IRI. ApoExos-induced microvascular congestion and rarefaction were reduced in C3KO mice compared with wild-type mice. Anti-LG3 titers were higher in wild-type mice injected with ApoExos compared to those without. The injection of ApoExos into C3KO mice led to a smaller increase in anti-LG3 titers than in the wild-type group, whether injected or not with ApoExos. This was associated with a decrease in splenic inflammation.

Conclusion: Collectively, these results suggest the direct implication of complement in the response to ApoExo and in the production of anti-LG3 and loss of PTC after IRI.

RÉSUMÉ 49 - An examination of multiple exposure situations in the Canadian Workplace Exposure Database (CWED)

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Introduction: Workers may be exposed to multiple agents in the workplace. Occupational exposure databases (OEDBs) present an opportunity to characterize multiple exposure work situations.

Methods: Industrial hygiene measurements of airborne chemicals from the Canadian Workplace Exposure Database from 1969 to 2012 were grouped by work situation (WS, an occupation within a company during the same year). A WS was considered exposed to multiple agents if it was associated with quantified measurements from two or more agents.

Results: From 124,573 quantified measurements, 163 agents across 5,399 companies were identified. The number of measurements per agent ranged from 2 to 9,364. Of the 15,533 WSs, 4,728 WSs (30.4%) were exposed to multiple agents, with the number of agents per WS ranging from 2 to 26 (median: 3). Among agents with >100 work situations, the proportion of multiple exposure WSs ranged from 0.2% (wood dust) to 93.8% (ethyl acetate) (median: 45.5%). This proportion varied across industries with >100 WSs ranging from 2.0% (Non-Metallic Mineral Mining and Quarrying) to 52.9% (Printing and Related Support Activities) (median: 34.4%). Frequent same-family combinations were metal-only combinations (e.g. manganese-nickel compounds, 318 WSs and cobalt compounds-iron oxides, 184 WSs). Meanwhile, frequent cross-family combinations were dust and metal combinations wherein calcium compounds were most implicated (e.g. calcium-magnesium compounds, 236 WSs and calcium-cadmium compounds, 218 WSs).

Discussion / Conclusion: Our analyses characterized the co-occurrence of agents measured by governmental agencies, a subgroup of agents actually present since not all exposures are monitored. They indicate frequent co-occurrence among substances of traditional concern in the workplace.

RÉSUMÉ 50 - Role of Regulator of G Protein Signaling 9 (RGS9) in Beta-Cell Proliferation and Insulin Secretion

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Introduction: Beta-cell function and mass are under control of G protein-coupled receptors (GPCRs) which are themselves subject to intracellular regulation by regulator of G protein signaling (RGS) proteins. Although the importance of GPCRs to beta-cell biology is well documented, the role of RGS proteins is largely unknown. Recent evidence suggests that RGS9 may have a role in the control of insulin secretion.

Methods: Quantitative (q) PCR and RNA in situ hybridization were performed on isolated male mouse islets and pancreatic sections, respectively. Male mouse islets and pseudoislets were infected with adenovirus encoding short-hairpin (sh) RNA against RGS9 or control. Beta-cell proliferation was assessed by flow cytometry and hormone secretion in 1h-static incubations.

Results: RGS9 transcripts were detected in beta, alpha and delta cells in pancreatic sections and both RGS9-1 and -2 isoforms were detected in whole islet extracts. RGS9 knockdown with two distinct shRNA against RGS9 decreased glucose-stimulated insulin secretion (Control: 2.7±0.7 versus shRNA1: 0.8±0.1% and shRNA2: 1.0% of insulin content, n=1-2) but had no effect on glucose-stimulated beta-cell proliferation (Control: 1.7±0.2 versus shRNA1: 1.5±0.3% of proliferating beta cells, n=5-8, ns). In contrast to RGS9 knockdown, glucose-stimulated insulin secretion was not reduced in RGS9 knockout (RGS9KO) male mouse islets (WT: 0.8±0.1 versus KO: 0.7±0.06% of insulin content, n=6, ns). Interestingly, expression of alternative, truncated RGS9 transcripts were detected in RGS9KO islets.

Conclusion: Our results suggest that RGS9 positively controls insulin secretion. The absence of a phenotype in RGS9KO islets may be due to compensation from truncated RGS9.

Funding agencies: NSERC, FRQNT

RÉSUMÉ 51 - SHORT- AND LONG-TERM IMPACT OF YOUNG FEMALE CBD USE ON FERTILITY AND OFFSPRING HEALTH

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Introduction: Legalizing cannabis has led to an increased use among the youth1. Cannabis contains cannabidiol (CBD), the second most prevalent cannabinoid to tetrahydrocannabinol (THC). CBD lacks the psychoactive effects of THC and marketed as a natural supplement for therapeutic use on stress, sleep, and nausea. However, safety of its chronic use in fertility remains unstudied. This research examines if CBD consumption affects reproductive health and offspring outcomes.

Methods: C57BL6 female mice are injected intraperitoneally with CBD (3mg/kg and 30mg/kg) or vehicle for 30 days before mating with untreated males. Following fertilization, females were euthanized, and embryos were collected on embryonic day E2.5, E3.5 and E18.5. Maternal plasma and organs, embryos, fetuses, and placentae were collected for downstream analysis using scRNA-seq, ChIP-seq, Western blots, and pathology.

Results: Preliminary findings suggest increased weight of maternal cardio-metabolic organs. No visible malformations or differences in fetal weight or sex ratio were observed. 30mg/kg CBD significantly decreased fertilization rate, with a reduced cellular compaction of 8-cell embryos and no blastocyst formation. Further, 3mg/kg CBD increased the rate of implantation loss.

Conclusion: Our data suggests that preconceptual CBD use among females may negatively affect their fertility. Detailed analysis on embryos and fetal tissues collected are envisioned. Further, we plan to determine the longer-term developmental impact on offspring with behavioral and metabolic testing. While CBD may have acute therapeutic effects, this study will be critical for advising women considering pregnancy on the developmental impacts of CBD consumption to their offspring and potentially their cardio-metabolic health.

RÉSUMÉ 52 - Intersectoral interventions for the well-being of people living with type 2 diabetes: A scoping review preliminary results

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Introduction: Diabetes type 2 (DT2) is a complex and multifactor disease. Moreover, the healthcare system contributes to only 20% of the health outcomes (HO) of PLD, while 80% of those are linked to socio-economic, environmental, and genetic factors. Intersectoral collaboration is a collaborative approach between the health sector and other sectors to address the interdependent nature of the HO and to increase the well-being of PL2D. This study aims to identify the characteristics of intersectoral interventions implemented within primary care and the community to improve the PL2D's well-being.

Methods: A scoping review based on Arksey and O'Malley's framework with the search terms covering the themes of intersectoral intervention and diabetes were used across MEDLINE, EMBASE, and specialized websites to identify grey literature published in French or English between 2000 and 2024. Two reviewers independently reviewed each abstract, and any conflict was resolved through consensus with a third reviewer. The same method has been used for full texts and selected intersectoral intervention characteristics.

Results and discussion: As of August 2024, 3517 abstracts and 251 full texts had been screened and read. Of those, 52 interventions have been identified and involve many sectors (academic, public and private health sectors, community, and theology sector). Preliminary results showed that most interventions occur in the United States and affect many HO (healthy habits, environment, socioeconomic factors). The HO of the included intervention have been extracted using the County Health Rankings framework (health behaviours, clinical care, socioeconomic, physical environment). The partnership level of selected interventions has been assessed based on Himmelman's definitions of collaboration levels.

Conclusion: These results will enable stakeholders to consider new organizational approaches between the health sector and the community, and to consider new perspectives on health outcomes in primary care with, for and by PL2D.

Funding: Centre d'expertise en diabète du CHUM

RÉSUMÉ 53 - Succès chirurgical d'un microstent du canal de Schlemm (Hydrus MicroStent) dans le traitement du glaucome à angle ouvert : une étude de cohorte rétrospective

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Introduction: Le mécanisme physiopathologique du glaucome implique une résistance augmentée au passage de l'humeur aqueuse à travers le trabéculum. Historiquement, lorsque les gouttes et les traitements au laser ne parvenaient pas à réduire la pression intraoculaire (PIO), on avait recours aux dispositifs de drainage de glaucome (GDD). Aujourd'hui, les dispositifs minimalement invasif (MIGS) offrent une alternative efficace et plus sécuritaire. Hydrus MicroStent est un MIGS permettant à l'humeur aqueuse de contourner le réseau trabéculaire, facilitant ainsi son drainage.

Méthodes: Cette étude rétrospective a pour objectif d'évaluer l'efficacité et l'innocuité de Hydrus, un an après implantation, chez les patients atteints de glaucome à angle ouvert (GAO). Les critères d'évaluation co-primaires constituaient la différence de PIO avant et après l'opération de même que le nombre de gouttes contre le glaucome à chaque visite postopératoire. Les critères d'évaluation secondaires représentaient le succès chirurgical complet (sans gouttes contre le glaucome) et qualifié (avec des gouttes contre le glaucome), défini par des seuils de PIO de 6 à 21 mmHg ainsi que de 6 à 18 mmHg à un an postopératoire.

Résultats: Au total, 138 yeux de patients ont été inclus dans l'analyse. La PIO moyenne est passée de 16,7 ± 3,8 mmHg à 15,0 ± 2,5 mmHg ($p < 0.05$), tandis que le nombre de gouttes moyen est passé de 2,3 ± 1,1 goutte à 0,7 ± 1,1 goutte ($p < 0.05$), à un an postopératoire. Pour l'ensemble des patients, les taux de succès chirurgical complet et qualifié pour une PIO entre 6 et 21 mmHg étaient respectivement de 63,7% et 88,4%. De plus, l'incidence de complications postopératoires était rare.

Conclusion: Hydrus Microstent s'est révélé efficace et sécuritaire en réduisant efficacement la PIO et le nombre de gouttes contre le glaucome, en obtenant un taux élevé de succès postopératoire et en minimisant les complications et événements indésirables.

RÉSUMÉ 54 - Lifetime Prevalence of Stroke Within an Adult Population with Sickle Cell Disease: A Cross-Sectional Study

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Introduction: Stroke is a potentially devastating complication among patients with sickle cell disease (SCD). In adult patients with SCD, stroke prevalence, etiology, and long-term functional impacts are limited. The primary goal of this retrospective study was to determine the lifetime prevalence of stroke within an adult population with SCD followed in a specialized referral center. Secondary objectives included stratification by stroke type, etiology, treatment received and functional outcome.

Methods: The study was designed as a cross-sectional study that quantified the prevalence of stroke at the end of the observation period (December 2023 or at the last visit). Adult patients (≥18 years old) with any SCD genotype (HbSS, HbS β°/β+-thalassemia and HbSC), that had at least one visit between 2011 and 2023 at CHUM were included. Patients were evaluated by vascular neurologists in a specialized clinic. Symptomatic stroke was defined as any cerebral infarction or intracranial hemorrhage on brain imaging with a corresponding focal neurological deficit. The project was approved by the local ethics committee.

Results: Overall, 450 patients met the inclusion criteria, of which 258 (57%) were women. Median age was 32 years [range; 18,79]. Genotypes included 215 patients with HbSS (48%), 10 HbSβ^0 (2%), 190 HbSC (42%) and 35 HbSβ+ (8%).

Sixteen patients (3.6%) were identified with at least one symptomatic stroke (median age at presentation 36 years [range 4-65]), including 10 (2.2%) with cerebral infarction (median age 25 years [range 4-58], 6 (1.3%) with intracranial hemorrhage (median age 45 years [range 20-65]). For the SS/ Sβ^0 and SC/S β^+, stroke prevalence was 2 % and 1.6 %, respectively.

Conclusion: This large cross-sectional study confirms that the lifetime prevalence of symptomatic stroke in adult patients with SCD is high. Studies with longitudinal neurovascular follow-up are needed to identify risk factors and opportunities for improving primary and secondary stroke prevention.

RÉSUMÉ 55 - AUTOPHAGY INHIBITION AGGRAVATES RENAL MICROVASCULAR INJURY SECONDARY TO ISCHEMIA-REPERFUSION.

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Ischemia-reperfusion injury (IRI) is an integral component of kidney transplantation. Programmed cell death (PCD) of endothelial cells in peritubular capillaries (PTC) post-IRI is a major predictor of long-term loss of renal function. We have shown that caspase-3-deficient mice show reduced PTC apoptosis post-IRI and preserved long-term renal function. Autophagy is known to prevent apoptosis but its precise role on PTC post-IRI remains unclear. Here, we characterize the dynamics of PCD activation and the effect of autophagy inhibition on the renal microvasculature post-IRI.

GFP-LC3 mice underwent unilateral renal artery clamping for 30 minutes with contralateral nephrectomy. Mice were injected intraperitoneally with PBS or chloroquine (CHQ) to inhibit autophagy, on surgery day and every day until sacrifice. Mice were euthanized from 1 to 21 days post-surgery. Kidney function was assessed by measuring BUN levels. Apoptosis and necroptosis were measured by immunohistochemistry (IHC) for cleaved caspase-3 and pRIPK3 respectively. Autophagy was evaluated through GFP-LC3 puncta using confocal microscopy. PTC rarefaction, myofibroblast accumulation, and collagen deposition were assessed at 21 days by IHC for MECA-32, α-smooth muscle actin (α-SMA), and Sirius red staining, respectively.

PTC showed sustained apoptosis over 1 to 21 days after renal IRI. Necroptosis exhibited a transient increase at 1-2 days post-injury, returning to baseline levels by day7. Autophagy was not increased in whole phases of renal IRI (from 1 to 21 days). Yet, blocking autophagy with CHQ increased PTC apoptosis at 21 days but did not affect PTC necroptosis. Microvascular rarefaction was increased in the CHQ-injected group. This was associated with increased renal fibrosis, α-SMA, and collagen deposition within the PTC.

These findings highlight the significant role of PTC autophagy in regulating microvascular integrity and emphasize the predominant influence of microvascular injury and rarefaction as drivers of progressive renal damage and fibrosis post-IRI.

CRCHUM, CST, IRSC, Fondation J.-Louis Lévesque

RÉSUMÉ 56 - A biomaterial-based local T-cell immunotherapy shows promising in vivo antitumor efficacy.

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Backgroud: Local T-cell growth and delivery scaffold has been recently proposed as an alternative to conventional intravenous T-cell immunotherapy against cancer. However, there is presently no ideal injectable scaffold with easy clinical transfer. In this work, we developed and optimized an injectable, macroporous and in-situ gelling scaffold containing immunostimulatory artificial antigen-presenting cells (aAPC) and interleukines.

Method: Chitosan hydrogel forms a solution with physiological pH at room temperature that can be easily mixed with T-cells, anti-CD3/CD28 coated aAPC and interleukines prior to in-situ gelation at 37°C. After measuring T-cell survival/proliferation (live-dead/alamar blue assays) in the scaffold, antitumor efficacy was tested in Transwells, where cancer cells killing was monitored with Incucyte and T-cell reactivity with flow cytometry. Scaffold in vivo efficacy was tested using a subcutaneous MC38-OVA/OT-I carcinoma tumor model in C57BL/6 mice. Tumor growth was followed with caliper. Tumors, hydrogels, lymph nodes and blood were retrieved for immunofluorescence or flow cytometry analysis.

Results and conclusions: We successfully increased matrix macroporosity by optimizing hydrogel formulation to enhance T-cell survival and colony growth. Addition of aAPC and interleukines increased human and murine T-cell proliferation, reactivity and antitumor efficacy in vitro. Our scaffold shows long-term antitumor efficacy in mice and significantly increased their survival over 7 weeks. T-cells reached systemic circulation and lymph nodes, showing potential distal effect.

This injectable, macroporous and immunoactive T cells-loaded chitosan hydrogel is easy to prepare and is a promising candidate for clinical transfer, as an alternative to intravenous T-cell cancer immunotherapy, with lower cell amount and reduced toxicity.

Funding sources : Fonds de recherche du Québec - Nature et Technologie ; Conseil de recherche en sciences naturelles et en génie du Canada ; Réseau de thérapie cellulaire,

RÉSUMÉ 57 - Implication de la voie des acides biliaires dans l'activité antitumorale du polyphénol castalagin

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Introduction: La modification du microbiome intestinal par les prébiotiques tel que le polyphénol castalagin représente une nouvelle option thérapeutique en oncologie. Le castalagin agit directement sur les bactéries du microbiome entrainant une augmentation des acides biliaires (AB) dans le microenvironnement tumoral se traduisant par un effet synergétique avec l'immunothérapie. Néanmoins, le mécanisme entre les acides biliaires et le castalagin reste encore inconnu.

Méthodes: Tout d'abord, nous avons mesuré la composition en AB par HPLC chez des souris traitées avec du castalagin dans différents compartiments.

Par la suite, pour établir un lien entre le castalagin et la voie des AB, plusieurs groupes de souris ont reçu i) une diète supplémentée à 2% en cholestyramine (séquestrant des AB), ii) un agoniste et iii) un antagoniste du récepteur Farnesoid X, principal récepteur des AB.

Nous essayons de voir à quel niveau de la voie des AB le castalagin possède un effet en utilisant des stimulations *in vitro*. Finalement, nous testons l'impact du castalagin sur le microbiome de patients de notre étude clinique (NCT05303493) avec le système de mini-bioréacteur DasBox®.

Résultats: Les analyses HPLC dans le plasma de souris traitées avec le castalagin ont montré une augmentation des AB produits par l'hôte et ceux dérivés du microbiome intestinal, notamment des AB non-conjugués. De plus, nous avons noté une augmentation des AB modulant les cellules T.

La séquestration des AB induit une augmentation de la croissance naturelle des tumeurs MCA-205 et diminue l'efficacité du castalagin. Lorsque nous avons modulé le récepteur FXR, une inhibition complète de l'activité du castalagin a été notée.

Les premiers résultats du DasBox® montrent que nous sommes capables de stabiliser la communauté bactérienne d'un échantillon humain pendant 10 jours.

Conclusion: Nos résultats montrent l'interaction entre la voie des AB et l'activité antitumorale du castalagin

Projet subventionné par Weston et CANTRAIN

RÉSUMÉ 58 - L'effet des acides gras oméga-3 sur l'encéphalopathie hépatique chez des rats avec ligature de la voie biliaire

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Introduction: Les maladies hépatique affectent un Canadien sur quatre et peut entraîner une encéphalopathie hépatique (EH), caractérisée par des troubles cognitifs en raison, entre autres, de l'accumulation d'ammoniac dans le corps. L'EH est associée à une inflammation systémique et neurologique, influençant le métabolisme énergétique cérébral en perturbant la production d'ATP. Une stratégie prometteuse pour améliorer les déficits cognitifs liés à l'EH consiste en une supplémentation en acides gras oméga-3 (AGPI ω3), connus pour leurs propriétés anti-inflammatoires et leur rôle dans le métabolisme énergétique. L'objectif de cette étude est de comparer l'effet de deux huiles sur la mémoire chez des ayant eu une ligature du canal biliaire (BDL).

Méthode: Des rats (BDL) pour induire une EH, puis divisés en groupes pour recevoir une supplémentation en huile végétale ou en huile de poisson riche en ω3. Les effets de cette supplémentation ont été évalués sur la mémoire. Après sacrifice, le plasma a été prélevé pour analyser les marqueurs hépatiques (ammoniaque, AST, ALT, bilirubine et albumine). Les niveaux de cytokines inflammatoires (TNF-α, IL-1β et IL-10) ont été mesurés par ELISA dans le plasma ainsi que dans le cerveau. L'ATP a été mesurée dans le cerveau.

Résultats: Les résultats montrent un effet potentiel sur la mémoire à long terme, bien que non significatif statistiquement. La supplémentation n'a pas réduit les niveaux de cytokines inflammatoires, mais a restauré les niveaux d'ATP dans l'hippocampe des rats BDL-ω3, suggérant une amélioration du métabolisme énergétique cérébral. Cependant, cette restauration n'a pas été observée dans le cortex frontal.

Conclusion: En conclusion, bien que la supplémentation en ω3 ne réduise pas l'inflammation systémique ou cérébrale, elle pourrait moduler le métabolisme énergétique, améliorant ainsi la fonction mitochondriale. Ces résultats suggèrent un potentiel thérapeutique des ω3 dans la gestion des déficits cognitifs liés à l'EH.

RÉSUMÉ 59 - EFFET DE LA TRANSPLANTATION DE MICROBIOTE FÉCAL SUR LE STRESS OXYDATIF CÉRÉBRAL CHEZ LES RATS ATTEINTS D'UNE MALADIE HÉPATIQUE CHRONIQUE PROVOQUÉE PAR LA LIGATURE DU CANAL BILIAIRE

Louis Le Pham-Archambault[1, 2], Alexandre Bourgeois[1, 3], Félix Veillette[1], Mariana Oliveira[1], Katherine Dubois[1], Mélanie Tremblay[1], Chantal Bémeur[1, 3], Christopher F Rose[1, 4]

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Introduction: L'encéphalopathie hépatique (EH) est une complication majeure de la cirrhose. Le stress oxydatif est impliqué dans la pathophysiologie de l'EH. Un modèle animal souvent utilisé pour la cirrhose et où le stress oxydatif est exacerbé est le rat ayant subi une ligature du canal biliaire (BDL). Ce modèle correspond à une cirrhose secondaire d'origine cholestatique présentant une encéphalopathie hépatique et l'évaluation de celle-ci se fait par des tests comportementaux tels que le rotarod (coordination motrice) et la reconnaissance d'objets nouveaux (NOR; mémoire). Durant l'EH, il y a présence d'une dysbiose intestinale. La transplantation de microbiote fécale (TMF) est alors un traitement potentiel. Nous avons précédemment démontré une amélioration des comportements des rats BDL (rotarod et NOR). Ce projet vise à évaluer l'effet de la TMF sur le stress oxydatif à l'aide de différents marqueurs oxydatifs tels que la superoxide dismutase mitochondriale (MnSOD), la lipoperoxidation (HNE) et la capacité antioxydante totale (CAT) dans différents compartiments cérébraux chez les rats BDL.

Méthodes: À partir des lysats cérébraux des groupes SHAM-VEH, BDL-VEH et BDL-TMF, des immunobuvardages pour la MnSOD et le HNE furent réalisés. De plus, la capacité antioxydante totale pour ces lysats cérébraux fut évaluée par essai CAT.

Résultats: L'expression de la MnSOD dans le cortex frontal, le cervelet et l'hippocampe ne présente pas de différence significative entre les groupes. Il en va de même pour les niveaux de HNE dans ces trois régions cérébrales. Enfin, aucune différence significative a été observée entre les groupes pour la capacité antioxydante totale dans les trois régions cérébrales.

Conclusion: Selon les résultats préliminaires, le stress oxydatif ne semble pas être impliqué dans l'effet thérapeutique de la TMF sur l'amélioration comportementale des rats BDL.

RÉSUMÉ 60 - Characterizing the microbiome/IL22 interaction during MASLD

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a growing epidemic disease worldwide comprising several liver diseases, ranging from fat accumulation, steatohepatitis (MASH), fibrosis to cirrhosis and cancer. MASLD could be induced by metabolic abnormalities, immune responses, and gut dysbiosis. IL22 is a pleiotropic cytokine exhibiting protective and inflammatory roles in MASLD. We recently demonstrated that a deficiency of IL22 signaling (IL22ra1$^{-/-}$), aggravated MASLD in female mice (not males) upon high fat diet (HFD) feeding. Given the crucial role of IL22 in maintaining gut homeostasis, signaling in our model may contribute to gut dysbiosis, promoting MASLD.

We hypothesize that IL22 has a sex-dependent effect on the microbiome composition during MASLD, influencing disease progression.

Our study **goal** is to investigate the microbiome relative to MASLD progression in female and male mice deficient in IL22 signaling.

Methods: Female and male IL22ra1$^{-/-}$ and WT mice will be placed on HFD or control diet for 30 WKs (n=10/group), under SPF conditions. Stool, liver and blood will be collected at baseline and 30 WKs.

Aim 1. Microbiome characterization in IL22ra$^{-/-}$ and WT mice with MASLD. Liver damage will be evaluated as we previously described[1]. Microbial genomic DNA extracted from stool will be 16S rRNA sequenced.

Aim 2. Correlation between the microbiome and gut permeability. Gut permeability will be assessed by measuring microbial translocation markers in plasma, and correlated with the microbiome data.

Aim 3. Mechanistic validation of microbiome changes through targeted metabolite analysis. Inferred metabolic pathways will be validated by assessing metabolites in stool and blood.

Conclusion: Results are expected to demonstrate major microbiome alterations in IL22ra1$^{-/-}$ female mice, and an association with the severity of MASLD, allowing for development of better microbiome-based strategies for disease management.

Fundings: Canadian Institutes of Health Research (CIHR) (PJ4-169659 and PJT-175134)

RÉSUMÉ 61 - Multiple Exposures to SARS-CoV-2 Spike induces a Cross-Reactive Antibody-Dependent Cellular Cytotoxicity response against SARS-CoV-1

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Introduction: Multiple coronaviruses are known to infect humans. These include coronaviruses which are known to usually cause mild symptoms (HCoV-OC43, HCoV-NL63, HCoV-229E and HCoV-HKU1) and others that can potentially cause severe symptoms including death (SARS-CoV-1, MERS-CoV and SARS-CoV-2). In decreasing order of Spike sequence identities with the original strain of SARS-CoV-2, there is SARS-CoV-1 (76%), HCoV-OC43 (38%), MERS-CoV (35%), HCoV-HKU1 (35%), HCoV-229E (31%) and HCoV-NL63 (31%). Following infection by and/or vaccination against SARS-CoV-2, antibodies present in the plasma of individuals exposed to the SARS-CoV-2 Spike were shown to be able to bind the Spike of SARS-CoV-1. These antibodies were also able to neutralize SARS-CoV-1, but to a lesser extent than against SARS-CoV-2. Although antibodies can neutralize, they can also mediate Fc-effector functions such as antibody-dependent cellular cytotoxicity (ADCC).

Methods: In this study, we analyzed Spike recognition, neutralization and ADCC against the D614G strain of SARS-CoV-2, a recent Omicron subvariant of SARS-CoV-2 (JN.1) and SARS-CoV-1. We tested these responses in a cohort of individuals before their first dose of vaccine and four months following the second, third and sixth dose of vaccine. Spike recognition and ADCC activity were measured by flow cytometry and neutralization was measured by a standard pseudoneutralization assay.

Results: Plasma from vaccinated individuals bound the Spike of JN.1 (before the advent of this variant) and SARS-CoV-1. While little neutralization was detected after the second and third vaccine dose, ADCC was readily detected. By the sixth dose, individuals could both neutralize and mediate ADCC against JN.1 and SARS-CoV-1.

Conclusion: Previous reports from our group and others have shown that Fc-effector functions were associated with survival from acute SARS-CoV-2 infection. Therefore, the results presented here suggest that ADCC could help in combating future SARS-CoV-2 variants as well as other closely related coronaviruses.

Funding: Fondation du CHUM, CIHR, CFI, CITF, PHAC, LSPQ, FRQS, FRQS PhD Fellowship, IRSC PhD fellowship,MITACS

RÉSUMÉ 62 - Regulation and function of de novo centriole biogenesis in preimplantation mouse embryos

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Introduction: Centrioles are the core component of centrosomes, major microtubule-organizing centers. Maintaining a correct number of centrioles in a cell is crucial for cellular function and health. Whereas new centrioles are usually generated by replicating pre-existing "mother" centrioles, cells can also generate centrioles '*de novo*' when there are no pre-existing centrioles. However, the mechanisms and functions of *de novo* centriole assembly remain unclear. Early mouse embryos do not possess centrioles but then generate them *de novo* at the blastocyst stage, providing a rare opportunity for studying *de novo* centriole biogenesis in a physiological setting.

Methods: Fluorescence live embryo imaging; Immunofluorescence

Results and Discussion: Here we show that centrioles start to be *de novo* assembled in developing implantation mouse embryos on average 93.9 hours post-hCG, and that this always occurs within pre-assembled hotspots of pericentriolar material (PCM). Using super-resolution Airyscan live imaging, we find that *de novo* centriole formation happens most commonly by the emergence of an entire centriole pair within a single cell cycle and that this pair is unilaterally inherited by just one daughter cell at the subsequent mitosis. However, various other combinations of centriole emergence dynamics were observed, alluding to a stochasticity of *de novo* centriole biogenesis. We show that Polo-like kinase 4 (PLK4) is required for *de novo* centriole formation. Furthermore, *de novo*-formed centrioles become associated with microtubules upon mitosis entry, suggesting their ability to organize microtubules shortly after their biogenesis. Work is ongoing to identify the factors that trigger *de novo* centriole assembly, and investigate the impacts of *de novo*-formed centrioles upon cell division.

Funding Agency FRQS

RÉSUMÉ 63 - Modulating the preoperative gut microbiota with dietary fiber to improve colorectal cancer surgical outcomes

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Introduction: Anastomotic leak (AL) is a postoperative complication that occurs in up to 20% of patients undergoing surgery for colorectal cancer (CRC). It is characterized by the poor healing of the intestinal reconnection and has been associated with increased mortality and cancer recurrence. The gut microbiota plays a key role in anastomotic healing, potentially through the production of beneficial short-chain fatty acids (SCFA). Supplementation with the dietary fiber inulin was shown to increase SCFA as well as microscopic and macroscopic anastomotic healing in a mouse surgical model. However, when considering clinical applications, differences in baseline microbiota composition and patient ability to respond to a dietary fiber must be taken into account.

Methods: In order to predict patient response to a dietary fiber and to allow for pre-stratification of responders end non-responders, wild-type C57BL/6 mice received fecal microbiota transplantation (FMT) from a human donor. Following a 2 week engraftment period, mice received one of four dietary fiber supplements for 2 weeks, after which fecal samples were collected for SCFA analysis.

Results: The microbiota response to each dietary fiber was estimated based on increased fecal SCFA levels at endpoint in comparison to a control diet supplemented with the poorly-fermented fiber cellulose.

Conclusion: Our FMT mouse model is able to detect increased SCFA levels in response to dietary fiber supplementation. Future validation will include measuring post-operative intestinal healing parameters in mice and comparing these results with an ongoing clinical trial.

Impact: By lowering the risk of AL, we aim to improve CRC patient surgical and oncological outcomes, shorten hospital stay and reduce associated healthcare costs.

This project is supported by grants from the Canadian Institutes of Health Research and the Fonds de recherche du Québec (FRQS, grant 347899), as well as a Research training scholarship from the CRCHUM

RÉSUMÉ 64 - Évaluation du rôle de la queue cytoplasmique de l'enveloppe du VIH-1 sur la conformation et la stabilité de l'enveloppe

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Introduction: Les glycoprotéines d'enveloppe (Env) du VIH-1 sont les seuls antigènes viraux exposés à la surface des particules virales et des cellules infectées. Ainsi, une bonne compréhension des différents domaines d'Env et des éléments affectant sa conformation et son antigénicité est importante pour guider le développement de vaccins et d'immunothérapies. Bien que le domaine extracellulaire d'Env ait été étudié de façon exhaustive, le domaine transmembranaire et la queue cytoplasmique d'Env (CT) demeurent sous étudiés, notamment en ce qui concerne leur effet sur la conformation de l'enveloppe. Ainsi, le but de ce projet est d'évaluer le rôle de la queue cytoplasmique dans la conformation et la stabilité d'Env à la surface des cellules infectées, ainsi que les impacts sous-jacents que cela pourrait avoir sur son antigénicité.

Méthodes: Nous avons inséré un panel de délétion de la queue cytoplasmique dans les Envs des souches YU2 et JRFL. Nous avons effectué des marquages de surface pour évaluer la liaison de différentes classes d'anticorps aux mutants CT comparativement aux Env sauvages exprimées à la surface de cellules 293T. Nous avons porté une attention particulière à l'exposition du site de liaison à CD4 (CD4bs). Nous avons aussi examiné comment la CT influence le niveau d'association et de clivage de l'enveloppe par marquage radioactif et immunoprécipitation.

Résultats: Nos résultats préliminaires suggèrent que la queue cytoplasmique influence la conformation d'Env, notamment en modulant l'exposition du CD4bs, et qu'elle permettrait d'augmenter la stabilité d'Env.

Conclusions: Ce travail contribuera à générer de nouvelles connaissances sur le rôle potentiel de la CT du VIH-1 sur la conformation de l'enveloppe et pourrait guider le développement de nouvelles immunothérapies contre le VIH-1.

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RÉSUMÉ 65 - Heart Transplant Outcomes in Patients with Substance Use Disorder History: A Nation-wide Retrospective Cohort Study

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Introduction: Background: Substance use history has been linked to unfavorable outcomes following heart transplantation. However, existing data lacks assessment of major clinical confounders. *Aims:* To compare heart transplant outcomes of patients with and without substance use disorders in terms of mortality, hospitalization, and organ rejection rates within one and between one- and five-years post-transplantation, adjusting for major confounding variables.

Methods: Our retrospective cohort study (n=7874) utilized electronic health records from the EVERSANA databank—a dataset of over 120 million patients in the United States (2015-present). We employed high-dimensional propensity score matching to control for confounding factors, including comorbidities and demographic variables (age, sex, race).

Results: Analyses revealed no significant differences in mortality, hospitalization, or organ rejection rates between patients with substance use disorders and those without, when appropriately matched on key variables at both post-transplant timepoints.

Discussion / Conclusion: Considering confounding factors is crucial when evaluating post-transplant outcomes in patients with substance use disorders. Additionally, this study informs current transplant eligibility criteria for this population.

Study funding: Dr. Nicolas Garel laboratory funds

RÉSUMÉ 66 - Effets de l'acide urique sur l'intégrité de la barrière hématoencéphalique dans le contexte de la cirrhose de foie

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Introduction: La barrière hématoencéphalique (BHE) est essentielle à la protection du cerveau. Dans le contexte de la cirrhose, très peu d'études se sont intéressées à l'intégrité de la BHE, et ce, malgré la présence de troubles cognitifs, l'encéphalopathie hépatique (EH). La molécule centrale dans l'EH est l'ammoniaque. Notre laboratoire a également démontré une implication de l'acide urique (AU). Ce projet vise à investiguer l'effet conjoint de l'AU et de l'ammoniaque sur l'intégrité de la BHE dans le contexte d'une cirrhose.

Matériel et méthode: Deux modèles sont utilisés pour ce projet. Le premier est un modèle de cirrhose induite par ligature de la voie biliaire (BDL), chez lequel une diète contenant 3% d'AU est administrée. Chez ces animaux, les concentrations d'AU et la co-localisation de la caspase-3 clivée et d'un marqueur de cellules endothéliales (CD31) sont évaluées dans le cortex cérébral. Le second modèle est des cellules microvasculaires de cerveau de rat (RBMEC). Ces cellules sont traitées avec des concentrations croissantes d'AU seul ou en combinaison avec l'ammoniaque. Dans les RBMECs, la viabilité est mesurée à l'aide de deux tests (Bleu d'Alamar et tetrazolium (MT)) et une coloration en immunofluorescence de la caspase-3 clivée est réalisée.

Résultats: Chez les animaux BDL, la diète à teneur élevée en AU augmente significativement les concentrations d'AU cérébrale, suggérant une diminution de l'intégrité de la BHE. Cela est confirmé par une augmentation de la coloration de la caspase-3 clivée dans les cellules endothéliales corticales de ces animaux. Dans les cellules RBMEC, la perte cellulaire est significativement augmentée lorsque les cellules sont exposées conjointement à l'ammoniaque et à l'AU.

Conclusion : L'ammoniaque et l'acide urique ont un effet synergique sur la perte d'intégrité de la BHE en contribuant principalement à la mort des cellules endothéliales.

Organismes subventionnaires: Université de Montréal, Ferring Pharmaceuticals

RÉSUMÉ 67 - Impact du trouble d'usage du cannabis, de l'alcool et des psychostimulants sur les comportements violents au cours des cinq premières années de suivi dans une clinique pour premiers épisodes psychotiques

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Introduction: Peu d'études ont investigué le lien entre comportements violents (CV) et troubles liés à l'usage de substances (TLU) en premier épisode psychotique (PEP). Elles ne démontrent pas de lien entre alcool et CV, et sont contradictoires pour les TLU cannabis et stimulants.

Objectifs: Décrire, durant les cinq premières années de suivi en PEP, la prévalence, les profils d'évolution et les facteurs associés aux CV (notamment l'impact des TLU).

Méthode: ESPEUM est une étude descriptive longitudinale de 5 ans des 567 patients de 18 à 30 ans admis, entre 2005 et 2013, à deux programmes d'intervention précoce pour la psychose à Montréal. Annuellement, des données sont collectées sur les CV verbaux, envers les objets et envers autrui, et d'autres facteurs potentiellement associés (selon la littérature). Des analyses descriptives déterminent la prévalence des CV annuellement et les profils d'évolution des CV sur 5 ans. Des analyses univariées déterminent les caractéristiques sociodémographiques et cliniques associées aux CV. La régression linéaire multivariée détermine le lien entre CV et TLU en contrôlant d'autres facteurs associés en univarié.

Résultats: 62% des PEP auront au moins un CV de tout temps. 45% des CV débutent avant l'admission et continuent pendant le suivi.

En univarié, les TLU alcool (OR=1.64), cannabis (OR=2.05), amphétamines (OR=3.06) et cocaïne (OR=2.24) sont associés aux CV de tous types.

En multivarié, aucun TLU ne prédit les CV de tous types dans la prochaine année. Les facteurs les prédisant sont : CV avant l'admission (OR=1.88), CV après l'admission (OR=1.85), maladie sévère (OR=1.20), mauvaise observance médicamenteuse (OR=1.67), personnalités du cluster B (OR=1.78), jeune âge (OR=1.05).

Discussion / Conclusion: Une proportion importante des patients en PEP ont des CV. Plusieurs facteurs prédisent (mieux que les TLU) ces CV. Des interventions les ciblant pourraient diminuer les CV.

Organisme subventionnaire: Université de Montréal

RÉSUMÉ 68 - Role of innate immune sensing in the selection of genetically intact HIV proviruses during antiretroviral therapy.

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[1]UdeM

Introduction: HIV persists in CD4+ T cells during antiretroviral therapy (ART) and these viral reservoirs are the main obstacle to a cure. We recently observed that in people on ART, the majority (61,4%) of the integrated HIV genomes that can be induced to produce the viral protein p24 (p24+) present genetic defects in the highly structured Ψ RNA packaging signal. Since viral RNA secondary structures can be sensed by innate immune sensors such as RIG-I and MDA5 and lead to cell death, we hypothesized that innate immune pressures can select for defective proviruses during ART.

Methods: We measured the expression levels of RIG-I and MDA5 in CD4+ T cells by Western Blot. CD4+ T cells from 3 people with HIV on ART were stimulated with PMA/ionomycin for 24h to induce HIV production in the presence or absence of the pan-caspase inhibitor QVD. The integrity of the PSI element in the remaining cells was assessed by sequencing HIV genomes in sorted p24+ cells.

Results: RIG-I and MDA5 were expressed in CD4+ T cells in the absence of stimulation and their levels of expression increased upon TCR engagement or after stimulation with IFN-a. The analysis of 44 sequences retrieved from single sorted p24+ cells did not show a significant enrichment in PSI-intact genomes when cells were treated with QVD.

Discussion / Conclusion: RIG-I and MDA5 are constitutively expressed in CD4+ T cells and their expression increase upon stimulation, suggesting that they could sense highly structured HIV RNA transcribed from intact proviruses. However, our preliminary results do not support the role of the structured PSI region of viral transcripts in the induction of cell death. To further test our hypothesis, similar experiments will be performed on longitudinal samples from people on ART.

Funding: CIHR, NIH

RÉSUMÉ 70 - Harnessing cell fate decisions in response to PARPi in HGSOC cells: a One - Two-Three punch strategy

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Introduction: High-grade serous ovarian cancer (HGSOC) is the most common and lethal type of ovarian cancer. Despite therapeutic advances, most patients relapse, indicating the need for new treatments. PARP inhibitors (PARPi) have shown promise, particularly for patients with specific genetic mutations, but resistance remains a challenge. We have previously shown that NAMPT inhibitors (NAMPTi) can sensitize PARPi-resistant cells. In parallel, we have demonstrated that PARPi induces a reversible senescence state, which can be targeted with senolytics, creating a one-two punch strategy that is presently being tested in a phase I clinical trial (NTC05358639). Here we hypothesize that the new NAMPT-PARPi combination will trigger cell fate decisions, and in particular senescence, in NAMPT-PARPi treated HGSOC cells that can be further synergized by senolytics.

Methods: We will investigate pathway alterations in transcriptome data from our cell line panel. We are also using the isogenic HGSOC cell lines to investigate the cellular outcomes when treated with NAMPTi-PARPi using live imaging and biomarker analysis to evaluate cell fate decisions that contribute to response.

Results: Based on our transcriptome analysis to date we have identified key pathways disrupted following treatment linked to different cell fate decisions, including senescence. We have shown that NAMPTi increases the sensitivity of PARPi in HGSOC-resistant cells both in vivo and in vitro and leads to significant DNA damage.

Conclusion: Our transcriptomic analysis indicates the disruption of senescence-associated pathways in response to PARPi, and we are currently investigating the use of senolytics and their potential contribution to enhancing the NAMPT-PARPi combination therapy. This "one-two-three-punch" approach additionally targets the metabolic adaptations utilized by cancer cells to evade therapy, providing an innovative way to overcome PARPi resistance in ovarian cancer.

RÉSUMÉ 71 - Single-cell RNA sequencing identifies effector Th17 and cytotoxic virus-specific CD4 T cells in spontaneous resolvers of HCV reinfection

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Introduction: Polyfunctional hepatitis C virus (HCV)- specific CD4+ T cells are essential in helping CD8 T cells leading to spontaneous viral clearance, but the underlying mechanisms are unknown. This study aims to identify gene expression signatures of expanded HCV-specific CD4 T cells during HCV reinfection with different outcomes using single-cell RNA sequencing (scRNA-seq).

Methods: PBMCs from early acute reinfection (< 3 months) of subjects who spontaneously resolved primary HCV infection and either cleared (SR/SR, n=4) or became chronic during subsequent reinfection (SR/CI, n=2) were stimulated by HCV peptides. HCV-specific CD4 T cells, identified by upregulation of the activation-induced markers (AIM) CD69, CD40L, OX40 and 4-1BB, were FACS-sorted and processed for scRNA-seq using 10X Genomics platform. We used gene set enrichment analysis (GSEA) (FDR < 0.1) to identify the top 10 significant pathways modulated in each cluster and within patient groups.

Results: Frequencies of AIM^+ CD4 T cells were significantly higher (P = 0.026) in SR/SR than SR/CI. scRNA-seq identified 12 distinct clusters including Tfh, Th17, Th2, Treg, naïve and cytotoxic CD4 cells. Proportional analysis showed that Th17 clusters were highly enriched in SR/SR compared to SR/CI (P<0.0001). GSEA revealed upregulation of pathways associated with antiviral IFN signature, viral sensing and immunity and type I interferon response pathways in SR/SR. Although other clusters were not significantly different among the two groups, total AIM^+ CD4 T cells from SR/SR showed upregulation of the effector molecules (*GZMA*, *IFNG*, and *TNF* (P<0.0001)) while SR/CI upregulated the exhaustion marker genes *TIGIT*, *HAVCR2* (Tim3), *PDCD1*(PD1), *CTLA4* and *TOX* (P<0.0001). More specifically, Cytotoxic CD4 T cells were enriched in *PFR1, GZMA, IFNG, and TNF* only in SR/SR.

Conclusion: Early expansion of Th17 and cytotoxic HCV-specific CD4 T cells exhibiting antiviral effector functions may contribute to protection from chronicity upon HCV reinfection.

RÉSUMÉ 72 - Activité physique et santé mentale positive chez les jeunes adultes : les stratégies d'adaptation jouent-elles un rôle médiateur dans cette association ?

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Contexte: La santé mentale est un enjeu majeur de santé publique, surtout chez les jeunes adultes. L'activité physique (AP) est associée à une réduction du stress et des symptômes anxieux et dépressifs ainsi qu'une amélioration de la santé mentale positive (SMP). Parmi les mécanismes psychologiques susceptibles d'expliquer ces bienfaits, les stratégies d'adaptation revêtent une importance particulière. D'une part, la pratique d'AP serait liée à une utilisation plus grande des stratégies d'adaptation centrées sur la résolution de problème et une utilisation moindre de celles centrées sur les émotions et l'évitement. D'autre part, les stratégies d'adaptation centrées sur la résolution de problème et celles centrée sur les émotions réduisent les symptômes anxieux et dépressifs, tandis que celles centrées sur l'évitement les aggravent. Ce projet vise à 1) Étudier l'association entre l'AP et la SMP chez les jeunes adultes et 2) Éxplorer le potentiel rôle médiateur des stratégies d'adaptation dans cette association.

Méthodes: Les données utilisées proviennent de l'étude longitudinale NICO (Dépendance à la nicotine chez les adolescents). L'échantillon initial inclut 1294 adolescents recrutés à l'âge de 12-13 ans en 1999-2000 dans 10 écoles de Montréal. L'AP a été mesurée au cycle 24 (âge~34 ans), les stratégies d'adaptation au cycle 25 (âge~36 ans) et la SMP au cycle 25B (âge~37 ans). Nous effectuerons des régressions linéaires (objectif 1) et des analyses de médiation basées sur les définitions contrefactuelles des effets naturels direct et indirect (objectif 2).

Résultats attendus : Nous nous attendons à observer une association positive entre l'AP et la SMP avec seulement les stratégies d'adaptation centrées sur la résolution de problème comme médiateur de cette association.

Contribution : Les résultats aideront à mieux comprendre comment l'activité physique influence l'utilisation de stratégies d'adaptation, et guideront également l'élaboration d'interventions ciblées en activité physique pour promouvoir la santé mentale des jeunes adultes.

RÉSUMÉ 74 - Sonde de spectroscopie Raman pour la détection intra-opératoire d'adénomes hypophysaires

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Introduction: Pituitary adenomas are intracranial tumors and are often treated with tumor resection surgery via the nasal cavities. Tumor margin assessment and precise localization are crucial steps of the surgery as gross total resection and tumor residual volume are the most important factors for local tumor control and recurrence. With the help of preoperative Magnetic Resonance Imaging (MRI), neurosurgeons currently identify and delimit pituitary adenomas visually, which is complicated by their heterogeneity in size, structure, and growth patterns.

The objective is to develop a real-time single-point Raman spectroscopy probe to differentiate adenomas from normal pituitary tissue with machine learning, during transsphenoidal resection surgery. The handheld probe would provide an additional tool to assess whether specific tissues need resection.

Methods: The design of a probe capable of accessing pituitary tissue through nasal cavities during surgery. Collecting Raman spectra of normal and adenoma tissues*, in-vivo* and *ex-vivo,* before and after their resection, with subsequent identification by a pathologist. Training a machine learning model with the identified Raman spectra to classify tissues as adenoma or normal.

Preliminary results: The capability of distinguishing spectra of different tissues encountered in transsphenoidal surgeries, collected in sheep heads with the designed probe. The capability of distinguishing glioblastomas and normal brain tissue, during intra-cranial surgeries, with a similar Raman probe. Analysis of the performance of the different classification models.

Conclusions: Results of the models with spectra obtained in sheep heads with the designed probe along with findings from similar probes used in other resection surgeries, suggest a high likelihood of achieving the objective.

RÉSUMÉ 75 - Stratégie du Programme pour la vaccination à l'horizon 2030 pour atteindre les enfants zéro-dose dans les pays à revenu faible et intermédiaire : une revue de la portée évolutive

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Introduction: 14,3 millions d'enfants n'ont aucune vaccination de routine («enfants zéro-dose (ZD)»). Le Programme pour la vaccination à l'horizon 2030 vise à réduire de 50% le nombre d'enfants ZD d'ici 2030. Cette revue de la portée évolutive est la première synthèse compréhensive de la littérature scientifique sur les enfants ZD dans les pays à revenu faible et intermédiaire depuis le lancement du Programme.

Méthodes: Nos stratégies de recherche, élaborées par une bibliothécaire de recherche, ont été appliquées aux bases MEDLINE (Ovid), CINAHL Complete (EBSCOhost), EBM Reviews (Ovid), EMBASE (Ovid), LILACS et Google Scholar pour des articles scientifiques publiés entre janvier 2020 et janvier 2024 avec des données quantitatives sur les enfants ZD. La sélection des articles a été réalisée en deux étapes par deux examinateurs indépendants via Covidence©, et les données ont été extraites à l'aide d'un formulaire pré-testé.

Résultats: Sur 5226 citations, 82 articles ont été inclus (79 articles de recherche primaire, 3 revues). Parmi eux, 72 études ont abordé la prévalence et la distribution, et 57 ont rapporté des données sur les obstacles à la vaccination, ainsi que sur les multiples privations auxquelles les enfants ZD, leurs familles et leurs communautés font face. Ces privations concernaient principalement : i) l'accès aux services de vaccination et à d'autres services de santé (comme la faible utilisation des services de santé maternelle); et ii) des indicateurs de développement (tel le faible niveau d'éducation des mères et le manque d'accès à l'eau et assainissement. Aucune étude n'a documenté d'interventions spécifiques pour les enfants zéro-dose.

Discussion / Conclusion: Nos résultats soulignent le besoin urgent de données probantes sur les interventions ciblant les enfants ZD, leurs familles et leurs communautaires, notamment celles qui renforcent les systèmes de vaccination tout en abordant les privations multiples.

Financement: Instituts de recherche en santé du Canada (IRSC) (MOP-130280)

RÉSUMÉ 77 - Confrontation des intelligences artificielles: comparaison entre Copilot, GPT-4o et Gemini dans le domaine des questions ophtalmologiques

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Introduction: L'intelligence artificielle (IA) a démontré son potentiel clinique auprès des ophtalmologistes, soulignant l'importance de valider leur précision. Notre objectif est d'étudier et de comparer les performances de GPT-4o, Copilot et Gemini qui n'ont pas encore fait l'objet d'une évaluation rigoureuse.

Méthodologie: Les modèles d'IA ont été évalués à l'aide de 300 questions ophtalmologiques, sélectionnées aléatoirement parmi 1 206 questions disponibles sur StatPearls. Les questions ont été classées en 10 sous-spécialités de l'AAO et une catégorie « Images » pour l'analyse de données visuelles. L'exactitude a été choisie comme principal critère d'évaluation. Les résultats ont été analysés à l'aide des tests du chi-carré et de Fisher, avec une correction de Bonferroni pour les comparaisons multiples.

Résultats et Discussion: Les modèles Copilot, GPT-4o mini, GPT-4o, Gemini et Gemini Advanced ont répondu correctement à 158/300 (52,67 %), 186/300 (62,00 %), 217/300 (72,33 %), 163/300 (54,33 %) et 186/300 (62,00 %) questions, respectivement ($p < 0,0001$). Aucune différence significative n'a été observée entre les sous-spécialités, sauf pour la rétine où GPT-4o a été le plus performant. Gemini et Gemini Advanced ont obtenu les résultats les plus faibles pour les questions d'images (2/21 et 5/21), tandis que les autres modèles ont répondu correctement à plus de la moitié de ces questions ($p = 0,0017$).

Conclusion: GPT-4o a été le plus performant, avec un taux de réponses correctes de 72,33 %. Cette étude souligne les limites des capacités ophtalmologiques des modèles d'IA disponibles, mettant en évidence la place à l'amélioration pour atteindre une précision optimale.

Subvention: Projet non financé

RÉSUMÉ 78 - BANC D'ESSAI VASCULAIRE POUR L'ÉVALUATION D'AGENTS EMBOLISANTS: AMÉLIORATION DE LA PRÉCISION ET DE LA COMPLIANCE

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Introduction: Les procédures d'embolisation sont largement utilisées pour interrompre les flux sanguins indésirables associés aux malformations vasculaires, tumeurs hypervasculaires, saignements et anévrismes. Pour garantir l'efficacité et la sécurité des agents embolisants et réduire l'expérimentation animale, des tests in vitro fiables sont essentiels, mais reproduire l'anatomie et la physiologie vasculaire humaines pose un défi majeur. Nous avons développé un banc d'essai et plusieurs fantômes en polydiméthylsiloxane (PDMS) imitant les vaisseaux sanguins afin d'évaluer les propriétés occlusives d'agents embolisants à base de chitosane. L'impact de l'ajout d'huile de silicone sur les propriétés mécaniques du PDMS a été étudié afin d'améliorer la compliance.

Expérimentation: Le banc d'essai comprend un fantôme vasculaire connecté à une pompe circulant une solution simulant la viscosité du sang maintenu à température physiologique. Ce système permet l'évaluation d'embolisation avec un contrôle précis de la pression et du débit. La migration des gels est observée et quantifiée après l'embolisation. Pour ajuster la compliance des fantômes vasculaires en PDMS, des échantillons contenant 0%, 15%, 30% et 40% v/v d'huile de silicone ont été fabriqués. Des tests rhéologiques et de traction ont permis d'identifier la concentration optimale pour imiter les propriétés des vaisseaux sanguins.

Résultats et discussions: Un fantôme artériel imitant l'anatomie rénale a été développé avec du PDMS et des moules imprimés en 3D. Les tests ont démontré qu'une concentration de 40% d'huile de silicone diminue le module de Young d'un facteur 4 ($p<0.05$), rapprochant la compliance des fantômes à celle des artères humaines. Les tests rhéologiques ont confirmé une réduction du module de stockage (G') et une modification de la densité de réticulation.

Conclusion: L'intégration de l'huile de silicone dans le PDMS améliore sa compliance, rendant ses fantômes plus représentatifs des vaisseaux humains. Afin d'obtenir une meilleure compliance, l'amincissement des parois du fantôme sera étudié.

Financement: CRSNG, Cook Medical

RÉSUMÉ 79 - Extracellular Adenosine-5'-Triphosphate Release Kinetics Following Microbubble Cavitation in Cultured Human Endothelial Cells

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Ultrasound Targeted Microbubble Cavitation (UTMC) causes vasodilation, which can improve radiotherapy efficacy, but the mechanisms remain unknown. Herein, we characterize extracellular Adenosine Triphosphate (eATP) release kinetics *in vitro* following UTMC using live microscopy.

eATP was measured in real-time with a bioluminescent Luciferin-Luciferase (LL) assay. Human endothelial cells were grown in microfluidic chips. A microbubble solution (Definity: 10^7 MB/mL) containing Propidium Iodide (25 ug/mL) and LL was added in the chips before sending a single ultrasound pulse (A303S-SU, 1MHz, 0.5 Inch, Olympus, pressure: 300kPa; 10, 100, or 1000 cycles). The bioluminescence signal of eATP reaction with the LL was captured with an EMCCD camera and converted into eATP released quantity, as in Tan et al., 2019. After the acquisition, a viability assay was done using calcein-AM (4 ug/mL).

We found a significantly higher total eATP released by dead cells compared to live sonoporated cells. The eATP release rate was also significantly higher in dead cells than in sonoporated cells at 4s after the pulse. At that time-point, we could estimate the eATP released by individual cells within a cell cluster before the individual bioluminescent signals merged due to diffusion. The resultas shown that a low cell density increase the release of eATP and the cell survival after sonoporation. This will able us to better understand the eATP release mechanism *in vitro* and *in vivo*.

Subvention: CRSNG, Université de Montréal, Réseau de Bio-Imagerie du Québec

RÉSUMÉ 80 - Rôle de la voie FXR - FGF19 dans le développement de la sarcopénie chez les patients cirrhotiques

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Introduction: La cirrhose hépatique est souvent associée à des complications telles que la malnutrition, la dysbiose intestinale et la sarcopénie. L'implication récente du facteur de croissance fibroblastique 19 (FGF19) dans la régulation de la masse musculaire suggère un rôle potentiel dans le développement de la sarcopénie observée chez les patients cirrhotiques. En particulier, la voie du récepteur farnésoïde X (FXR) et du FGF19 pourrait être perturbée, affectant l'intégrité musculaire. Cette étude a évalué les altérations de la voie FXR-FGF19 dans un modèle de cirrhose induite par ligature des canaux biliaires (BDL) chez le rat. L'objectif était de mesurer l'expression des gènes FXR, FGF19 ainsi que des contrôles, dont le transporteur intestinal de l'acide biliaire sodium-dépendant (ASBT) et la protéine de liaison des acides biliaires intestinaux (I-BABP) dans l'iléon, le foie et le jéjunum pour identifier les perturbations de cette voie.

Méthode: Les rats ont été répartis en trois groupes, SHAM (témoin), BDL 3 semaines et BDL5 semaines. L'expression des gènes a été mesurée par réaction de polymérisation en chaîne(PCR) quantitative.

Résultats: Les résultats ont montré une différence significative dans l'expression de FXR entre les groupes SHAM et BDL 5semaines, tandis qu'une diminution de l'expression de FGF19 a été détectée dès la 3ème semaine après la chirurgie BDL par rapport au groupe SHAM.

Conclusion: Ces résultats montrent que les altérations de FXR se manifestent plus tard, tandis que celles de FGF19 apparaissent plus tôt, soulignant le lien entre ces perturbations et le développement des complications musculaires associées à la cirrhose.

RÉSUMÉ 81 - Rôle modérateur de la perturbation du sommeil dans la relation entre le stress et la douleur chez les personnes vivant avec de la douleur lombaire chronique

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La relation entre le stress et la douleur est complexe; l'effet du stress varie de l'hypoalgésie à l'hyperalgésie. Parallèlement, la perturbation du sommeil est prévalente dans une population de douleur lombaire et elle est associée à l'intensité de la douleur. Celle-ci pourrait permettre de mieux comprendre la relation stress-douleur. Cette étude examine l'effet modérateur de la perturbation du sommeil sur la relation entre le stress et la douleur chez les adultes vivant avec une douleur lombaire chronique.

Les participants (n=181) ont complété un questionnaire initial, puis des journaux électroniques trois fois par jour pendant sept jours. Le questionnaire initial incluait le questionnaire NIH Douleur au bas du dos mesurant la perturbation du sommeil. Les journaux incluaient des échelles de notation numérique mesurant l'intensité du stress et de la douleur. Des modèles multiniveaux ont été utilisés pour étudier les associations entre le stress et la douleur avec la perturbation du sommeil comme modérateur.

Les participants (58,3 % de femmes) avaient un âge moyen de 48,3 ans (ÉT= 12,1). La perturbation du sommeil (aucune/faible vs. Modérée/sévère : β= -0,551), la fluctuation intra-individuelle de l'intensité du stress (β= 0,239) et la moyenne de l'intensité du stress des 21 journaux (β= 0,421) étaient significativement associées à l'intensité de la douleur ($p < 0,001$). L'association entre le stress et la douleur est plus forte chez ceux rapportant aucune/faible perturbation du sommeil comparativement à ceux rapportant une perturbation modérée/sévère (β= 0,099, $p < 0,05$).

Cette étude montre que la perturbation du sommeil modère la relation entre le stress et la douleur, cette relation étant plus forte lorsque le sommeil est moins perturbé. Le stress est une cible d'intervention pertinente pour les personnes vivant avec de la douleur lombaire chronique, et le sommeil pourrait être un facteur psychosocial intéressant à intégrer dans cette intervention.

RÉSUMÉ 83 - Exploring the therapeutic benefit of novel inhibitors of the small GTPase Ran in human ovarian cancer patient samples

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Introduction: Ovarian cancer (OC) is the deadliest gynecological disease in North America, with a 5-year survival rate of 45%. High grade serous ovarian cancer (HGSC), the most common histotype of epithelial OC, is a disease of high inter- and intra-tumour heterogeneity with few recurring mutations other than TP53. Despite this heterogeneity, all tumor cells display high levels of aneuploidy, making this an attractive feature for new therapeutics. We have shown that downregulation of the small GTPase Ran decreases cell proliferation and promotes apoptosis of aneuploid cells, with little effect on normal diploid cells. We have developed a series of novel small-molecule inhibitors of Ran and have identified a series of inhibitors that disrupt aneuploid HGSOC cell line proliferation without affecting normal diploid cells. Going forward towards more pre-clinical assays, this study aims to test various Ran GTPase inhibitors on *ex vivo* live human OC samples using microfluidic models.

Methods: Micro-dissected tumors (MDTs) of OC patient samples were loaded into microfluidic devices and treated with selected Ran GTPase inhibitors at various concentrations and different time-points. The MDTs were then formalin-fixed, paraffin embedded and analyzed via immunofluorescence for markers of proliferation (KI67) and apoptosis (cleaved-caspase 3 (CC3)).

Results: We compared the tumour epithelium of OC MDTs treated with Ran inhibitors to that of controls. Preliminary results from patient samples demonstrate a concentration-dependent decrease in the area of KI67+ cells after 24 hrs of incubation, followed by an increase in the area of CC3+ cells after 72 hrs of incubation.

Conclusions: OC MDTs provide a rich model to test new small molecules that inhibit Ran. While a larger patient sample cohort needs to be further studied, our data suggest the potential therapeutic efficiency of these inhibitors for tumors displaying high aneuploidy.

RÉSUMÉ 84 - CAN AGE-RELATED OOCYTE ANEUPLOIDY BE PREVENTED BY PHARMACOLOGICAL TREATMENTS?

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Female fertility declines in the mid-thirties due to a decline in oocyte quality, with an increasing proportion of aneuploid oocytes that, when fertilized, become embryos that are mostly incompatible with development. Aging also causes a progressive deterioration of the ovaries, including a characteristic fibrosis, and pharmacological approaches were recently developed capable of preventing these organ-level changes, raising hopes of prolonging female fertility. Importantly, however, whether age-related changes in oocyte biology are 'downstream' of organ-level ovarian aging is unknown. Therefore, to investigate whether oocyte aneuploidy is caused by ovarian fibrosis or whether it is an inherent feature of aged oocytes that have long remained arrested in the ovary, we have constructed detailed time-courses of organ-level fibrosis and oocyte-level aneuploidy development with age. Strikingly, we find a steep increase in oocyte aneuploidy that precedes the age-related onset of ovarian fibrosis. Moreover, preliminary data using metformin treatment to prevent fibrosis suggest that premature sister separation, the major cause of aneuploidy, occurs regardless of the apparent health of the ovary. Using Rotenone to induce ovarian fibrosis precociously, we are investigating its effects on oocyte mitochondrial function and aneuploidy. Our data so far raise the possibility that oocyte aging is not simply a knock-on effect of ovarian aging, but rather that damage that occurs to the chromosome segregation machinery during decades of prophase arrest could prove difficult to prevent or reverse with pharmacological treatments.

Funding Sources: NSERC, IRSC, Fondation J. Louis Lévesque, Canada Foundation for Innovation, CRRF, CRRD

RÉSUMÉ 85 - Dietary methionine restriction limits neuroinflammatory and neurodegenerative processes in preclinical models of multiple sclerosis

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Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) more common in women. Dietary methionine restriction (MR) displays anti-inflammatory properties and improves metabolic health through sexually dimorphic mechanisms. We previously showed that methionine pathway is induced upon T cell activation and MR affects the effector function and proliferation of TH17 lymphocytes, pathogenic in MS and its animal model, experimental autoimmune encephalomyelitis (EAE). Therefore, our objective is to study the manipulation of T cell methionine metabolism as a therapeutic avenue for neuroinflammatory diseases such as MS. We immunized C57BL/6 mice with MOG to induce active EAE and used transgenic TCR1640 mice developing spontaneous EAE and exposed to MR vs. control or methionine supplemented (M+) diet to test the impact of methionine intake on clinical course and immune cell distribution and activation (flow cytometry and RNAseq). We assessed the impact of methionine intake on gut microbiota composition and levels of serum neurofilament light chain (sNfL) were measured to evaluate neuroaxonal injury. In male and female C57BL/6 mice exposed to MR compared to control diet, we observed a significant delay in symptom onset following immunization with MOG. In the sex-biased spontaneous EAE model, MR compared to control or M+ diet reduced by more than half the proportion of females developing neurological deficits and nearly abrogated disease onset in males. Clinical amelioration was paralleled by lower numbers of peripheral and CNS-infiltrating pro-inflammatory immune cells during EAE and induced major shifts in the transcriptional profile of immune cells. Finally, MR was associated with lower levels of sNfLs during EAE and significantly influenced the composition of the gut microbiota compared to control and M+ diets in a sex-biased manner. In conclusion, MR impacts gut bacteria, ameliorates EAE clinical course, limits neuroinflammatory processes and reduces neuroaxonal injury in two distinct MS preclinical models.

RÉSUMÉ 86 - Vascular Injury Derived Apoptotic Exosome-like Vesicles Trigger Tertiary Lymphoid Structure Formation in the Renal Cortex of Lupus Prone Mice

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Background: Microvascular damage is an emerging contributing factor to lupus nephritis (LN) leading to end stage renal disease. We have demonstrated that apoptotic exosomes derived from vascular injury (ApoExo) trigger the production of lupus-associated antibodies and LG3/perlecan autoantibodies (anti-LG3) in wild-type mice. ApoExo injections induce anti-LG3 generation and tertiary lymphoid structure (TLS) formation in a murine vascular allograft model. Anti-LG3 can be found in humans and our previous work demonstrated their implication in microvascular rarefaction and renal fibrosis in different contexts. We hypothesize that ApoExos induce an autoimmune response that accelerates the development of LN. We aim to evaluate the impact of ApoExos by evaluating humoral response, renal infiltration, interstitial damage and dysfunction in lupus prone mice.

Methods: 20 weeks old NZBWF1/J mice were injected with ApoExos or vehicle every second day for 3 weeks. Circulating autoantibodies and ApoExo levels were measured by Microarray, ELISA and hs-FCM. Kidneys were collected for renal histology, immunofluorescence and 3D in vivo micro computed-tomography (MicroCT).

Results: NZBWF1/J mice injected with ApoExos showed higher levels of circulating anti-LG3 compared with the vehicle group. MicroCT data demonstrated a 35% microvascular involution associated with LN development. In addition, ApoExo injected NZBWF1/J mice demonstrated significant renal inflammatory infiltration compared to vehicle injected mice. ApoExos triggered the recruitment to the renal cortical region of mature TLS. Finally, heightened renal damage and decreased renal function were observed in ApoExo infused NZBWF1/J mice compared to the ones infused with vehicle.

Discussion / Conclusion: ApoExo injections increased renal TLS formation, autoantibody production and renal damage in lupus prone mice. This project is the first to evaluate the contribution of vascular injury derived extracellular vesicles in LN development.

Funding: CIHR, CRSNG, KFoC and CHUM Fundation

RÉSUMÉ 87 - L'utilisation des inhibiteurs de PARP en combinaison séquentielle dans le cancer du sein triple négatif

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Introduction: Le cancer du sein triple négatif (CSTN) se caractérisant par une absence de surexpression des récepteurs aux œstrogènes/progestérones et HER2, avec un fort risque de développement de métastases. Les inhibiteurs de PARP (PARPi), ciblant les enzymes PARP, sont impliqués dans la réparation des dommages à l'ADN. Les PARPi sont devenus un traitement oral important pour les patients atteints de CSTN avec des mutations germinales de BRCA1/2. Cependant l'émergence de résistance en réponse aux PARPi représente un défi majeur. Pour surmonter cette résistance, une combinaison avec des agents comme la carboplatine est envisagée. Les travaux de notre équipe ont démontré qu'une administration séquentielle des PARPi suivie de carboplatine est la stratégie la plus efficace pour inhiber les métastases *in-vivo* et régule négativement les gènes de la réponse aux dommages à l'ADN. Notre hypothèse est que la combinaison séquentielle des PARPi suivie des agents de dommages à l'ADN induit une réponse aux dommages de l'ADN soutenue participant ainsi à son efficacité anti-métastatique.

Méthodes et résultats: Des expériences d'immunoblotting et d'immunofluorescence dans des lignées cellulaires CSTN ont été réalisés afin d'étudier l'expression de marqueurs de la réponse aux dommages à l'ADN (g-H2AX, 53BP1) ainsi que des protéines impliquées dans la réponse de dommages à l'ADN (p-ATM,p-BRCA1,p-CHK1..) avec la combinaison de PARPi en concurrence ou séquentielle avec les agents endommageant l'ADN.

Conclusion et pertinence: Nous visons à identifier les bases moléculaires de l'efficacité de la combinaison séquentielle des PARPi et des agents de dommages à l'ADN. Nos travaux permettront d'améliorer l'approche thérapeutique visant à inhiber les métastases à distance chez les patients atteints de CSTN.

RÉSUMÉ 88 - Investigating lifestyle behaviors and modifiable risk factors associated with cardiovascular outcomes among cancer survivors: A scoping review protocol and initial findings

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Background: Cancer survivors are at a higher risk of developing cardiovascular diseases and face worse morbidity and mortality outcomes compared to the general population. The American Heart Association (AHA) has defined the Life's Essential 8 framework, which encompasses eight modifiable risk factors and lifestyle behaviors (i.e., diet, physical activity, nicotine exposure, sleep health, body mass index, blood lipids, blood glucose, and blood pressure) for maintaining ideal cardiovascular health (CVH). Although these metrics are well-established for estimating CVH in the general population, studies on their association with cardiovascular outcomes among cancer survivors remain scarce. This highlights the need for a thorough examination of these associations in this vulnerable population.

Objective: This scoping review summarizes evidence on modifiable risk factors and lifestyle behaviors and their associations with cardiovascular outcomes among cancer survivors.

Methods: The frameworks proposed by Arksey and O'Malley and the methodology for conducting scoping reviews published by the Joanna Briggs Institute were used. A structured literature search was conducted through databases including Ovid Medline, Ovid Embase, Ebsco CINAHL, and the Cochrane Library.

Preliminary results: Of 2163 records identified, 18 articles met eligibility criteria (15 empirical studies, one study protocol, and two correspondences). A majority of the articles (N=17) were published after 2021. Thirteen empirical studies followed the AHA's framework to conceptualize CVH. However, measurements for lifestyle behavior factors varied across studies. Findings show that ideal CVH is associated with cardiovascular outcomes among cancer survivors. Associations with social inequalities, psychological distress, neighborhood characteristics are also evidenced.

Implications: This is the first scoping review to summarize the evidence surrounding ideal CVH associated with cardiovascular outcomes among cancer survivors. The preliminary results demonstrated a breadth of emerging studies on ideal CVH in cancer survivorship research.

Funding: Fonds de recherche du Québec - Santé (FRQS): Bourse de formation postdoctorale

RÉSUMÉ 90 - Développement d'un modèle d'insuffisance hépatique aigue-sur-chronique: injection lipopolysaccharides chez des rats ayant subi une ligature des voies biliaires

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L'insuffisance hépatique aigue-sur-chronique (ACLF) est un syndrome qui se caractérise par une décompensation aigue d'une maladie chronique du foie et provoque la défaillance de plusieurs organes et une mortalité élevée à court terme. Un des critères pour diagnostiquer l'ACLF est l'encéphalopathie hépatique (EH), une complication neurologique dont la forme la plus sévère est le coma. L'inflammation systémique joue un rôle important dans le développement de la pathologie. Il existe plusieurs modèles de ce syndrome, dont le modèle de la ligature des voies biliaire (BDL) (insuffisance hépatique) surimposée par une injection de lipopolysaccharide (LPS) (insulte aigue), un agent provoquant une inflammation systémique. Il n'existe pas de consensus sur la dose et le type de LPS à injecter et le moment d'injection après la chirurgie BDL. Le but de ce projet est de déterminer la dose de LPS à injecter chez des rats BDL permettant d'observer un symptôme neurologique (réflexe de redressement). La ligature des voies biliaires fut effectuée chez 16 rats males Sprague-Dawley. Après 28 jours, une dose (150, 75, 37.5, 20 ou 5µg/kg) de LPS Klebsiella pneumoniae fut injectée. Les signes neurologiques furent gradés objectivement et évalués à chaque 5min pour la première heure et ensuite à chaque 30min. Le temps pour atteindre chaque grade et le temps passé dans chaque grade est indépendant de la dose. La perte du réflexe de redressement (grade 4) s'avère létale et non réversible, alors que l'échec du test de suspension (grade 3) est réversible. Le temps de survie minimal et maximal est de 2.5h (75µg/kg) et de 7h (5µg/kg), respectivement. Le modèle optimal sera une injection de LPS sera de 5µg/kg à 28 jours post-chirurgie BDL, jusqu'à l'observation de l'échec du test de suspension. Une caractérisation biologique complète est en cours. Ce modèle pourra éventuellement servir à tester diverses solutions thérapeutiques.

RÉSUMÉ 91 - Impact of EIF4A1 on stress granule assembly in ALS TDP-43 mouse models

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Stress granules form when cells are subjected to an external stress. This stress response, which is suspected to be deficient in Amyotrophic Lateral Sclerosis (ALS) patients, is essential for cell viability. Our lab has shown in vivo that stress granule (SG) formation is deficient in an ALS mouse model expressing mutated TDP-43 (TDP-43 M337V). We also found that eIF4A1, a protein important for translation, is increased in spinal cord lysates in TDP-43 M337V mice. Given that eIF4A1 could also act as an RNA chaperone and affect LLPS, we hypothesize that high eIF4A1 levels in TDP-43 M337V mice could correlate with defective SG formation. To test this, we will use antisense oligonucleotides (ASOs) to decrease levels of eIF4A1 in attempt to restore SG formation. Furthermore, we are expanding our work to an ALS mouse model which expresses high levels of cytoplasmic TDP-43, the ΔNLS model. We hypothesize that lowering eIF4A1 levels could restore defective SG dynamics in these models. First, the ASOs will be tested in vitro using the N2A cell model. Then, to assess the effect of eIF4A1 ASOs on SG in vivo, we will inject ASOs into TDP-43M337V and ΔNLS mice followed by performing acute hyperthermic stress. SG formation will be assessed by detecting polyadenylated RNA, an obligate component of SG. Our preliminary data using the ΔNLS model demonstrates that TDP-43 is expressed in the cytoplasm following transgene activation and this correlates with a slight loss in their motor function. Ongoing work includes looking at how SG formation is impacted in the ΔNLS mouse model. Our current data demonstrates that ASOs lower eIF4A1 levels in the N2A cell model, and we have confirmed that the ΔNLS model shows TDP-43 mislocalization and a loss in the motor function, as has been previously published.

RÉSUMÉ 92 - Real-world outcomes to systemic therapies for patients with advanced uveal melanoma

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Introduction: Long-term outcomes to metastatic uveal melanoma (UM) are poor, and there is a paucity of randomized trials to guide clinicians. Therefore, real-world evidence (RWE) to compare outcomes between treatments is becoming increasingly important.

Methods: We assessed real-world outcomes of patients with metastatic UM not amenable to liver resection treated with systemic therapy at the CHUM between 2013-2024. Objective response rate (rate of partial and complete response), median progression-free survival (PFS), and median overall survival (OS) were assessed and compared between groups.

Results: Among 37 patients with advanced UM, median age was 68 (24-85) and 20 (54%) were male. 31 (84%) had liver metastases at baseline and 18 (49%) had abnormal LDH. Regarding first-line treatments, 18 patients (50%) were treated with single-agent anti-PD-1, 6 (16%) were treated with anti-PD-1/CTLA-4 with nivolumab and ipilimumab combination, 7 (19%) were HLA*02*01 positive and treated with tebentafusp (following approval 2023), and 2 (5%) were treated with ipilimumab alone. For single-agent anti-PD-1, ORR was 5% compared to 0% for anti-PD-1/CTLA-4 (p=1.0). Median PFS for single-agent vs. combination was 2 months vs. 2.7 months (p=0.77). Median OS for single agent vs. dual agent was 7.9 months vs. 9.9 months (p=0.49). The incidence of ≥grade 3 immune-related toxicities was 11% in the anti-PD-1 group, including one case of nephritis and one case of encephalitis, while the anti-PD-1/CTLA-4 group exhibited a 17% incidence, attributed to a case of colitis (p=1.0). 16 (43%) patients received second-line systemic therapy (e.g., chemotherapy, ipilimumab alone), and post-progression survival was 7.7 months.

Conclusion: These real-world results reinforce that novel therapies are required to improve outcomes for patients with UM. In addition, RWE for tebentafusp will be presented during the conference.

Funding: Montreal Cancer Institute

RÉSUMÉ 93 - Évaluation de la relation entre la fragilité et l'aire du muscle psoas en chirurgie vasculaire : étude prospective

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La fragilité est un syndrome multidimensionnel qui inclut des aspects physiques, cognitifs et sociaux. Cette condition rend les personnes âgées plus susceptibles aux stress externes, tels que les maladies aiguës, les interventions chirurgicales, ou même les changements mineurs dans leur environnement. Les patients fragiles présentent donc un risque accru de complications post-opératoires, de ré-hospitalisations et de mortalité et bien qu'il existe plusieurs façons de mesurer la fragilité des patients, mais aucun test ni questionnaire ne fait consensus dans le domaine médical. En parallèle, la sarcopénie, condition médicale caractérisée par la perte progressive de la masse musculaire, de la force et de la fonction des muscles squelettiques, a été reconnue comme un indicateur de fragilité des patients en raison de ses implications significatives sur la mobilité, l'autonomie et la qualité de vie des personnes âgées. L'une des façons de mesurer la sarcopénie se fait à l'aide du muscle psoas. Notre étude expérimentale et longitudinale vise donc à d'évaluer la fragilité de patients vus en clinique externe de chirurgie vasculaire du CHUM et qui auront une intervention vasculaire. Elle comportera une collecte de données prospective et une période de suivi post-chirurgical sur deux ans. La fragilité sera mesurée à l'aide d'un questionnaire validé et de l'aire du muscle psoas, grâce à l'application CoreSlicer. Le suivi de 24 mois permettra d'évaluer le taux de mortalité, le taux de complications, le taux de réadmission, le taux de réintervention ainsi que l'invalidité et la qualité de vie des patients. La période de recrutement n'ayant pas encore débuté, aucun résultat n'est disponible pour le moment. En démontrant une relation entre l'aire du muscle psoas et la fragilité des patients qui auront une intervention vasculaire, cette étude pourrait améliorer l'évaluation des patients à risque, et alors mieux prédire leur trajectoire de soins.

RÉSUMÉ 94 - Cross-Species analysis Of Wnt pathway Involvement During Preimplantation In the Human and the Mouse

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Introduction: The first week post-fertilization is critical to human development but poorly characterized. Current knowledge of preimplantation is primarily based on mouse models, but their development differs from the human. Here, we compare the role of the Wnt pathway in both the human and the mouse preimplantation embryo. We **hypothesize** that pluripotency is maintained by Wnt activation in the mouse and Wnt inhibition in the human.

Method: Our re-analysis of a human scRNA-seq dataset reveals multiple components of the WNT pathway showing a lineage-dependant expression and that the switch in their expression (on/off) coincides with lineage specification. Human (at 8 cell stage) and mouse embryos (at 4 cell stage) were treated to activate/inhibit (CHIR99021, IWP2, n=2-15/group) the Wnt pathway, followed by 1) immunofluorescence or 2) scRNA-seq.

Results: IWP2 arrested human development around E4-E5 as expected, but not in mouse. CHIR99021 slowed mouse development in a dose-dependant manner, and lineage markers were impacted in both species. This suggests that the WNT pathway is required for lineage segregation in the human and retainment of pluripotency in the mouse. Further, in the mouse, removal of CHIR99021 at the 16-cell stage reversed its impact, allowing development catch-up, but removal at the 32-cell stage did not revert the phenotype, possibly due to lineage commitment.

Discussion: Our results demonstrate species differences in the pathways driving ICM-TE segregation, emphasizing the need for human focused studies. Knowledge from these studies will shed light onto early human embryogenesis and may be translated to the fields of Stem Cell Biology and ART.

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RÉSUMÉ 95 - HIV transcription in multiple tissues collected postmortem in a person with HIV on ART

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Background: The human immunodeficiency virus (HIV) remains a major public health challenge. Antiretroviral therapies have improved the quality of life of people with HIV but do not eradicate the virus, which has the ability to persist in viral reservoirs. Current knowledge on these reservoirs stems mainly from studies performed on peripheral blood samples. However, CD4+ T lymphocytes, the main reservoir for HIV, are preferentially located in lymphoid tissues. We hypothesized that lymphoid tissues are favourable environments for HIV persistence.

Methods: We measured the levels of HIV infection and HIV transcription in multiple tissues isolated from a person with HIV who donated his body through the End-of-Life study. Extractions of cell-associated DNA and RNA were performed jointly on 11 lymphoid tissues and cells from peripheral blood. Using ultra-sensitive qPCRs, the frequency of infected cells and viral transcriptional activity were measured and compared with those in the blood.

Results: HIV DNA and RNA were detected in all tested samples (mean HIV DNA copies/million cells: 23, range: [3;49]; mean HIV RNA copies/infected cell: 0.15, range: [0.01;0.56]). HIV DNA copy numbers were higher in gut associated tissues compared to other compartments (means of 65.5 and 5.6 HIV DNA copies/million cells in intestinal and non-intestinal tissues, respectively). HIV transcriptional activities were higher in 4 of the 11 tissues studied when compared to blood (mean of 0.32 and 0.10 Env RNA copies/infected cell, in tissues and blood, respectively).

Conclusions: Our results suggest that HIV reservoir cells from lymphoid tissues may be more transcriptionally active than their circulating counterparts. Whether these transcriptionally active viral genomes are genetically intact and can cause viral rebound upon ART interruption remains to be determined.

RÉSUMÉ 96 - Proinflammatory IL-32 isoforms potentially contribute to vascular calcification and CVD by promoting osteoblast differentiation

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Introduction: People with HIV (PWH) have a higher risk of developing cardiovascular diseases (CVD) compared to the general population. Our data demonstrated that multi-isoform proinflammatory cytokine IL-32 is upregulated by HIV infection and associated with subclinical CVD in PWH. However, mechanisms by which IL-32 contributes to the pathogenesis of CVD remain unclear. Here, we investigated the impact of IL-32 isoforms on the differentiation of human mesenchymal stem cells (hMSC) and primary human monocytes into cells involved in crosstalk between heart and bone diseases; osteoclasts (for calcium resorption) and osteoblasts (for calcium deposition).

Methods: Human CD14+CD16- monocytes or hMSC (precursors of osteoblasts) were stimulated with IL-32 isoforms (α,β,γ) with/without the osteoclast differentiation factors RANKL and M-CSF, for 21 days. Multiplex confocal imaging was used to identify the differentiated cells. Quantitative ELISA was performed for soluble secreted proteins.

Results: The inflammatory IL-32β and IL-32γ isoforms, but not IL-32α, induced the differentiation of hMSC and primary monocytes into osteocalcin+osteoblast cells. In contrast, IL-32α induced differentiation of monocytes into giant multi-nucleated osteoclasts expressing F-actin-ring and TRAcP5b (typical osteoclast markers). When IL-32β or IL-32γ were combined with the osteoclast-specific inducer RANKL, both IL-32 isoforms counteracted RANKL and induced osteocalcin+osteoblast differentiation from monocytes, confirming their dominant role in osteoblastogenesis. Our mechanistic work demonstrated that this dominant osteoblastogenesis is mediated by the capacity of IL-32β and IL-32γ to inhibit TGF-β production. In support of these observations, exogenous TGF-β supplementation in IL-32β and IL-32γ-stimulated monocytes diminished osteoblast differentiation and rescued the osteoclast phenotype.

Conclusion: Our data reveal a new function for highly active IL-32 isoforms β and γ (dominantly expressed isoforms in PWH) in inducing differentiation of primary monocytes into osteoblasts. Higher expression of these IL-32 isoforms in PWH is likely to contribute to higher levels of vascular calcification by inducing more osteoblast formation. Further studies on atherosclerotic tissues are warranted.

Funding: NIH

RÉSUMÉ 97 - Innovative Ran Inhibitors: Pioneering a Novel Therapeutic Approach for Epithelial Ovarian Cancer

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Introduction: Ovarian cancer, particularly epithelial ovarian cancer (EOC), is the most lethal gynecological malignancy and the fifth leading cause of cancer-related deaths among women in North America. High-grade serous carcinoma (HGSC), the most common histological subtype of EOC, exhibits significant intra-tumoral heterogeneity and widespread aneuploidy. Aneuploid cells rely heavily on the small GTPase Ran for survival, and Ran is overexpressed in HGSC. Ran regulates DNA repair pathways, including homologous recombination and nonhomologous end joining, by suppressing the nuclear receptor NR1D1. Knockdown of Ran significantly inhibits the growth of EOC cells with minimal impact on normal diploid cell proliferation.

Methods and Results: In this study, we developed and characterized small molecule inhibitors targeting Ran, prioritizing the most promising compounds for further testing. These inhibitors selectively inhibit proliferation and induce apoptosis in aneuploid cells while sparing normal diploid cells. We evaluated the effect of these inhibitors on Ran's downstream signaling by using NR1D1 as a biomarker, and found that active compounds modulate the stability of NR1D1 mRNA in EOC cells, as measured by Q-PCR. No changes in NR1D1 mRNA expression were observed with non-active compounds or other anti-proliferative drugs like Olaparib or Carboplatin. Furthermore, cellular thermal shift assays (CETSA) confirmed the direct binding of some inhibitors to Ran. Ongoing mass spectrometry studies aim to elucidate how these compounds affect the interaction between Ran and its partners.

Conclusion and Perspective: Our results thus far support targeting Ran as a promising therapeutic strategy for treating HGSC. Future studies will focus on testing the most promising candidates in pre-clinical models.

RÉSUMÉ 99 - La salle d'attente active: une approche novatrice pour améliorer la santé physique et mentale des jeunes adultes souffrant de psychose émergente.

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Introduction: Malgré les bénéfices de l'activité physique (AP) sur la santé (mentale+physique) des jeunes atteints de psychose débutante, leur motivation à s'y engager demeure un défi. La supervision, le soutien social, et le respect des préférences d'AP, favorisent sa pratique. Une "salle d'attente active (SAA)" dans la clinique d'un programme pour premiers épisodes psychotiques (PPEP) permettrait de saisir le temps d'attente comme une opportunité d'exposition agréable à l'AP supervisée.

Objectifs: Déterminer la faisabilité et les facilitateurs/barrières de l'intégration d'une SAA dans un PPEP. Déterminer l'acceptabilité d'une SAA visant à améliorer la motivation à l'AP. Explorer son impact sur la motivation et la pratique de l'AP.

Méthodologie: Étude ouverte descriptive évaluant un programme clinique novateur à la Clinique JAP (CHUM) de septembre-2023 à aout-2024. Des séances d'exercices animées par des étudiants en sciences santé dans la SAA avec des vélos stationnaires/elliptiques/Stairmaster, jeux-vidéo actifs et programmes d'exercice/étirements élaborés par des kinésiologues sont proposées. Faisabilité : proportion de jeunes approchés qui ont participé à au moins une séance. Acceptabilité (satisfaction), impact sur la motivation : questionnaire-maison post-AP.

Résultats / Conclusion: Lorsque non animée/supervisée pendant 2 mois, une personne a participé à la SAA. Sur 6 mois, 67 demi-journées d'AP ont été animées dans la SAA, durant lesquelles 83 des 205 patients approchés ont fait de l'AP (jeux-vidéo actifs (57.7%), vélo stationnaire (24.4%), elliptique (7.7%), Stairmaster (2.6%), exercices de renforcement (5.1%), étirements (2.6%)) pour en moyenne <5-10min. La majorité a trouvé l'expérience agréable (95.7%), a ressenti une confiance accrue en leur capacité à pratiquer l'AP (moyenne=8.1/10, 10=confiance totale), et a rapporté une influence positive sur leur motivation à continuer l'AP en dehors du PPEP (moyenne=7.87/10, 10=influence maximale).

L'approche pourrait enrichir les interventions visant à augmenter la motivation à l'AP. Toutefois le personnel requis pour l'animer/superviser demeure un obstacle à son implantation.

RÉSUMÉ 100 - The mediating effect of quality on the relationship between attachment to Interprofessional Primary Care teams and health service use

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Interprofessional primary care teams, comprised of family physicians, and other health professionals, are considered an effective strategy to counteract the expected increased use of health services associated with aging. While the literature has studied the separate effect of interprofessional teams on quality of care and health service use, little is known about their interrelations. This study aims to explore the impact of interprofessional teams on health service use mediated by quality of care.

This is a retrospective longitudinal cohort study, using Quebec's administrative health data linked to results from the Canadian Community Health Survey (CCHS). The target population is community-dwelling adults (18+) who participated in the 2015 CCHS (n≈5480). Causal mediation, utilizing VanderWeele's four-way decomposition, and a weighting-based approach were employed. The total effect of interprofessional teams on the outcome health service utilization (emergency department (ED) use, and hospitalizations), that is mediated by quality of care (access, continuity, and coordination) was decomposed into four components,the effect due to: mediation, interaction, both mediation and interaction, and neither mediation nor interaction. The results are reported as excess relative risk (ERR) with 95% confidence intervals (CI).

For the total effect, being in an interprofessional primary care team was not associated with a decrease in nonurgent ED visits for access (ERR=-0.16; 95%CI [-0.29, 0.01]), continuity (ERR=-0.15; 95%CI [-0.30, 0.04]), and coordination (ERR=-0.09; 95%CI [-0.26, 0.13]). Quality of care did not mediate the impact of interprofessional teams. Results for ED visits and hospitalizations were mixed.

No association was found between interprofessional teams and nonurgent ED. For total ED visits, and hospitalizations, our results showed no clear decrease in either outcome. The impact of interprofessional teams was not mediated by quality of care indicators. Further investigation should consider other mediators, or organizational characteristics of interprofessional teams to better understand this impact.

Funding agencies: FRQS, CIHR

RÉSUMÉ 101 - Early life iron supplementation attenuates atopic dermatitis severity in adulthood

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Introduction: During the first years of life, the immune system develops simultaneously with the gut microbiota, and it has been previously shown that perturbations to gut microbiota establishment can lead to altered immune phenotypes later in life. One factor that may influence the gut microbiota in early life, and therefore immune development, is iron supplementation.

Methods: BALB/c mice were given either an iron sufficient or an iron excess diet beginning at weaning until adulthood at 8 weeks of age. All mice were then placed on the iron sufficient diet for two weeks. Mice were then sensitized and subsequently challenged ten times on the ear with oxazolone (OXA) to induce atopic dermatitis.

Results: Mice that received iron supplementation in early life had significantly decreased ear thickness, indicating attenuated dermatitis. Furthermore, a dermatitis severity score was calculated daily based on ear thickness, ear redness, excoriation, and incrustation. Mice that received iron supplementation had significantly decreased dermatitis severity scores. We further measured epidermal thickness using H&E-stained cross-sections of ear tissue and found that mice that received iron supplementation had significantly decreased epidermal thickening. Finally, we measured immune markers of allergy and inflammation, including serum immunoglobulin E (IgE) and ear tissue interleukin (IL)-4. Mice that received iron supplementation had decreased levels of both IgE and IL-4.

Conclusion: Taken together, these data indicate that iron supplementation in early life attenuates atopic dermatitis severity in adulthood. We next plan to evaluate the role of the gut microbiota using antibiotic-treated mice.

FRQS, CIHR, CRCHUM, Université de Montréal

RÉSUMÉ 102 - New Imidazole-derived Resolvin D1 Analogues for Osteoarthritis treatment

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Introduction: Oxidative stress is a key factor in osteoarthritis, causing cartilage breakdown. Current treatments, like HA injections, can be ineffective due to HA degradation. Resolvin D1 (RvD1), a lipid mediator, has the potential to reduce inflammation, combat oxidative stress, and promote tissue repair in osteoarthritis.

Methods: Herein, newly designed, and synthesized Imidazole-derived RvD1 analogues were introduced to compare their potential antioxidant properties with commercially available RvD1. Their antioxidant capacities were investigated by several *in vitro* chemical assays including Oxygen Radical Absorbance Capacity, 2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging, Ferric Ion Reducing Antioxidant Power, Hydroxyl Radical Scavenging, and HA Fragmentation Assay.

Results and Discussion: All results proved that Imidazole-derived RvD1 analogues showed excellent antioxidant performance compared to RvD1 due to their structural modifications. Interestingly, they scavenged the formed ROS and protected HA from degradation, as verified by agarose gel electrophoresis and gel permission chromatography. A computational study using Gaussian 09 with DFT calculations and B3LYP/6-31 G (d, p) basis set was also employed to study the relationship between the antioxidant properties and chemical structures as well as calculation of the molecular structures, frontier orbital energy, molecular electrostatic potential, and bond length. The results showed that the antioxidant activity of our analogues was higher than that of RvD1.

Conclusion: The findings suggest that Imidazole-derived RvD1 analogues can be good candidates as antioxidant molecules for the treatment of oxidative stress-related diseases like OA. Therefore, they can prolong the longevity of HA in the knee and thus may improve the mobility of the articulation.

RÉSUMÉ 103 - Transient increase of AT1R expression at the infarct site and not in the kidneys in a rat model of heart failure

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Introduction: *In vitro* studies revealed altered myocardial Angiotensin (Ang)II type 1 receptors (AT_1Rs) during left ventricular (LV) remodeling in the context of heart failure (HF). The goal of this work was to evaluate cardiac function and concomitant changes in cardiac and renal AT_1R expression in murine models of HF.

Methods: Sprague-Dawley rats were randomized into: A:SHAM; B:Ischemia/Reperfusion 20 min ligation (IR20) of the left anterior descending artery (LAD); C:Permanent ligation of LAD (PL). Echocardiography was performed weekly. Cardiac and renal AT_1R levels were determined by i*n vitro* ^{125}I-[Sar^1, Ile^8]AngII autoradiography at: 1,3days; 1,3,5,7 and 12weeks post-surgery. The fibrotic areas were evaluated by picrosirius red (PSR) staining in LV infarcted and remote areas, and kidney cortex and medulla.

Results: Compared to SHAMs, LV ejection fraction was decreased 1 day after surgeries in IR20 and PL rats. As expected, a more profound decline was observed in PL rats. PSR along with autoradiographic images revealed a colocalization between fibrotic areas and [^{125}I]AngII uptake. Renal cortex and medulla exhibited a 40-fold higher expression of AT_1R than LV in SHAMs. Compared to SHAMs, AT_1Rs were increased in the infarcted area in IR20: at 3 days; 1, 3weeks (881%, 1312%, 539%, respectively; $p<0.0001$); and PL at 3,7 and 12weeks (775%, 690%, 635%, respectively; ($p<0.0001$)). There was a significant difference between the infarcted and the remote LV areas in IR20: $p<0.01$(3days), $p<0.05$(1week); and PL: $p<0.05$(3days), $p<0.0001$(7weeks), $p<01$(12weeks).

Discussion / Conclusion: In contrast to the expected transient increase of cardiac AT_1Rs in HF animal models, renal AT_1R expression was not changed throughout the study. Therefore, PET imaging in AT_1R-rich kidneys cannot be utilized as organ of interest in our ultimate goal to study disease progression and guide therapy. Cardiac AT_1R PET imaging will need to be considered in HF patients.

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RÉSUMÉ 104 - S6K INHIBITORS TO TREAT PANCREATIC CANCER

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Introduction: Cellular senescence is a cell state triggered by stressful insults and certain physiological processes, characterized by a prolonged and generally irreversible cell-cycle arrest with secretory features, macromolecular damage, and altered metabolism.

Activating the program of senescence in tumor cells seems an attractive approach to cancer treatment. This response to chemotherapy is induced by a wide variety of anticancer agents. This is the case of FOLFIRINOX a powerful senescence inducer. However, some cells escape from the senescent program and become more aggressive.

The ribosomal protein S6K (S6 kinase) represents a widely studied effector of the TORC1 complex [TOR (target of rapamycin) 1]. Recent studies developed in the laboratory of Dr. Ferbeyre reveal that the S6K protein could be involved in the escape of tumor cells from the cellular senescence processes induced by FOLFIRINOX.

Methods: The experimental approaches include biomarker identification through transcriptomic (RNA seq) and proteomic assays (Western Blot, mass spectrometry). We will carry out SA-β-gal assays to measure the number of senescent cells against treatment with FOLFIRINOX and in its absence (negative control). To respond to our second objective, we will carry out *in vitro* assays using KP4 control cells (V5) and KP4 escapers cells (E5). These cells will be treated with FOLFIRINOX and with an S6K protein inhibitor LY2584702 (S6Ki).

Results and Conclusions: FOLFIRINOX-induced senescence was characterized, identifying biomarkers (increase in pERK and p21 and decrease in STAT3, ribosome biogenesis factors and pH3). It was demonstrated in *in vitro* assays that the S6K inhibitor prevents the escape of cancer cells from senescence induced by FOLFIRINOX after 7 days.

Funding agencies: CRCHUM, Institut du cancer de Montréal, The Terry Fox Foundation

RÉSUMÉ 105 - Investigating the role of cryptic G3BP1 in ALS neuropathogenesis

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Introduction: The nuclear depletion of TDP-43 is present in most ALS patients, as well as in approximately half of FTD cases. In ALS and FTD, TDP-43 nuclear depletion leads to a dysregulation in mRNA splicing, including the de-repression of “cryptic” exons that are normally excluded from mature transcripts. These cryptic inclusion events can occur in-frame or out-of-frame to yield premature polyadenylation sites or termination codons, resulting in altered protein products and/or abundance, we reveal that the loss of TDP-43 leads to a cryptic exon inclusion event in *G3BP1*. G3BP1 maintains roles in stress granule assembly, viral infection, ribosome quality control, translation, mRNA stability and neuronal survival. We have previously shown that TDP-43 regulates *G3BP1* stability, and *G3BP1* to be decreased in ALS/FTD patient neurons with TDP-43 nuclear depletion.

Methods: We applied splicing analysis (MAGIQ) and validated results using RT-qPCR. We performed multiple biochemical assays including co-immunoprecipitation, immunofluorescence and immunohistochemistry.

Results: Our analysis of public RNA-seq datasets of human cortical and motor- like iNeurons depleted for TDP-43 identified *G3BP1* as a novel splicing target of TDP-43. TDP-43 depletion led to the inclusion of a 30 bp cryptic exon in human *G3BP1*, which encodes 10 amino acids in-frame. We report the presence of this cryptic event in ALS patient datasets, which correlated with nuclear TDP-43 depletion. We show that cryptic exon-bearing *G3BP1* is capable of being translated and demonstrate its impact on G3BP1 protein stability and interactome. Finally, we present the significance of this cryptic inclusion event on G3BP1’s function in stress granule assembly and translation.

Discussion: This work addresses a major gap in our understanding of how cryptically spliced *G3BP1* may contribute to ALS/FTD neuropathogenesis, with implications for therapeutic strategies.

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RÉSUMÉ 106 - The potential cardioproctection effect of the short chain fatty acid caproic acid through reversion of endothelial cell inflammation and dysfunction

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Background: We have recently shown that the proinflammatory cytokine IL-32 is upregulated in people with HIV and is associated with arterial stiffness and cardiovascular disease. We also showed that IL-32 induces coronary artery endothelial cell (CAEC) inflammation and dysfunction. In this study, we aimed to investigate the beneficial effect of the intestinal microbiota-driven short-chain fatty acids (SCFAs), acetate, butyrate, propionate, valerate and caproate to alleviate the IL-32-mediated CAEC dysfunction.

Methods: Primary CAEC were conditioned with 1 mM of SCAFs before being stimulated with either IL-32 (500 ng/ml) or LPS (100pg/ml). Following 48 h, the impact of SCFAs on IL-32-mediated upregulation of the CAEC typical dysfunction markers IL-6, CCL-2, ICAM-I and VCAM-I was measured in cell supernatant by ELISA. Finally, the SCFAs impact on peripheral blood mononuclear cells (PBMCs) was also investigated by stimulating these cells with LPS (100 pg/ml) and measuring TNF-α.

Results: Caproic acid was the only SCFA being able to diminish the upregulation of all the CAEC dysfunctional markers IL-6, CCL-2, ICAM-I and VCAM-I, simultaneously. When LPS was used as a comparator stimulant, all SCFAs including caproic acid, significantly diminished the upregulation of IL-6, suggesting that caproic acid has a dominant positive effect in restoring endothelial cell functions and protecting against cell inflammation. However, in PBMCs, the anti-inflammatory potential of caproic acid to suppress TNF-α production in response to LPS was less pronounced compared to the other candidates.

Conclusions: Our results uncover the potential benefit of caproic acid in reversion of the endothelial cell dysfunction and inflammation mediated by either the inflammatory cytokine IL-32 or the endotoxin LPS. This effect is more selective to endothelial cells compared to peripheral blood cells. Work is in progress to understand the mechanisms involved in these selective functions including the potential differential expression of SCFA receptors in different cell types.

Funding: NIH

RÉSUMÉ 108 - OLAPARIB: A Promising Candidate for Pancreatic Cancer Treatment

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Pancreatic cancer is a major public health issue in Canada, with a survival rate of less than 10% five years after diagnosis. Current treatments like FOLFIRINOX are effective but have significant side effects, limiting their optimal use. Our laboratory aims to develop alternative therapeutic strategies by leveraging cellular senescence to eliminate cancer cells.

Our project aims to study the effect of olaparib (a PARP enzyme inhibitor) on ribogenesis, nucleolar structure, and the induction of senescence as an alternative to oxaliplatin in pancreatic cancer treatment. We aim to determine if its synergistic action with 5-Fluorouracil (5-FU) and leucovorin can halt proliferation and induce senescence in pancreatic cancer cells while reducing oxaliplatin-associated side effects.

First, we will characterize the cellular senescence induced by olaparib, leucovorin, and 5-FU by monitoring proliferation and measuring SA-ß-Galactosidase activity. We will also analyze the expression levels of p53, p21, p16, IL-6, IL-8, and Ki67 using qPCR. Additionally, we will assess their impact on ribogenesis and nucleolar structure using qPCR, Western Blot, and immunofluorescence to target markers like RSL1D1, Nucleostemin, and Nucleophosmin.

Finally, we will evaluate the efficacy of this new therapeutic cocktail in preventing the escape from cellular senescence by tracking proliferation, SA-ß-Galactosidase activity, and cell cycle progression through flow cytometry. We believe this new therapeutic cocktail will lead to proliferative arrest and induce senescence in cancer cells, with alterations in nucleolar structure and ribogenesis, enhancing senescent markers. We expect more pronounced senescence in the cell population compared to the oxaliplatin-containing cocktail and a similar or slowdown in the escape from senescence.

This research will advance fundamental knowledge and highlight a potential alternative, less harmful therapy for pancreatic cancer patients.

Institut du Cancer de Montréal, Terry Fox Foundation

RÉSUMÉ 109 - The mouse embryo is susceptible to mitotic slippage

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Erroneous chromosome segregation results in cells with an incorrect number of chromosomes, termed aneuploidy, common in preimplantation embryos. In somatic cells, a safeguard called the spindle assembly checkpoint (SAC) prevents mitosis completion and chromosome segregation in until chromosomes are correctly aligned to prevent segregation errors. However, prolonged SAC activation eventually leads to mitosis exit without chromosome segregation, a scenario termed mitotic slippage. Indirect observations allude that mitotic slippage might play a role in complex aneuploidies in human embryos. Here, to determine whether mitotic slippage can occur in a mammalian embryo, we induced prolonged M-phase arrest by treating 2-cell mouse embryos separately with two different SAC-activating agents, nocodazole and monastrol, during live timelapse imaging. M-phase arrested embryos underwent actin-dependent cortical 'bulging' activity ~18-20 hours after mitosis entry, transiently taking the appearance of a 'fragmented' embryo. However, the cortical activity ceased and and nuclei reformed ~20h after mitosis entry, confirming slippage. Approximately 2/3 of embryos (63% monastrol- and 65% nocodazole-treated) returned to ostensibly-normal-looking 2-cell stage embryos, with the rest maintaining a fragmented appearance. Using micro-injection of H2B-RFP and live 3D time-lapse imaging, we found that chromosomes migrated and spread across the cell cortex and chromosomal location coincided with the cellular bulges. Chromosome position denotes the site of nuclear reformation, many blastomeres ultimately becoming multinucleated (72% monastrol-treated, 69% nocodazole-treated). Preliminary data suggests mitotic slippage occurs faster at later developmental stages, as M-Phase duration is ~13 and 16 hours at the 4-cell and 8-cell stage respectively compared to ~23 hours at the 2-cell stage. Our data allude that slippage could cause multinucleation in early embryos and affect embryo health, and provides a possible explanation for high levels of embryo fragmentation observed in the clinic.

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RÉSUMÉ 110 - Neuroligin-1 knockout female mice express alterations in their scale-free dynamics of the electro-corticogram during sleep

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Neuroligin-1 (NLGN1) is a synaptic adhesion molecule with roles in the regulation of behavioral states and cognitive function. It was shown to shape electrocorticographic (ECoG) activity during wakefulness and sleep in male mice, including arrhythmic activity under baseline (BL) conditions. Given that the expression of *Neuroligins* (*Nlgn*) differs between sexes, we here aim to characterize the impact of the absence of NLGN1 on the wakefulness/sleep architecture, spectral and aperiodic activity dynamics, and responses to sleep deprivation (SD) in female animals. ECoG and electromyographic (EMG) signals of *Nlgn1* knockout (KO) female mice and wild-type (WT) female littermates were recorded for 48 h comprising a 24-h BL, a 6-h SD and 18 h of undisturbed recovery (REC). Time spent in states (*i.e.*, wakefulness, slow wave sleep [SWS], paradoxical sleep [PS]) and their alternation were interrogated, and ECoG activities were quantified using spectral and multifractal analyses. *Nlgn1* KO females spent more time in PS during the BL light period and showed a fragmented PS in comparison to WT female littermates. Additionally, *Nlgn1* KO females displayed less high theta activity during wake, and less delta activity during SWS and PS in comparison to WT females. Under both BL and REC conditions, the absence of NLGN1 in female mice increased the value of the most prevalent Hurst exponent (*Hm*) during SWS in comparison to WT females, suggesting a higher persistence across scales of ECoG aperiodic activity. Alterations in the daily dynamics of the dispersion of Hurst exponents around *Hm* were also found in KO females during SWS. Altogether, the present study highlights differences in wake/sleep architecture, and in rhythmic and arrhythmic/multifractal activities of female mice lacking NLGN1. These findings provide additional support to a role for NLGN1 in shaping the ECoG organization of synchronous and asynchronous brain activities, especially during SWS and PS.

CIHR

RÉSUMÉ 111 - Estimating the prevalence of Spastic Paraplegia type 7 using genomics data from the CARTaGENE Biobank in Quebec.

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Spastic Paraplegia Type 7 (SPG7) is an autosomal recessive neurologic disorder caused by variants in the *SPG7* gene. Like many neurological disorders, SPG7 is challenging to diagnose due to its varied clinical presentations which include heterogeneous disease onset, severity, and phenotypes. The clinical variability is a major barrier to diagnosis. The global prevalence for SPG7 is estimated at 0.22:100,000 births. In Quebec, founder effects have altered the population's genetics landscape, increasing the prevalence of several rare neurological diseases. This study aims to estimate the prevalence of SPG7 in Quebec to determine if it could be underdiagnosed in this population. We analysed 1,016 RNA-sequencing and exome sequencing samples, along with 2,173 whole-genome sequencing samples from the CARTaGENE (CaG) cohort. CaG is composed of 43,000 Quebecers aged 40 to 69 years old. Using a bioinformatics pipeline, we extracted and identified all pathogenic and likely pathogenic variants in the *SPG7* gene. An enrichment analysis was performed to identify possible founder variants in Quebec. The prevalence of SPG7 in Quebec was estimated using the Hardy-Weinberg equation. The pathogenic variant p.D765N was identified in RNA, exome and whole-genome sequencing samples. It was found to be enriched in Quebec's population, suggesting a founder variant. The estimated prevalence of SPG7 in Quebec was estimated at 20.37:100,000 births using the RNA and exome sequencing samples, and 8.47:100,000 births using the whole-genome sequencing samples. These increased prevalences suggest SPG7 may be underdiagnosed in Quebec. The identified possible founder variant and the development of a disease registry could be used to improve diagnosis of this disorder. Our findings highlight the importance of prospective cohorts, such as CaG, to identify potential founder variants as well as demonstrate the genetic heterogeneity in founder populations such as Quebec.

RÉSUMÉ 112 - Développement d'une technique de quantification des provirus intacts du VIH

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À l'échelle mondiale, l'infection par le virus de l'immunodéficience humaine (VIH) touchait encore 39 millions de personnes en 2023. Malgré l'existence de traitements antirétroviraux, ceux-ci ne sont pas curatifs puisque le virus persiste dans un état de latence sous forme de réservoirs stables et persistants dans le sang et divers sites anatomiques. Une quantification robuste et sensible de la fréquence des cellules infectées par des provirus intacts est essentielle pour évaluer l'efficacité des traitements thérapeutiques ayant pour but d'éliminer le VIH. Toutefois les méthodes de quantification actuelles présentent des limites que ce soit dans leur spécificité, leur sensibilité ou même leur faisabilité dans un contexte clinique. Ce projet vise à développer une technique de quantification des provirus intacts, qui serait rapide, précise et facile d'emploi, nommée l'*Intact Retroviral Mesurement Assay* (IRMA). Dans un premier temps, nous avons optimisé la préparation des échantillons. Ainsi, l'extraction d'ADN améliore la détection des provirus. Celle-ci doit être effectuée à partir de cellules enrichies en lymphocytes T $CD4^+$, nécessite la digestion des cellules par de la Protéinase K à 1.82mg/mL, et le volume d'élution doit être de 100µL pour 1 million de cellules. Nous avons ensuite conceptualisé deux paires d'amorces et une sonde afin de distinguer les provirus intacts des génomes viraux défectueux. À l'aide de cet essai optimisé, nous avons déterminé que la fréquence moyenne de cellules portant des provirus intacts est de 109 cellules par million de cellules T $CD4^+$ chez 19 personnes avec le VIH sous traitement antirétroviral. Une comparaison avec la fréquence de provirus intacts mesuré par séquençage pan-génomique permettra d'évaluer l'exactitude de notre essai.

RÉSUMÉ 113 - Optimisation d'une stratégie afin d'identifier les facteurs de résistance des cellules infectées par le VIH aux effecteurs cytotoxiques

Julien Gigan[1], Nicolas Chomont[1]

[1]CRCHUM

L'éradication du VIH fait face à un obstacle majeur : Le virus persiste dans des réservoirs malgré les thérapies antirétrovirales (TAR) efficaces. Les mécanismes au cœur de la persistance des cellules infectées et de leur résistance aux cellules cytotoxiques restent mal compris. Précédemment, nous avons montré une décroissance 5 à 10 fois plus rapide des réservoirs du VIH chez les participants ayant initié la TAR immédiatement après l'infection (<6mois, *groupe immédiat*) comparé à une initiation plus tardive (>6mois, *groupe différé*). Par conséquent, les mécanismes responsables de l'élimination/le maintien des cellules infectées semblent différent en fonction de la date d'initiation de la TAR. Dans le but de caractériser la résistance des cellules infectées aux effecteurs cytotoxiques, nous avons mis en place une stratégie d'analyse en miroir d'échantillons de sang longitudinaux de participants des groupes *immédiat* et *différé*. D'une part, nous avons développé un panel de cytométrie en flux pour mesurer le degré de dysfonction des cellules effectrices cytotoxiques NK et TCD8 (PD-1, TIM3, TIGIT, LAG3, NKG2A, NKG2C, Siglec7). D'autre part, nous avons optimisé les étapes de marquage et de stimulation permettant de caractériser les cellules cibles (VIH+). Nous avons amélioré la méthode de détection des cellules infectées produisant la protéine virale p24 (HIV-Flow) : En utilisant des inhibiteurs de caspases et de maturation lysosomale, nous avons augmenté jusqu'à 1,5 fois la fréquence mesurable de cellules cibles, tout en préservant partiellement leur phénotype d'origine. Cette méthode permettra de mesurer l'expression de protéines exprimées à la surface des cellules infectées et impliquées dans la résistance aux cellules cytotoxiques. Ainsi, notre approche en miroir permettra d'identifier protéines cellulaires associées à la persistance des réservoirs, ce qui permettra d'explorer de nouvelles stratégies thérapeutiques pour éradiquer les réservoirs du VIH.

Organisme subventionnaire: NIH

RÉSUMÉ 114 - An Electronic-Free Smart Capsule for the Targeted Sampling of Microbiota within the Gastrointestinal Tract

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Introduction: It is currently known that the gut microbiota plays a critical role in essential functions, such as digestion, metabolism and the immune system. To better understand the microorganisms within our gastrointestinal (GI) tracts, and how their dysbiosis can contribute to digestive diseases, accurate sampling of these microbial communities is crucial. However, current sampling methods such as colonoscopies and stool samples are invasive and non-specific respectively. To overcome these limitations, we have developed an electronic-free ingestible capsule designed to sample GI fluid from targeted areas of the tract. This device uses pH-sensitive polymers to ensure localized sampling.

Methods: The capsule was designed on Solidworks (Dassault Systems) and fabricated with a 3D printer (Form3B, Formlabs). A hydrogel-based swelling mechanism which thrusts a seal onto the capsule opening forces the device shut post-sampling. Polyacrylamide hydrogel elongation was characterized, and UV spectrophotometry was used to detect any leakage of the sampled fluid from the capsule post-sampling. Lastly, the dissolution of alginate films coated with Eudragit at target pH levels has been assessed.

Results: The capsule has been successfully designed and 3D-printed. Hydrogel elongation has proven to be sufficient. Capsule effectively sampled simulated fluid, with no leakage observed in 24 hours post-sampling. Eudragit-coated alginate films were fabricated and demonstrated complete dissolution in pH 7.5 (representing the large intestine) within three hours, while they did not dissolve in pH 1.0 (representing gastric fluid).

Discussion / Conclusion: This device has proven to be capable of sampling at targeted areas and properly preventing sample contamination from other regions of the tract. It can then be used to collect data on the microbial communities within the GI tract while improving our understanding of the gut microbiota impact on human health.

Funding agencies: Canada Graduate Scholarship - M. Sc. (NSERC) and the CHUM Foundation Training Bursary - M. Sc.

RÉSUMÉ 115 - Assessment of the Hexoskin Biometric Shirt in Measuring Body Position During Sleep

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Introduction: Patients with uncontrolled epilepsy are at increased risk of sudden unexpected death in epilepsy (SUDEP). Evidence suggests that sleeping or being in a prone position after a seizure may increase the risk of SUDEP. A few wearable devices have the potential to track sleeping habits. These devices could eventually be used to screen patients with epilepsy with a tendency to sleep in a prone position, allowing interventions such as sleep training to influence an ideal sleep position. Additionally, they could continuously monitor body positioning, allowing for responsive alarms and/or interventions when necessary. In this study, we prospectively assessed the accuracy of the Hexoskin biometric shirt, which incorporates a sleep position classification algorithm, in identifying sleep body positions.

Methods: Patients were recruited at the University of Montreal Health Center (CHUM) epilepsy monitoring unit and were asked to wear the Hexoskin biometric shirt. A built-in algorithm identified prone, supine, right, left, or sitting/standing body positions using an accelerometer. Sleeping positions predicted by the algorithm were compared to “true” values collected via blind simultaneous video analysis.

Results: Across 10 patients and 347 hours of sleep analyzed, 65% of prone, 75% of supine, 94% of right lateral decubitus, 81% of left lateral decubitus, and 65% of sitting/standing positions were correctly classified by the Hexoskin algorithm. Balanced accuracy was 0.76 and weighted F1-score was 0.85.

Conclusion: Our results show promise in the use of the Hexoskin shirt for detecting sleep positions.

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RÉSUMÉ 117 - Détermination des paramètres cliniques, biologiques et psychométriques pour le diagnostic de l'encéphalopathie hépatique

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Introduction: L'encéphalopathie hépatique (EH), une complication de la cirrhose, peut être détectée cliniquement, biologiquement ou par des tests psychométriques. Toutefois, il existe à ce jour aucune valeur de référence pour la population canadienne. Cette étude a donc pour but de déterminer ces paramètres pour le diagnostic de l'EH et d'établir des valeurs de référence pour la population montréalaise.

Matériel et méthodes: Il s'agit d'une étude prospective exécutée du 1er janvier 2024 au 1er août 2024. Elle comprend une cohorte de témoins composée de toute personne âgée de 18 ans et plus sans maladie hépatique ; et une cohorte de patients atteints de cirrhose, mais sans charge virale détectable pour les virus de l'hépatite B, C et VIH. L'étude a été acceptée par le comité d'éthique du CHUM (projet 22-276).

Résultats: 31 témoins ont été inclus, ainsi que 18 patients atteints de cirrhose. Nos résultats pour chacun des tests psychométriques sont pour les témoins : « Psychometric Hepatic Encephalopathy Scale » (PHES), de 4 à 5 ; « Animal Naming Test » (ANT), de 13 à 34 ; Stroop, le temps est de 91 à 183 secondes. Les résultats des scores entre la cohorte de témoins et celle des patients sont significativement différents ($p < 0,001$) pour chacun des tests. Finalement, l'analyse selon les différents grades d'EH révèle une tendance d'augmentation de la concentration d'ammoniac et d'une aggravation des scores totaux médians de tous les tests.

Conclusion: L'étude a permis d'établir une cohorte de témoins afin de définir des valeurs de référence pour la population montréalaise. Les résultats montrent une différence significative entre les deux cohortes pour les volets biologique et psychométrique, ainsi qu'une tendance selon les différents grades d'EH.

RÉSUMÉ 118 - Caractérisation de la signature inflammatoire en sclérose tubéreuse de Bourneville

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La sclérose tubéreuse de Bourneville (STB) est une maladie autosomale dominante qui touche 1 personne sur 6000. La STB est causée par une activation chronique et soutenue de la voie mTOR. Les complications reliées à la STB sont multiples et complexes, notamment au niveau neurologique. D'entre elles, l'épilepsie représente un défi majeur, la grande majorité étant résistante aux traitements antiépileptiques.

Le rôle de l'inflammation dans l'épilepsie est de plus en plus reconnu. Cependant, l'implication de l'inflammation en STB est encore méconnue. Nous avons étudié l'inflammation périphérique chez un groupe de personnes vivant avec la STB. Nous avons notamment identifié des molécules sériques inflammatoires propres à la STB, indépendamment des manifestations cliniques, notamment CXCL8, EGF et IL-1β. Nous avons également identifié des marqueurs associés à l'épilepsie démontrant un patron de cytokines pro-inflammatoires, notamment l'IL-17A, l'IL-6, la TNFα et la GFAP. Cette dernière a pu être confirmée dans une cohorte de validation indépendante, démontrant son association en épilepsie et supportant l'implication d'une astrogliose en STB. Finalement, nous avons procédé à l'immunophénotypage par analyse non-supervisée des cellules périphériques du sang, qui démontre une altération des populations lymphocytaires et myéloïdes en STB. Le séquençage d'ARN de lymphocytes T activés diffère en STB et touche des voies reliées à l'immunité innée et aux voies cytotoxiques.

Nos résultats témoignent de changements en inflammation périphérique associés à la STB. Ils identifient des mécanismes impliqués en STB et en épilepsie jusqu'ici inconnus, et soutiennent la théorie que l'inflammation contribue à l'épilepsie. Ces nouveaux biomarqueurs permettront d'élargir les nouvelles approches thérapeutiques et préciser le suivi des personnes vivant avec la STB.

RÉSUMÉ 119 - Le microenvironnement immunitaire du carcinome intracanalaire de la prostate: vers l'immunothérapie

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Introduction: Le carcinome intracanalaire de la prostate (IDC) est caractérisé par l'infiltration de cellules épithéliales malignes à l'intérieur des canaux prostatiques et il répond peu aux traitements habituels. Cette étude décrira l'infiltration immunitaire de l'IDC puisque les cellules immunitaires dans les canaux de la prostate sont associées à une maladie plus dangereuse. De plus, cette étude explore la possibilité qu'un complexe de transfert d'hydrure (HTC) empêchant l'arrêt de la division cellulaire dans les cancers mortels puisse être impliqué dans l'IDC et causer son agressivité.

Méthodes: Nous utiliserons l'immunofluorescence cyclique pour visualiser plusieurs marqueurs immunitaires et du microenvironnement tumoral simultanément sur une coupe unique sur un « tissue microarray » (TMA) composée de lésions d'IDC d'une cinquantaine de spécimens de patients. Nous utiliserons l'essai de ligature de proximité (PLA) pour déterminer si l'HTC est présent dans l'IDC et s'il est associé à une survie sans récidive biochimique (taux d'antigène prostate spécifique [APS] sanguins élevés) plus courte. Enfin, la présence d'HTC sera corrélée à la signature immunitaire.

Résultats anticipés: Nous nous attendons à ce qu'il y ait plus de cellules immunitaires à l'extérieur de l'IDC qu'à l'intérieur et que l'IDC exprime l'HTC.

Discussion et conclusion: Nous nous attendons que les hommes présentant une forte inflammation à l'intérieur de l'IDC et/ou qui expriment l'HTC aient une survie sans récidive plus courte. Finalement, en caractérisant le microenvironnement immunitaire de l'IDC cela nous permettra de suggérer de potentielles cibles pour l'immunothérapie.

Organismes subventionnaires: Ride for Dad, Institut de Cancer de Montréal, Canderel, IRSC, Fondation du CHUM

RÉSUMÉ 120 - Assessing the potential of targeting 14-3-3ζ to restore functional β-cell mass

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Introduction: Increasing functional β-cell mass via promoting β-cell proliferation is a potential approach to restore normoglycemia in patients with diabetes. β-cell proliferation is regulated by the nuclear translocation of Cyclin-CDK complexes, activation of signaling pathways, and mitogenic stimuli [eg. High fat diet (HFD), Exendin-4]. We previously reported that acute inhibition of 14-3-3 proteins promotes β-cell proliferation and that β-cell-specific 14-3-3ζ knockout (β14-3-3ζKO) mice had increased β-cell proliferation. Thus, I hypothesize that targeting 14-3-3ζ in β-cells could increase β-cell mass.

Methods: β14-3-3ζKO mice were fed chow or 60% HFD diets for 8 weeks. A separate cohort of β14-3-3ζKO mice were treated with Exendin-4 (10 nmol/kg b.i.d, 7 days). To selectively deplete 14-3-3ζ in β-cells, an *Ywhaz* antisense oligonucleotide conjugated to GLP-1 (GLP-1-ASO$_{Ywhaz}$) was administered to 12-week-old male C57BL6/J mice (*s.c.* 1 mg/kg weekly) for 4 weeks. GLP-1-ASO$_{Ywhaz}$-treated mice were also fed HFD for 10 weeks. β-cell mass and proliferation were measured by co-immunostaining for insulin and PCNA, Ki-67, or EdU (200 microgram/day for 3 days before sacrifice).

Results and Discussion: Chow-fed β14-3-3ζKO mice showed no difference in β-cell mass, despite increased PCNA-positive β-cells. In contrast, HFD-fed β14-3-3ζKO mice had significant increases in β-cell mass and PCNA-positive proliferating β-cells, suggesting increased sensitivity of 14-3-3ζ-deficient β-cells to mitogenic stimuli. This was further confirmed with significantly increased Ki-67-positive β-cells and β-cell mass in Exendin-4-treated β14-3-3ζKO mice.

Islets from GLP-1-ASO$_{Ywhaz}$-treated mice had significantly decreased *Ywhaz* (the gene for 14-3-3ζ) mRNA levels, demonstrating efficacy of this approach. Similar to β14-3-3ζKO mice, GLP-1-ASO$_{Ywhaz}$ increased β-cell proliferation but not β-cell mass. However, GLP-1-ASO$_{Ywhaz}$-treated HFD-fed mice showed trends towards increased β-cell proliferation and mass.

Conclusion: This study demonstrates a “priming” effect of reducing 14-3-3ζ in β-cells, increasing their sensitivity to mitogenic stimuli. 14-3-3ζ may represent a key checkpoint or brake to regulate β-cell proliferation.

Funding: CIHR, FRQS, CRC Program

RÉSUMÉ 121 - Establishing methods to measure mitochondrial output in young and aged mouse oocytes

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Maternal aging is associated with an increase in oocyte aneuploidy, which is widely regarded as the principal cause of age-related infertility. Oocytes also experience other changes during aging, however, such as alterations in mitochondrial function. Importantly, the relationship between mitochondrial output and aneuploidy remains unclear. For this reason, we have recently been trialling a variety of approaches to measure mitochondrial function in oocytes, including some that were widely used previously, and some not yet applied to the mammalian oocyte. Trials of commercially-available dyes have yielded mixed results, and we will describe a number of artefacts that we have encountered using such approaches in mouse oocytes. In contrast we find that Optical Redox Ratio, an autofluorescence-based approach for measuring mitochondrial redox state that has been used before in oocytes, sensitively detects changes in mitochondrial function, including the shift experienced during natural aging. In addition we have optimised the use of PercevalHR, a genetically encoded probe that measures ATP:ADP ratio, and find that it sensitively detects changes in mitochondrial output. Our ongoing work seeks to determine whether there is a causal relationship between aneuploidy and mitochondrial function in oocytes.

Funding Sources: Supported by CIHR (Canadian Institutes of Health Research), NSERC (Natural Sciences and Engineering Research Council of Canada), FONDATION JEAN-

RÉSUMÉ 122 - How Does Cognition Impact Healthcare Transition Skills, Engagement and Utilization in Young Adults Living with Sickle Cell Disease

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Introduction: Young adulthood is a period of increased risk in individuals with sickle cell disease (SCD). This study looks at the cognitive results of young adults (YA) with SCD and explores whether these results are linked to transition skills, healthcare engagement, and utilization.

Methods: A retrospective study was conducted at CHUM, Montreal, Canada. Patients with SCD aged 18-25 had to undergo the Montreal Cognitive Assessment Test (MoCA) and the Rowland Universal Dementia Assessment Scale (RUDAS), along with routine neurological exams, between August 2021 and December 2023 and have a minimum follow-up period of 12 months to qualify for the study. Individuals with cognitive comorbidity (CC) had either a diagnosis of intellectual disability (ID) or attention deficit (AD), a RUDAS score <28, or a MoCA <27. The Mann-Whitney U-test was used for comparison.

Results: 30 participants were eligible for the study. The participants were on average 20 during cognitive testing, ranging from 18 to 23. Of these, 19 (63%) were female, 20 (67%) carried the SS/Sβ^0 genetic variant, three (10%) had experienced strokes, eight (27%) had been diagnosed with AD, and one (3%) had an intellectual disability.

It was noticed that people with CC had better attendance at their hematology appointments (88% vs. 81%, p=0.04). There were no significant differences in the mean number of ED visits (1.0±1.1 vs. 0.8±0.6, p=0.95), day hospital visits (0.3±0.7 vs. 0.3±0.4, p=0.37) or hospitalizations (0.4±0.5 vs. 0.5±0.6, p=0.54) per year between those with and without CC.

Conclusion: Our study found that YA with SCD and CC had similar transition skills and healthcare engagement as those without. This small study didn't include young adults with the most severe cognitive deficits, but we think obstacles posed by CC in YA with SCD may be reduced with the right support.

A BRPC scholarship from IRSC funded the study

RÉSUMÉ 123 - Sensibilité des différents sous-types de cancer du sein triple-négatifs à la thérapie virale du cancer

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Au Canada, le cancer le plus diagnostiqué chez les femmes est le cancer du sein avec près de 28600 nouveaux cas en 2022. Il existe 5 sous-types de cancers du sein, classifiés selon l'expression des trois récepteurs hormonaux principaux soit des récepteurs de l'œstrogène, de la progestérone et de HER2. Le sous-type basal inclut les cancers du sein triple-négatifs (TNBC). Les TNBC nous intéressent dû à l'absence de thérapie ciblée, à leur agressivité accrus, ainsi qu'à leur plus haut taux de récidive en comparaison avec les autres types de cancer du sein. Notre laboratoire travaille avec un virus oncolytique nommé virus de la stomatite vésiculaire (VSV). Les virus oncolytiques tuent préférentiellement les cellules cancéreuses et représentent une approche intéressante comme traitement pour le cancer du sein. Notre équipe a préalablement observé que les TNBCs étaient généralement plus résistantes envers VSV, en comparaison avec les autres types de cancers de sein. Dans le cadre de mon projet, j'ai remarqué que la sensibilité virale était hétérogène avec certaines lignées très sensibles et d'autre résistantes. De ce fait, nous posons l'hypothèse que différents sous-types de TNBCs seront plus ou moins sensibles à VSV et que la virothérapie serait une approche efficace pour le traitement des TNBC sensibles. Pour l'instant, nos résultats montrent que les lignées de type apocrines moléculaire sont plus sensibles à l'infection par VSV. Il serait donc intéressant de caractériser différentes lignées de TNBCs selon leurs sous-types et leur sensibilité à VSV. Par la suite, les sous-types les plus sensibles seront étudiés afin d'identifier les facteurs de transcription/voies de signalisation qui rendent ce sous-type plus sensible. Ultimement, cela pourrait permettre de rendre d'autres sous-types de TNBCs tout aussi sensibles à VSV et ainsi, améliorer la thérapie oncolytique chez les TNBCs.

Organismes subventionnaires: CRCHUM, ICM, CIHR

RÉSUMÉ 125 - Development of an Innovative in vitro 3D Model of an Aggressive Subtype of Prostate Cancer

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Introduction: An aggressive subtype of prostate cancer (PC) and a threat to the survival of patients is intraductal carcinoma of the prostate (IDC). IDC is characterised by malignant cells growing within pre-existing benign prostatic ducts. Current restricted understanding of the molecular mechanisms forming IDC is impeding the advancement of much-needed targeted therapies for these men that do not respond well to standard treatments. Indeed, it is necessary to establish an *in vitro* model of the lesion that is suitable for the evaluation of therapeutic approaches.

Methods: To mimic IDC, we have developed an accurate *in vitro* model by embedding benign and cancerous prostatic cell lines in Matrigel matrix. Utilizing point spread function (PSF) microscopy, emitted light from nuclear stained GFP PC cells and mCherry benign ducts is modulated by a phase mask, so its 3D information that is encoded in the 2D image that the point emitter will generate on the camera (the PSF) can undergo image analysis to establish the emitter's 3D position (localization).

Results: Benign prostatic cells form 3D ducts after three days on Matrigel matrix, to which malignant cells invade the ducts without destroying their already formed structures. Impressively, the number of malignant cells found inside the lumen of the ducts and their distances to the nearest duct can be determined and monitored for up to 80 days of live-cell imaging.

Discussion / Conclusion: This is the only *in vitro* model of IDC, and our effective model remarkably recreates the *in vivo* conditions of IDC. Ultimately, our model will enable a throughout understanding of the development of IDC and will be imperative in the initial identification of target therapies for this terrible disease.

RÉSUMÉ 126 - Impact of antibiotic exposure on patients treated with BRAF-positive advanced melanoma targeted BRAF/MEK inhibitors

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Introduction: The gut microbiome is a biomarker of response to immune checkpoint inhibitors (ICI) in melanoma. Antibiotics prior the initiation of ICI is now a validated negative prognostic factor. However, 50% of patients will harbour mutations in the BRAFV600 oncogene, and will be treated with BRAF/MEK inhibition (BRAFi/MEKi). While the impact of antibiotics pre-ICI is clear, the impact of antibiotics on BRAFi/MEKi is unknown.

Methods: In this retrospective analysis in metastatic BRAF-positive melanoma treated with BRAFi/MEKi, patients were classified into the antibiotic group if they were exposed to antibiotics 60 days before the start of BRAFi/MEKi. Response rate (rate of partial response and complete response) was compared between the groups. Progression-free survival (PFS) and overall survival (OS) were compared between the groups using the Kaplan-Meier Method and log-rank test.

Results: 58 patients with advanced cutaneous melanoma treated BRAFi/MEKi were included. Median follow-up was 33 months. Median age was 57 (47, 66) and 31 (54%) were male. 53 (95%) had BRAFV600E mutations. A total of 8 (14%) were exposed to antibiotics. Age, sex, performance status, and line of therapy were balanced between the groups (p>0.5). There was no difference in ORR between the groups (63% vs. 60%, respectively, p=1). There was no difference in PFS (11 vs 11 months, respectively, hazard ratio (HR) 1.2, 95%CI 0.5-3, p=0.8) or OS (19 vs 29 months, respectively, HR 0.8, 95%CI 0.3-2.3, p=0.7) between groups.

Conclusion: Unlike observations in the ICI landscape, we did not observe any negative impact of antibiotic use in the 60 days prior to initiation of BRAFi/MEKi therapy in patients with advanced melanoma. Although limited by small sample size, these data suggest that the negative impact of antibiotics is specific to cancer ICI and reinforces the importance of the gut microbiome.

Funding: Fonds de Recherche du Québec - Santé (FRQS)

RÉSUMÉ 128 - Investigating the Impact of Nucleolus-Associated Domains (NADs) Opening on Senescence

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[1]Presenter, [2]Co-author, [3]Supervisor, [4]Contributor

Introduction: Understanding cellular processes such as growth, dormancy, senescence, and death is essential for healthy development and for addressing diseases like cancer and aging. Chromatin dynamics play a crucial role in these processes, with pathways like RAS-MAPK influencing cellular decisions. Our study investigates how chromatin opening impacts cellular senescence and cancer, focusing on the role of Nucleolus-Associated Chromatin Domains (NADs) in these mechanisms.

Methods: We manipulated HRAS protein activity using 4-hydroxytamoxifen (4-OHT) to control growth signals in cells. Chromatin structure changes were monitored through ATAC-seq to assess how chromatin accessibility shifts in response to these signals. We further explored NADs by conducting bioinformatics analyses on chromatin domains in senescent and non-senescent cells, comparing these findings across various cancer types.

Results: Our findings demonstrate that chromatin opening is crucial for promoting cellular senescence. Specifically, NADs exhibited increased chromatin accessibility in senescent cells compared to their non-senescent counterparts. Bioinformatics analyses of NADs across several cancer types also revealed significant mutations within these domains, suggesting a link between NADs opening and disease progression.

Discussion / Conclusion: This study highlights the pivotal role of chromatin dynamics, particularly Nucleolus-Associated Chromatin Domains, in regulating cellular senescence and cancer. Our findings suggest that NAD mutations may play a significant role in both senescence and cancer development, offering new insights into chromatin's role in age-related diseases and potential therapeutic targets.

Funding: This research is supported by a CHIR grant

RÉSUMÉ 129 - Early-life iron supplementation: altering recovery from gut dysbiosis through modulation of the gut microbiota

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Introduction: Iron is an essential micronutrient, but its supplementation can cause some serious intestinal problems. Free iron in the intestine promotes development of pathogenic bacteria which alters the gut microbiota and associated intestinal health. Early-life is a key period for the gut microbiota establishment, and little is known about how iron impacts it. This is concerning regarding future ability to recover from intestinal stresses such as gut dysbiosis which can lead to development of colorectal cancer in worst-case scenarios.

Methods: C57BL/6 mice were given either an iron sufficient or an iron excess diet from their weaning to their adulthood, after which they were all placed on the iron sufficient diet for 2 weeks. Dysbiosis was then induced, using two different models, either giving dextran sulfate sodium (DSS) to induce colitis, or giving antibiotics. Mice were then given 8 weeks to recover from gut dysbiosis. Frequent sampling of stools is made to follow impact on gut microbiota composition (16S rRNA DNA sequencing) and the building of a bio-informatic pipeline is required to follow the recovery of the gut microbiota and impact of iron.

Results: Preliminary results show that the colitis model worked, as we measured a disease severity index, showing that mice responded to DSS exposure. Young mice exposed to excess iron exhibited a stronger response than mice which were exposed to sufficient iron. The bio-informatic pipeline works on data from other experiments and has been optimized to reduce computational time.

Conclusion: Data indicates that excess iron in young mice induces a stronger response to DSS-induced colitis. Analysis of 16S sequencing data will further help to elucidate differences in recovery from dysbiosis. This could bring some important insight on iron's impact on future intestinal health and could lead to better recommendations when supplementing young infants.

CRCHUM, ICM, Université de Montréal

RÉSUMÉ 130 - RÔLE DU MÉTABOLISME DU FER DANS L'ÉLIMINATION DES CELLULES SÉNESCENTES CANCÉREUSES PANCRÉATIQUES

Audrey Langlois[1, 2]

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Le FOLFIRINOX est la chimiothérapie utilisée en clinique contre le **cancer du pancréas**. Ce composé permet l'arrêt de la prolifération cellulaire et l'induction de la sénescence des cellules cancéreuses. Malgré son efficacité, la plupart des patients développent une résistance et vont en succomber.

Effectivement, nous avons observé un échappement à la sénescence induite par le FOLFIRINOX dans des lignées cancéreuses pancréatiques. De plus, un criblage par CRISPR-Cas9 a permis d'identifier des vulnérabilités des cellules cancéreuses sénescentes, dont l'enzyme GPX4 impliquée dans la réponse anti-ferroptotique. Une thérapie ***one-two punch*** a ensuite été proposée pour éliminer de façon sélective ces cellules : le **FOLFIRINOX**, suivi d'**inhibiteur de GPX4** menant à la mort cellulaire par **ferroptose**. Celle-ci est caractérisée par une accumulation de fer libre et la production d'espèces réactives à l'oxygène (ROS) conduisant à la peroxydation des lipides membranaires. Nous avons démontré une accumulation de fer libre post-FOLFIRINOX ce qui rendrait les cellules sénescentes plus susceptibles à la mort par ferroptose. Nous voulons mieux comprendre le mécanisme moléculaire pouvant expliquer cette sensibilité à l'inhibition de GPX4.

De nouvelles données RNA-seq nous ont orientées vers le métabolisme du fer mitochondrial. Des expériences de cytométrie en flux démontrent une augmentation du fer libre mitochondrial en réponse au traitement FOLFIRINOX. **L'hypothèse est que la sensibilité de nos cellules sénescentes à la mort par ferroptose serait d'origine mitochondriale**. Pour tester cela, nous étudions l'expression de marqueurs indicateurs de ferroptose, tels que la peroxydation des lipides mitochondriaux, les ROS mitochondriaux et l'expression de transporteurs du fer mitochondrial dans des cellules cancéreuses sénescentes.

En somme, nos travaux pourront permettre de mieux comprendre les mécanismes moléculaires sous-jacents de la thérapie *one-two punch* dans le cancer du pancréas.

Terry Fox Research Institute (TFRI), Canderel (ICM), Fondation du CHUM

RÉSUMÉ 131 - Mitotic aneuploidy and its consequences on preimplantation mouse embryo development

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Preimplantation embryos obtained from IVF procedures contain a mixture of euploid and aneuploid cells, termed "mosaic embryo aneuploidy." However, the impact of aneuploidy on early development and its relationship to embryo morphology remains poorly understood, and is important in the context of choosing the best embryos to transfer during clinical IVF. To investigate this, we treated mouse embryos at the 2- to 4-cell transition with a mitotic motor CENPE inhibitor and/or a spindle checkpoint inhibitor. The combined use of both increased aneuploidy in healthy cells to ~80% of cells (high aneuploidy), while treatment with a single drug led to embryos with ~50% (medium aneuploidy), while untreated embryos had ~20% as expected. We studied the morphogenetic events of preimplantation development in these embryos using bright-field time-lapse imaging. All groups showed similar mitosis durations, cell cleavage timings during the 4 to 8-cell division, and timing of morula formation. Medium-aneuploid embryos could develop into blastocysts at rates comparable to controls, but high-aneuploidy exhibited substantially inhibited development at the morula-blastocyst transition, including reduced blastocyst formation and cell counts. Lineage tracing in high-aneuploid embryos using H2B-RFP and live microscopy revealed significantly prolonged interphases after 8-cell stage compared to controls. Using live apoptosis imaging we also found that high-aneuploid embryos experienced increased cell death in later preimplantation development. Altogether our data suggest that cells of the early embryo are insensitive to aneuploidy and that aneuploid cells divide and behave morphologically similar to euploid cells, but that aneuploidy profoundly alters embryo development starting around the morula-blastocyst transition. Our data has important implications for the development of techniques for selecting embryos based on their morphokinetic behaviour.

Funding Agency: FRQS postdoctoral fellowship

RÉSUMÉ134 - Retinoic Acid Counteracts the Antiviral Activity of Aryl Hydrocarbon Receptor in Macrophages by Promoting its Non-Genomic Functions

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Background: SAMHD1 restricts HIV-1 replication by limiting dNTPs required for efficient reverse transcription. Among regulators of SAMHD1 activity, ligands of aryl hydrocarbon receptor (AhR) were reported to decrease SAMHD1 phosphorylation via transcriptional repression of kinases CDK1/2, and thereby promoting its antiviral activity. Conversely, we demonstrated that retinoic acid (RA) promotes HIV-1 replication in macrophages by inducing SAMHD1 phosphorylation. Considering the role of macrophages in HIV-1 infection in anatomic sites rich in both AhR ligands and RA, such as the intestine, here we investigated how the crosstalk between these two pathways governs SAMHD1 activity and HIV-1 replication in macrophages.

Methods: Monocyte-derived macrophages (MDM) were exposed to *all trans* RA (ATRA) and/or AhR agonist (FICZ) and exposed to single-round VSV-G-pseudotyped HIV-1. HIV replication was measured by p-24 ELISA and nested real-time PCR using specific primers for early/late reverse transcripts and integrated HIV-DNA. Western immunoblot for SAMHD1/pSAMHD1 were performed and validation of AhR associated genes were performed by RT-PCR.

Results: Exposure to FICZ inhibited HIV-1 replication in MDM at the level of reverse transcription, integration, and translation. This antiviral effect was absent in the presence of ATRA, which significantly increased HIV-1 replication. FICZ decreased SAMHD1 phosphorylation, but not in the presence of ATRA, consistent with the robust RA-mediated increase in CDK1 expression. Quantification of AhR associated genes in ATRA treated MDMs revealed the downregulation of the AhR nuclear translocator (ARNT) and the upregulation of the gene for AhR repressor (AHRR), indicating a blunted AhR signaling pathway.

Conclusions: Our results demonstrate opposing roles for AhR and RA pathways in the modulation of the antiviral activity of SAMHD1 and reveal a blunted AhR-mediated antiviral program in MDMs in the presence of RA. These studies identify the need for natural SAMHD1 modulators as novel therapeutic targets for HIV-1.

RÉSUMÉ 135 - Observing apoptosis using live imaging in early mouse embryos

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Preimplantation development in mammals involves the progression of a single fertilized oocyte into a blastocyst, comprising approximately 128 cells. During this period, cells divide and ultimately differentiate into inner cell mass and trophectoderm. It is well known however that some cells undergo apoptosis during this period. To date however, analysis of the regulation, mechanism, and functional impact of apoptosis within embryo development has been hampered by the lack of a live-imaging approach to assess cell death and elimination. Here we have optimized the use of the apoptosis-detecting CellEvent Caspase3/7 probe with live confocal microscopy. We assessed the rate of apoptosis across all stages of mouse preimplantation embryo development**.** We find that apoptosis is extremely rare prior to 16-cell stage, but occurs at a rate of ~2.3 apoptotic cells per embryo in 32-cell stage embryos. Our data suggest that apoptosis is selectively activated in in the inner cell mass compared to the trophectoderm cells. Additionally, we induced double-strand DNA breaks in 2-cell stage embryos, and found this did not activate an apoptotic response. However, DNA damage does substantially increase cell death in later developmental stages. Our work so far thus suggests that the very early embryo is unusually resilient to DNA damage-induced apoptosis, but as embryos progress to the blastocyst stage, apoptotic pathways become more responsive. Future work will address the nature of this developmental shift, and the physiological benefit of preventing apoptosis in the very early embryo.

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RÉSUMÉ 137 - Dissecting the molecular mechanisms of FIG4-related neuropathies using patient-specific mutations in C. elegans

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FIG4-related neuropathies are a group of severe neurodegenerative disorders associated with mutations in the *FIG4* gene, which encodes a phosphoinositide phosphatase located on the late endosomal and lysosomal membranes. Pathogenic variants in *FIG4* have been implicated in several disorders, including Charcot-Marie-Tooth disease type 4J (CMT4J), Yunis-Varon syndrome (YVS), amyotrophic lateral sclerosis (ALS), and polymicrogyria. These neuropathies are characterized by a range of severe phenotypes, including progressive muscle weakness and atrophy, motor neuron degeneration, and sensory deficits, with additional skeletal abnormalities in YVS. Despite the genetic identification of *FIG4* as a key player in these diseases, the precise molecular mechanisms by which *FIG4* mutations contribute to such diverse neuropathologies remain poorly understood.

The FIG4 protein forms a complex with PIKfyve and VAC14 that regulates the important lipid signaling molecules PI(3)P and PI(3,5)P2. These molecules orchestrate fundamental cellular functions, including membrane homeostasis, endocytosis, stress signaling, and endolysosomal acidification. Disruption of these pathways may underlie the neurodegenerative processes observed in *FIG4*-related diseases, but this remains largely unexplored.

To dissect *FIG4*-related pathogenic mechanisms, we used CRISPR/Cas9 to introduce patient-specific mutations into *figo-1*, *the C. elegans* ortholog of *FIG4*. Given the conservation of key molecular pathways between *C. elegans* and humans, this model enables us to investigate the cellular effects of *FIG4* mutations *in vivo*. Our preliminary results reveal distinct disease-like phenotypes, including motor dysfunction and lysosomal abnormalities, associated with specific mutations. Ongoing RNAseq analysis will further characterize the molecular changes associated with each mutation, while future lipidomic experiments will quantify PI(3)P and PI(3,5)P2 levels. By integrating these datasets, we aim to build a comprehensive model of *FIG4*-related disorder pathogenesis and identify critical dysregulated pathways, ultimately paving the way for novel therapeutic approaches, such as small-molecule inhibitors or gene-based therapies.

RÉSUMÉ 138 - Exploring T Cell-Microglia interaction mediated by ICAM-1 in Multiple Sclerosis

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Context: Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Activated microglial/myeloid cells and infiltrating T cells are found in chronic active lesions in MS, suggesting a potential for T cell-microglia interactions. Our team found that expression of cell adhesion molecule ICAM-1, implicated in tissue retention, is elevated on peripheral and CNS-infiltrating T cells in MS. Its main ligand LFA-1 is upregulated on human microglia in MS lesions. We hypothesize that harmful interactions between T cells and microglia in MS sustain chronic CNS-compartmentalized inflammatory processes, and that ICAM-1 mediates such interactions.

Methods: Primary human microglia from rapid autopsy brain material were co-cultured with autologous or allogeneic CD4+ and CD8+ T cells (n=3). T cells were pretreated with ICAM-1 blocking antibody or an isotype control prior to co-culture (n=2). We investigated cell-cell interactions *in vitro* using live imaging to analyze T cell and microglia/CNS myeloid cell behavior in MS.

Results: We found that 90% of human CD4T cells and 55% of CD8 T cells can make prolonged contacts (>15 minutes) with autologous primary microglia *in vitro*. Autologous and allogeneic CD4 T cells made 6 contacts on average during a 30-minute period. Autologous CD8 T cells made 19 contacts vs 10 for allogeneic CD8 with microglia during the same period. These contacts are associated with more static behavior for autologous CD4 and more scanning behavior for autologous CD8 T cells. Prolonged contacts were associated with altered speed, arrest coefficient and meandering index, suggesting biologically meaningful interactions. Blocking ICAM-1 on T cells before co-culture preserved T cell speed.

Conclusion: These preliminary data suggest that human autologous T cells and microglia can form prolonged contacts and that ICAM-1 contributes to modulating T cell-microglia interactions. This project is supported by the Faculty of Medicine at University of Montreal, MS Canada and CIHR

RÉSUMÉ 140 - Étude de biais des réseaux d'estimation de pose pour l'analyse de la marche

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Les réseaux d'estimation de pose (EP), basés sur l'apprentissage profond permettent d'estimer la position des centres articulaires (CA) d'une personne à partir d'une image. Ils représentent ainsi une potentielle alternative aux méthodes traditionnelles d'analyse de la marche (fluoroscopie, OMU etc.) qui s'avèrent coûteuses. Ces réseaux sont généralement entraînés sur des bases de données publiques (comme COCO), où les CA ont été manuellement positionnés. Des erreurs ont été observé entre les CA prédits par ces modèles et ceux donnés par les méthodes traditionnelles. La cause de ces erreurs reste cependant peu étudiée et le nombre de réseaux choisis dans les études est généralement restreint. L'objectif de cette étude est donc d'analyser l'impact du choix du réseau d'EP sur les prédictions des CA et de définir la cause des erreurs.

Dix-neuf participants ont été recrutés pour marcher pendant 45 secondes sur un tapis roulant. Ils portaient le système KneeKG, synchronisé avec une caméra vidéo, ce qui nous a permis de connaître la position de leur CA, notamment au niveau de la hanche, du genou et de la cheville. Nous avons ensuite sélectionné cinq réseaux d'EP: OpenPose, ViTPose, HRNet, SimpleBaseline2D et RTMPose entraînés sur COCO pour prédire les trois CA précédents.

On remarque que dans 85% des cas les modèles placent le genou plus haut que sa position réelle. Les cinq modèles produisent donc tous un biais. Nous avons donc décidé d'entraîner SimpleBaseline2D avec les données de 12 de nos sujets et avons constaté que ce biais tend à disparaître et que l'erreur moyenne pour la hanche passe de 8,25 à 6,51 pixels.

Notre étude montre que les modèles entraînés avec des données publiques présentent un biais mais qu'il est possible de le corriger en réentraînant ces modèles avec une quantité restreinte de données de qualité.

Organismes subventionnaires: CRSNG, MEI, FRQNT

RÉSUMÉ 141 - Microfluidics based culture and treatment of micro-dissected tissues, a novel ex vivo models to predict clinical response to carboplatin-paclitaxel chemotherapy in high-grade serous ovarian cancer patients

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Introduction: Ovarian carcinomas are initially a largely asymptomatic diseases and thus frequently diagnosed at an advanced stage. Current treatment for this often-lethal gynecological cancer is a combination chemotherapy based on carboplatin and paclitaxel either before or after extensive resection surgery. While initial response to chemotherapy is high, approximately 20% of patients will demonstrate innate resistance to the chemotherapeutic regimen causing severe side effects without appreciable clinical benefit. Therefore, a main challenge in ovarian cancer research remains to identify patients with resistant or refractory disease before starting treatment.

Methods: To predict treatment response and adapt therapeutic strategies for each patient, we have developed a new *ex-vivo* tumor-derived model as a tool for personalized medicine. In brief, micro-dissected tissues (MDTs) are generated from patient's ovarian tumors, then cultured and treated in microfluidic devices within a window of time suitable for clinical decision making. Response to drug is monitored via Ki67 expression for proliferation cells in epithelium and cleaved caspase-3 to assess apoptosis.

Results: By comparing response biomarker expression in treated and non-treated MDTs, we classified *ex vivo* tumor response as either resistant or sensitive. The designation is subsequently compared to the observed patient clinical response as determined up to 6 months after the end of treatment.

In 2 patients with ovarian carcinosarcoma detected at the same stage, we observed significantly higher expression of Ki67 in epithelial cells after drug treatments in MDT from clinically refractory patient. We are presently extending the analysis to optimize discrimination thresholds for biomarkers and achieve statistical significance.

Conclusion: Our study provides initial promising results for the use of microfluidics-based *ex vivo* testing as a predictive tool for treatment response of ovarian cancer patient.

This research project is funded by Miso Chip Company

RÉSUMÉ 142 - Baseline Neurological Morbidity Assessment in Adult Patients with Sickle Cell Disease: The Montreal Brain-SCD Cohort

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Background: Individuals with sickle cell disease (SCD) face significant risks of stroke, vascular brain lesions, and cognitive impairment. Data on adult cohorts are limited, and the effect of disease-modifying treatments on these neurovascular complications remains unclear. In 2021, a multidisciplinary neurology-hematology clinic was established at the Centre Hospitalier de l'Université de Montréal (CHUM) to address this gap. This study aims to evaluate the prevalence of symptomatic stroke and cognitive impairment in the Montreal-Brain-SCD cohort and assess the impact of the specialized clinic on diagnosing cognitive comorbidities.

Methods: This prospective study at CHUM is creating a database of SCD patients aged 18 and older with various genotypes who had at least one visit between September 2021 and June 2024. Symptomatic stroke is defined as cerebral infarction or intracranial hemorrhage with neurological deficits. Cognitive disorders are diagnosed based on criteria from the International Society of Vascular Behavioral and Cognitive Disorders (VasCog), including major cognitive disorder (MCD), mild cognitive disorder, and attention disorders, which encompass both general attention difficulties and formal attention deficit disorder (ADD).

Findings: The study involved 292 adults with SCD, median age 32 years, 57% female; 62% were on hydroxyurea, 20% on chronic transfusions, and 6% received both treatments. Prior to clinic assessment, 4% had a confirmed history of stroke, 1% had MCD, and 5% had ADD. Post-assessment, MCD diagnoses increased significantly to 5%, with mild cognitive disorder identified in 6% of patients. ADD diagnoses rose to 14%. Stroke prevalence increased with age, and cognitive disorders were more common in older patients. A significant association was found between prior stroke and cognitive disorders.

Interpretation: The study highlights a high prevalence of stroke and cognitive disorders in adults with SCD, revealing an initial underdiagnosis. It underscores the need for comprehensive neurological evaluations, particularly in those with a history of stroke.

RÉSUMÉ 143 - Améliorer la reconnaissance des métastases hépatiques du cancer colorectal par les lymphocytes T et la capacité d'expansion ex-vivo des CD8+ anti-tumoraux pour des fins immunothérapeutiques

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Introduction: Les cancers solides représentent 90% des décès liés au cancer et les métastases hépatiques du cancer colorectal demeurent résistantes aux immunothérapies. Les études en mélanome révèlent que 50% des patients bénéficient des transfusions de lymphocytes T intra-tumoraux (TIL), menant à son approbation dans plusieurs pays. Les faibles réponses en cancers gastro-intestinaux nous incitent à améliorer l'expansion *ex-vivo* des TIL réactifs aux néoantigènes pour minimiser leur épuisement cellulaire.

Disposant de 23 tumeurs avec TIL et néoantigènes caractérisés, nous testerons différentes conditions de culture *in vitro* pour favoriser un phénotype pré-épuisement.

Méthodes standards: - Isolement des TIL : fragments tumoraux en G-REX avec IL-2 pendant 14-28 jours. - Protocoles d'expansion rapide (REP) des TIL : milieu enrichi en IL-2 et anti-CD3 (OKT3) avec des cellules nourricières irradiées.

Nous évaluons diverses conditions d'expansion, notamment la supplémentation en inosine, d'agonistes CD28 et CD137 pour costimulation, la réduction des concentrations d'IL-2 ou remplacement par HT9 (agoniste partiel) et l'ajout de cytokines activant STAT3. Notre analyse inclut cytométrie en flux, séquençage du TCR, séquençage d'ARN messager, analyses épigénétiques (ATAC-seq) et tests de prolifération cellulaire.

Résultats: Nos travaux, suivant les protocoles standards, démontrent que l'expansion ex-vivo des TIL est possible dans 80% des cas, avec une réactivité variable (5% à 85%) et une prédominance de CD4+ (*helper*) vs CD8+ cytotoxiques. L'épuisement des CD8+ est notable, possiblement dû à l'IL-2. Nos expériences en cours testent la supplémentation en inosine lors des REP, et son impact sur le phénotype des TIL reste à évaluer.

Conclusion: Peu d'études s'intéressent au transfert adoptif de TIL en cancers gastro-intestinaux et encore moins à l'échelle clinique. Il est donc essentiel de viser à développer produit cellulaire TIL de haute qualité. De nombreuses options, applicables en clinique, restent à encore à explorer pour améliorer la *fitness* métabolique des TIL tant au niveau transcriptionnel qu'épigénétique.

RÉSUMÉ 144 - Understanding how itaconate regulates antiviral immunity during OV therapy/ Comprendre comment l'itaconate régule l'immunité antivirale lors de la thérapie de Virus Oncolytiques

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Les virus oncolytiques sont une piste de futur traitement contre le cancer et parmi lesquels se trouve VSV,un rhabdovirus.Le métabolisme des cellules est l'une des clés à leur développement.On y trouve l'itaconate, un métabolite dérivé du cycle de Krebs produit en haute quantité chez les cellules tumorales et régulant le système immunitaire d'autres cellules.Sachant que l'itaconate,par son gène irg1,est induit par la réponse interféron et que VSV est sensible à cette dernière, nous hypothésons qu'il jouerait un rôle antiviral sur le virus, rendant le traitement moins optimal.En ciblant la production d'itaconate, nous pensons augmenter la replication du VSV et améliorer son efficacité.Pour caractériser la production d'itaconate par les cellules cancéreuses ainsi que ses effets sur la réplication de VSV,une quantification de cette dernière chez des cellules tumorales humaines et murines infectées par VSV-Δ51-YFP sera effectuée par GC-MS.Elle sera précédée d'une analyse d'induction du gène irg1 par Western Blot et RT-qPCR.Une infection par d'autres virus sera également analysée.L'effet du métabolite sur les différentes lignées cellulaires sera observé par microspcopie à fluorescence.Les effets de l'itaconate sur l'immunité antivirale via la voie JAK/STAT seront étudiés par Western Blot ou Immunofluorescence tandis que sa production par les cellules tumorales et son effet sur leur métabolisme seront déterminés par SITA,SeaHorse analysis et profilage métabolique.Des modèles murins seront utilisés pour déterminer l'impact de l'itaconate sur le microenvironnement tumoral pendant la virothérapie.Son impact sur la réponse TCD8+ sera également étudié par cytométrie en flux.Les résultats exposent une augmentation par 1000 de la production d'itaconate chez des cellules murines CT26 infectées au VSV comparées au non-infectées.On observe également par RNA-seq et Western Blot,qu'*irg1* est l'un des plus exprimés chez les cellules infectées et est y fortement induit.Cela est également observée chez différentes lignées cancéreuses.Mieux caractériser la production de l'itaconate permettrait d'optimiser la thérapie oncolytique.

CIHR, ICM, CR-CHUM

RÉSUMÉ 145 - Bénéfices subjectifs perçus de l'utilisation du cannabis non-thérapeutique chez les personnes avec épilepsie.

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Introduction: Plusieurs études suggèrent qu'une majorité de personnes atteintes d'épilepsie consomme du cannabis non-thérapeutique (CNT; i.e., sans supervision médicale), principalement en se fondant sur ses propriétés anti-crises, malgré le manque de données probantes quant aux bienfaits du CNT sur l'épilepsie. Le CNT, souvent riche en THC et faible en CBD, est associé à des effets délétères sur la santé mentale. Considérant les potentiels effets nocifs du CNT, il est pertinent de mettre en lumière les bénéfices perçus de l'utilisation du CNT en épilepsie afin de mieux déterminer les corrélats associés à son usage.

Méthode: Un total de 100 personnes avec épilepsie a rempli un questionnaire portant sur les bénéfices subjectifs perçus du cannabis sur le contrôle des crises, la motivation et la perception des effets positifs/négatifs de l'usage du CNT, ainsi que des questionnaires évaluant la présence de symptômes dépressifs et anxieux.

Résultats: Au cours des 12 derniers mois, 29% des participants ont consommé du cannabis, avec une consommation plus fréquente chez les hommes (42%) comparativement aux femmes (19%), et principalement pour les motivations récréatives (48%). Parmi les 23% de participants ayant consommé du cannabis au cours des 3 derniers mois, 35% considèrent que le CNT aide au contrôle des crises d'épilepsie, alors que seulement 7% sont en désaccord avec cette affirmation. Concernant la perception des effets positifs du CNT, le sommeil arrive en tête (21%), suivi par l'épilepsie (13%) et la santé mentale (13%), bien que ce bénéfice perçu ne soit pas corroboré par les questionnaires sur la santé mentale standardisés. Les effets négatifs sont perçus principalement sur la cognition (12%) et la sphère travail/étude (14%).

Discussion: Les résultats ne montrent pas de bénéfices significatifs du CNT, malgré des ressentis positifs chez certains. Cela suggère que les bénéfices perçus pourraient être liés à un effet placebo plutôt qu'au cannabis.

RÉSUMÉ 147 - Les souris C57Bl/6 contrôlent efficacement l'infection par l'assemblage A de Giardia duodénalis.

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Introduction: *Giardia duodenalis* (GD) figure parmi les parasites intestinaux les plus répandus. Ses assemblages A et B, agents zoonotiques capables d'infecter humains et animaux, peuvent provoquer un état asymptomatique avec une colonisation chronique de l'intestin induisant plusieurs séquelles intestinales et extra intestinales liées à une altération du système immunitaire. Nous proposons de développer un modèle murin afin de caractériser la réponse inflammatoire et immunitaire des individus infectés par Giardia. Nous émettons l'hypothèse que l'infection de souris C57Bl/6 avec des kystes de GB permettra de reproduire les symptômes classiques de la Giardiose.

Méthodes: L'assemblage A, historiquement le plus utilisé dans les études *in vitro*, est cultivé pour produire des kystes servant à l'infection de souris C57Bl/6. Au sacrifice, entre 5 et 21 jours post infection, la charge parasitaire dans les selles est quantifiée par microscopie, les profils cytokiniques circulants sont déterminés par multiplex, les cellules immunitaires isolées à partir de la rate, sont caractérisées en cytométrie de flux et les lésions intestinales évaluées par score histologique.

Résultats: Les souris, qu'elles soient infectées à une ou deux doses, n'excrètent pas de parasite et ne présentent aucune diminution de l'état général ni lésions intestinales. Cependant, à deux doses nous observons des modulations de certaines cytokines (CCL5, LIF, IL-4, IL-7 et TNFα) et une variation transitoire dans la composition des populations de lymphocytes B et T, 5 jours après l'infection. Ceci indique une réponse immunitaire élicitée par la présence d'antigènes.

Discussion / Conclusion: L'absence de charge parasitaire et de signes cliniques et histopathologiques ainsi que les changements immunologiques transitoires observés chez les souris infectées suggère que celles-ci sont en mesure de contrôler l'infection à l'assemblage A efficacement. L'utilisation de l'assemblage B et/ou l'administration d'antibiotiques permettront de déterminer si cette résistance dépend de l'assemblage ou d'un effet protecteur du microbiote.

RÉSUMÉ 148 - Analyse descriptive préliminaire de la cohorte TRENDS sur les PUDI

Ahmed Thiam[1], Gerardo Martinez[1], Lucie Lebranchu[1], Tarek Lajnef[1], Sarah Larney[1], Valérie Martel-Laferrière[1]

[1]CRCHUM

Introduction: L'usage de drogues injectables est un facteur de risque majeur pour plusieurs infections graves, notamment les infections de la peau et des tissus mous (IPTM), les infections ostéo-articulaires, et l'endocardite infectieuse. Le projet TRENDS vise à développer des algorithmes pour identifier les personnes utilisant des drogues injectables (PUDI) à partir des données administratives de santé afin d'améliorer la prévention et la gestion de ces complications. Cette analyse préliminaire fournit un aperçu descriptif de la population étudiée.

Méthodes: La cohorte inclut tous les patients admis à l'urgence du CHUM entre 2012 et 2022 pour une infection potentiellement liée aux drogues. Les infections d'intérêt ont été identifiées à partir du champ de diagnostic ER disponible dans Clinibase ADT, intégré à CITADEL.

Résultats: La cohorte comprend 27249 épisodes de soins, incluant 18429 patients uniques. Les IPTM représentaient 86% des cas (23542 épisodes), avec la cellulite étant la plus fréquente (85% des IPTM), suivi des abcès (14%). Les infections ostéo-articulaires étaient moins courantes avec 2428 épisodes, l'ostéomyélite était prédominante (1549 cas). L'endocardite infectieuse a été observée dans 415 épisodes.

L'âge médian des patients variait selon l'infection: IPTM (55 ans, IQR : 39-68), infections osseuses (63 ans, IQR : 52-73) et endocardites (65 ans, IQR : 42-77). Les hommes étaient plus représentés dans l'ostéomyélite (70%) et l'arthrite septique (61%), tandis que les femmes étaient plus touchées par la myosite (51%). Environ 7638 épisodes étaient associés à une infection ou une colonisation à Staphylococcus aureus résistant à la méthicilline (SARM), et 542 à une infection par le VIH.

Conclusion: Cette analyse met en évidence l'ampleur des IPTM, des infections ostéo-articulaires et de l'endocardite, soulignant les disparités démographiques et l'importance d'utiliser les bases de données administratives pour mieux comprendre cette problématique.

RÉSUMÉ 149 - Short-term retrospective comparative study between 45 µm and 63 µm lumen gel microstents in uncontrolled open-angle glaucoma

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Introduction: Minimally invasive glaucoma devices (MIGS) were invented to offer a safer alternative to traditional filtering surgeries (Ahmed, Baerveldt) and more effective than laser treatments and drops. This study aims to compare the surgical results of two MIGS, XEN-45 and XEN-63, which differ by their diameter, respectively 45 and 63 µm.

Methods: This is a retrospective cohort study of patients with uncontrolled open-angle glaucoma implanted with XEN-45 and XEN-63. The primary endpoint is surgical success, i.e. intraocular pressure (IOP) between 6 and 21 mmHg with at least 20% reduction, with (qualified) or without (complete) glaucoma drops. Surgical failure is defined as an IOP greater than 21 mmHg during 2 consecutive follow-up visits, less than 20% reduction in IOP, additional surgery as well as loss of light perception. Secondary outcomes included success rates for IOP between 6-15 mmHg and 6-18 mmHg, changes in IOP, changes in number of IOP-lowering drops, and post-operative complications. The data was analyzed using GraphPad Prism 10.3.

Results: 82 patients have been implanted with XEN-45 and 15 patients with XEN-63 so far. XEN-45 achieved a complete success rate of 45% and a qualified success rate of 63%, while XEN-63 achieved a complete postoperative success rate of 57% and a qualified success rate of 92%.

Conclusion: XEN-63 demonstrated better results than XEN-45 in reducing IOP and achieving surgical success. Studies including a larger sample of patients and with longer follow-up are needed to further explore the results of this study.

RÉSUMÉ 150 - Patient Identification in Epileptic Monitoring Units for Seizure Detection: A Machine Learning-Enhanced Computer Vision Approach

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Introduction: Epileptic seizures pose substantial risks to patient safety and can lead to neurological damage if uncontrolled. Continuous monitoring and reliable seizure detection are crucial for timely intervention. While electroencephalography is effective, it's limited in outpatient settings. Video monitoring offers an alternative, but occlusions and complex scenes create challenges. Training seizure-detection algorithms based on video recordings is often biased by staff movement and other elements. Isolating patients is key to extracting relevant features. This project aims to develop a fully automated algorithm to detect and track patients, serving as a preprocessing step for seizure detection based on patient motion.

Methods: 1) Database: We used a subset of the CHUM Epilepsy Monitoring Unit (EMU) database, comprising 133 patients, 485 clips, and 1598 frames from four EMU rooms; **2) Labeling**: Patients were manually labeled using LabelIMG with bounding boxes around each patient in every frame; **3) Data augmentation:** Color adjustment, scaling, flipping, and other techniques were applied to enhance variability; **4) Data split:** Data was divided into 70% training, 20% validation, and 10% testing, ensuring no patient overlap between sets; **4) Model Training**: We used four pre-trained YOLOv8 models for retraining; **5) Fine-tuning:** Hyperparameters were optimized across 100 epochs, adjusting batch size, image size, learning rate, dropout, and detection parameters; **6) Performance Evaluation:** Performance was evaluated in terms of precision, recall, F1-score, and accuracy.

Results: The model effectively tracked patients across various scenarios, including night recordings, occlusion. It achieved an accuracy of 94%, a recall of 96.03%, and a precision of 96.64%.

Discussion / Conclusion: Results show potential to identify patients in an EMU setting. Building on this, the seizure detection algorithm will extract features from the patient's sub-frame to train a deep learning model. This approach aims to minimize biases and will enable seizure detection through continuous analysis.

Funding: Savoy Foundation

RÉSUMÉ 151 - Heterogeneity in Mortality Risk Prediction: A Study of Vulnerable and Frail Adults in the Canadian Longitudinal Study on Aging

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Introduction: Mortality prediction models play a vital role in healthcare, guiding decision-making and improving patient outcomes. While general models offer broad applicability, their accuracy in vulnerable subpopulations is not well described. Using the Canadian Longitudinal Study of Aging (CLSA), we sought to evaluate the performance of prediction models in five subgroups (age, frailty, multimorbidity, cognitive function, and functional impairment).

Methods: We analyzed data from 49,266 participants. Cox proportional hazard regression with LASSO was used for variable selection and developing the mortality prediction model. Model performance was assessed with discrimination, calibration, and Brier score for overall performance. Subgroups were defined by age, frailty, multimorbidity, cognitive function and functional impairment, with model performance evaluated within each subgroup.

Results: Our cohort included 49,266 participants (mean age 63 years, SD 10; 51% female). Frailty was present in 5.2% and 21% had at least two chronic conditions. During the median follow-up of 5.96 years (IQR 1.27), 3672 participants died. The general mortality prediction model showed strong overall performance with a c-index of 0.82 (95% CI 0.80-0.84) and a Brier score of 0.036 (95% CI 0.032-0.040). However, significant variability was noted across subgroups. Notably, the model tended to underestimate risk in frail individuals (c-index 0.73, 95% CI 0.71-0.75), those with cognitive impairment (c-index 0.79, 95% CI 0.74-0.85) and multiple chronic conditions (c-index 0.76, 95% CI 0.75-0.78). The model's performance varied across risk categories, with lower accuracy in higher-risk groups (c-index: 0.59 (95% CI: 0.55-0.62), Brier score: 0.22 (95% CI: 0.20-0.24)).

Conclusion: Our findings reveal significant performance variability of a general mortality prediction model across different subpopulations. This underscores the limitations of a one-size-fits-all approach to mortality risk prediction and highlights the need for better predictive models that account for subpopulation-specific characteristics to enhance prediction in diverse aging populations.

RÉSUMÉ 152 - EXPLORING THE ROLE OF THE ACETYLTRANSFERASE TIP60 (KAT5) DURING DNA DAMAGE-INDUCED CELL FATE DECISIONS

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Introduction: Senescent cells are characterized by multiple senescence-associated (SA) phenotypes including a pro-inflammatory secretory phenotype (SASP). Multiple signaling pathways contribute to the regulation of SASP factors including the DNA-damage response (DDR), which can modulate the activity of NF-κB, the master transcription factor controlling the SASP. TIP60 (KAT5) can acetylate multiple histone and non-histone proteins involved in the DDR, DNA repair, p53 signaling, NF-κB activity and general transcription.

Objective: Our objective is to test the idea that TIP60 modulate a dynamic cell fate decision program in response to DNA damage, which include a choice between senescence and apoptosis. We will clarify the regulation of senescence, particularly SASP and other senescence hallmarks by TIP60 in the context of DDR.

Methods: Using lentiviruses, we have overexpressed and genetically depleted (shRNA) TIP60. Senescence was induced using irradiation (DNA damage). We have characterized SA phenotypes including proliferation arrest using live-imaging, SA-beta-galactosidase activity, genomic instability, and persistent DNA Damage Foci (DDF) using immunofluorescence of 53BP1/γ-H2AX, telomeric DDF (Telomeric FISH) and SASP (ELISA for Il-6/Il-8). We have also performed transcriptome and functional analysis to understand the mechanism involved in TIP60 regulation under the influence of senescence and DDR.

Results: We find that global histone acetylation decreases as cells enter senescence. We have observed that the genetic depletion of TIP60 has a negative impact on IL-6 secretion and others SASP factors (IL-8, MCP-1, and IL-1), genomic instability and SAPA but increased 53BP1/γ-H2AX accumulation induced by irradiation. We find opposite effects on SASP, SAPA and DDR when TIP60 is overexpressed.

Impact: Our data refine the specific SASP regulatory network and elucidate new ways to manipulate senescence phenotypes, which can further be employed to generate therapeutics targets for cancer treatment response and aging-related pathologies.

RÉSUMÉ 153 - Modalités d'inscription à un médecin de famille: facteurs prédictifs et association avec l'utilisation des services d'urgence

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Introduction: Au Québec, près d'un quart de la population ne dispose pas d'un médecin de famille. Pour centraliser les demandes d'inscription à un médecin, le Guichet d'Accès à un Médecin de Famille (GAMF), une liste d'attente centralisée, a été mis en place à l'échelle provinciale. Les médecins peuvent cependant toujours recruter des patients hors GAMF, ce qui peut encourager des pratiques d'écrémage et exacerber les iniquités. Cette étude vise à : 1) déterminer les facteurs prédictifs de la modalité d'inscription (GAMF vs hors GAMF) ; 2) examiner l'association entre cette modalité et le recours aux services d'urgence.

Méthodes: Cette étude de cohorte populationnelle inclut les patients adultes inscrits auprès d'un médecin de famille entre avril 2017 et juin 2021 et utilise les données administratives de la RAMQ et du MSSS. Un modèle de forêt aléatoire a évalué l'importance relative des facteurs prédictifs de la modalité d'inscription. Un modèle binomial négatif a estimé l'association entre la modalité et les visites non-prioritaires aux urgences dans l'année suivant l'inscription.

Résultats: L'année d'inscription est apparue comme le principal facteur prédictif de la modalité d'inscription, suivie de l'âge, de la ruralité et de l'utilisation antérieure des services de santé. Les résultats indiquent que le GAMF s'est établi avec le temps, et que les médecins de famille qui recrutaient en dehors du GAMF le faisaient surtout en milieu urbain, en privilégiant les patients plus jeunes et en ayant des besoins de santé moins importants. La modalité d'inscription était associée à une réduction des visites non-prioritaires à l'urgence, après ajustement des facteurs sociodémographiques et de santé, suggérant l'influence de variables non mesurées.

Conclusion: Le GAMF semble prometteur pour réduire les iniquités d'accès aux soins. Il est crucial de soutenir et mettre en place davantage des politiques visant à augmenter la participation au GAMF et à limiter les pratiques d'écrémage.

RÉSUMÉ 154 - Exploration des biomarqueurs pour évaluer le vieillissement prématuré induit par la thérapie anticancéreuse

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Introduction: Certains survivants de cancer présentent des morbidités associées à l'âge, semblable à un vieillissement prématuré. Ces personnes nécessitent très souvent un suivi à long terme avec de nombreux bilans de santé. Identifier des biomarqueurs d'âge biologique s'avère nécessaire. Le vieillissement étant segmentaire, chaque organe peut être évalué séparément. Le but est d'évaluer les biomarqueurs d'immunosénescence pour la mesure du vieillissement prématuré.

Méthodes: À partir d'ADN génomique de 248 survivants de leucémie aiguë (LAL), de 488 patientes de cancer de l'ovaire et de 281 participants contrôles, nous avons mesuré un marqueur d'immunosénescence nommé TREC par PCR. Ensuite, des souris sont traitées par IR ou au carboplatin/paclitaxel et suivies en mesurant les TREC.

Résultats / Discussion: Les analyses ont montré un vieillissement fonctionnel très accentué du thymus associé aux marqueurs inflammatoires chez les jeunes survivants de LAL. Ces résultats suggèrent la présence d'un *inflammaging,* une des conséquences de l'immunosénescence. Cependant, l'accentuation du vieillissement n'est pas de la même ampleur que pour le cancer de l'ovaire où un sous-groupe de patientes est affecté. Cela pourrait être le fait de la différence d'âge, du type de cancer ou des modalités de traitements. Plus intéressant, les niveaux de TREC bas sont associés à un risque accru de mortalité. Des résultats préliminaires dans un modèle murin confirment que la sénescence fonctionnelle thymique est concomitante à une forte expression de marqueurs de sénescence.

Conclusion: Les survivants de cancer liquide et de cancer solide souffrent différemment d'immunosénescence prématurée. L'irradiation semble en être une des causes chez les LAL. L'immunosénescence pourrait cependant être un des médiateurs dans la survenue du cancer, mais aussi des effets adverses des traitements. L'identification de cibles moléculaires afin de moduler les effets de traitements anticancéreux est nécessaire.

Fundings: ICM Bal masqué, SRC, PCBF, Canderel, Programme de biologie moléculaire

RÉSUMÉ 155 - Hyperemesis gravidarum and risk of severe maternal hepatic morbidity

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Introduction: Hyperemesis gravidarum is a leading cause of morbidity during pregnancy. Our objective was to examine the association between hyperemesis gravidarum and severe maternal hepatic morbidity in a large population-based cohort.

Methods: We conducted a retrospective cohort study of hospital deliveries between 1989 and 2021 in Quebec, Canada. We used discharge data from the Maintenance and Use of Data for the Study of Hospital Clientele registry. The main exposure was hyperemesis gravidarum (mild, mixed, severe). The main outcome was severe maternal hepatic morbidity during pregnancy or within 42 days postpartum. Severe maternal hepatic morbidity included life-threatening conditions such as acute fatty liver disease and hepatic failure. We used log-binomial regression models to calculate risk ratios and 95% confidence intervals (CI) for the association between hyperemesis gravidarum and severe maternal hepatic morbidity.

Results: This study included 2,569,269 pregnancies, 17,735 of which were affected by hyperemesis gravidarum. Rates of severe hepatic morbidity were greater for patients with hyperemesis gravidarum compared with no hyperemesis gravidarum (112.8 vs. 16.6 per 100,000 pregnancies). Patients with hyperemesis were 6.8 times more likely to have severe hepatic complications overall. In adjusted models, hyperemesis gravidarum was associated with 5.39 times greater risk of acute fatty liver disease (95% CI 2.51-11.57) and 7.01 times greater risk of hepatic failure (95% CI 3.97-12.39) compared with no hyperemesis.

Conclusion: This study found that hyperemesis gravidarum is associated with severe maternal hepatic morbidity, including acute fatty liver disease and hepatic failure at delivery or up to 42 days postpartum.

Funding: Canadian Institutes of Health Research, Fonds de recherche du Québec-Santé

RÉSUMÉ 157 - Evaluation of beta cell function and connectivity in mice islets

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Background: The adult beta cell is highly specialized and long-lived, and deploys epigenetic control to maintain its stability over time. These mechanisms may also be important to achieve beta cell functional heterogeneity, which is important to ensure normal glucose-stimulated insulin release. Our objective is to study beta cell function using the Ins-Cre:GCaMP6^{LoxP} mouse model in order to visualize calcium response to glucose stimuli.

Methods: We recorded calcium waves using confocal microscopy, extracted the signal in ImageJ and analysed connectivity within the islet in Matlab. We additionally transduced the islets with an adenovirus expressing Photo Activatable-mCherry. Highly connected cells were then labelled by photoexcitation after imaging and analysis, and immunostaining was carried on.

Results: Our analyses revealed that the 25% best connected cells show increased synchronicity with the whole islet calcium response compared to the 25% worst connected beta cells. In addition, best connected beta cells have longer duty cycles and peak width than worst connected cells. In contrast, no difference was seen in the average fluorescence, peak amplitude or the incremental area under the curve between the two groups. Our preliminary results shows that highly connected cells seem to be enriched in CD24, a cell surface marker that has been associated a subpopulation of beta cells with higher insulin content and release, mitochondria number and trimethylation on lysine 27 of histone 3 (H3K27 me3), which was named “Beta Hi”.

Conclusion: Our study suggest that highly connected beta cells are more active and synchronous than worst connected beta cells and may belong to the “Beta Hi” subpopulation.

Funding: These studies were supported by the Wellcome Trust Investigator Award, UK MRC Programme grant. Diabetes UK Project grant, CRCHUM start-up funds, an Innovation Canada John R. Evans Leader Award and NIH-NIDDK project grant to Dr. Rutter and FRQS post-doctoral fellowship to GO

RÉSUMÉ 158 - Epileptic Seizure Detection Based on Electromyography Signals and Machine Learning

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Introduction: Epilepsy is a neurological condition characterized by unpredictable seizures due to abnormal neuronal discharges. Uncontrolled seizures are associated with cognitive impairment and elevated mortality rates. While electroencephalography is the most suitable method to detect seizures, it is limited to inpatient settings. Consequently, there is growing interest in developing wearable seizure-detection devices that generate alarms. This project aims to develop a real-time seizure-detection algorithm based on electromyography (**EMG**) signals recorded with miniaturized wearable sensors.

Methods: Data Acquisition: Six tonic-clonic seizures from five patients were recorded using eight miniaturized EMG sensors placed on the left and right trapezius, deltoid, biceps, and tibialis anterior muscles. **Pre-processing:** Signals underwent high-pass and notch filtering.

Feature extraction: Time-domain and frequency-domain features were extracted using 5-second sliding windows with 50% overlap.

Classification: A random forest classifier was trained to identify seizure epochs based on single-channel recordings. A nested cross-validation was implemented, leaving one patient out per fold (5 outer folds, 4 inner folds). To mitigate dataset imbalance, only one hour of EMG recording surrounding the seizures was used.

Results: The average sensitivity across all muscle channels was 58.7% [20 - 100%]. The highest performances were achieved by the left trapezius, right deltoid, and right biceps, detecting 4/4, 5/5, and 5/6 seizures, respectively, without producing false alarms. Conversely, the left tibialis anterior, right tibialis anterior, and right trapezius showed the lowest sensitivity, detecting only 2/6, 1/5, and 1/3 seizures. Of all channels, only the right trapezius and the left biceps generated false alarms, totaling 366 and 15 instances over 3 and 5 hours, respectively. The cause of these false alarms is currently under investigation.

Conclusion: While more data is necessary to identify the most relevant muscles to integrate into a seizure-detection system, our preliminary findings suggest that EMG could be a promising modality for wearable-based seizure-detection.

Funding: FRQS

RÉSUMÉ 159 - Le pronostic à long terme d'une réimplantation de kératoprothèse de Boston type I

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Introduction: La kératoprothèse Boston de type I (KPro1) est une cornée synthétique pour restaurer la vision en cas de cécité cornéenne. Bien que KPro1 puisse atteindre une acuité visuelle supérieure à 20/200, il comporte un risque d'échec. Cependant, la réimplantation d'un deuxième KPro1 offre une autre chance de restauration de la vision. Cette étude vise à évaluer les résultats à long terme des patients subissant une réimplantation de KPro1 après l'échec de l'implant initial.

Méthodologie: Cette étude rétrospective a analysé les données de 18 patients ayant subi deux implantations de KPro1 dans le même œil, avec une période de suivi moyenne de 8,82 ± 2,49 ans. Les critères d'évaluation primaire étaient le taux d'échec de l'implant et l'acuité visuelle lors du dernier rendez-vous de suivi.

Résultats: Le taux d'échec du deuxième KPro1 (11,11 % à 5 ans) était significativement inférieur à celui du premier KPro1 (88,89 % à 5 ans) (valeur $p < 0,0001$). 30,09 % et 24,07 % des patients avaient une acuité visuelle supérieure à 20/200 à 3 ans et 6 ans respectivement après le deuxième KPro1, ce qui était similaire durant leur première KPro1. Le taux de phtisie était supérieur durant le deuxième KPro1, mais les taux d'endophtalmie, de fonte cornéenne et d'extrusions étaient inférieurs durant le deuxième KPro1 par rapport au premier KPro1.

Discussion / Conclusion: La réimplantation KPro1 offre un moyen d'étendre une vision meilleure que 20/200 après échec du premier KPro1. L'exploration plus approfondie d'une réimplantation KPro1 avec une cohorte plus large permettra d'élucider les avantages et les risques associés.

RÉSUMÉ 160 - Senescence unveiled: a signature approach to treatment response in ovarian cancer patient avatars

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Introduction: High grade serous ovarian cancer (HGSOC) patients initially respond well to therapy, but subsequent treatment resistance and relapse demands further research to improve survival. HGSOC treatment induces DNA damage, which can lead to therapy-induced senescence (TIS), a stable proliferative arrest with opposing roles in cancer. A short-term positive relation between TIS and survival prompted the “One-Two Punch” clinical trial, where senescence is induced by treatment, then removed with senolytics to avoid late adverse effects. We aim to identify a treatment-response signature over time in patient-resembling models, uncovering early resistance factors and providing actionable targets to prevent relapse.

Methods: We developed patient-derived xenografts (PDX) mice from HGSOC patient tumors. PDX tumors harvested 3, 7, 10, 14 or 21 days post-treatment and matched patient samples underwent bulk RNA sequencing, RT-qPCR, single-cell multiplex immunofluorescence and ELISA. Findings were compared with public single-cell datasets of patients pre/post-treatment.

Results: We successfully derived 4 PDX from 4 HGSOC patients. Analyses revealed PDX closely mimic their matched patient, while also reproducing inter-patient heterogeneity. Early treatment-response pathways involved TIS or inflammation, confirming our hypothesis. A similar TIS/inflammation signature was found in post-treatment patient cancer cells from public datasets.

Conclusions: Our findings highlight pivotal roles for TIS and inflammation in HGSOC’s early treatment response. Ongoing efforts involve single-cell sequencing of ~200 HGSOC patients and models at various post-treatment timepoints. Resulting transcriptomic Atlas aims to offer the first exploration of HGSOC’s treatment-response signature over time, to expedite identification of targets with direct clinical relevance for improved patient survival.

RÉSUMÉ 161 - L’activité physique pendant la grossesse : Une opportunité manquée lors des consultations prénatales

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Introduction: Au cours des dernières décennies, les complications gestationnelles ont augmenté en association avec l'obésité maternelle et l’âge maternel avancé. Bien qu'il ait été démontré que l'activité physique (AP) pendant la grossesse a des effets bénéfiques sur la santé de la mère et de son fœtus, très peu de femmes font de l’AP tel que recommandé.

Objectif: Compte tenu de l'impact positif que les professionnels de la santé peuvent avoir sur les changements de mode de vie, le premier objectif de cette étude est de documenter l'information donnée par les professionnels de la santé aux femmes enceintes concernant la pratique de l'AP pendant la grossesse. Le deuxième objectif est d'évaluer le niveau d'activité physique des femmes enceintes au cours de leur premier trimestre de grossesse.

Méthodes : Un questionnaire a été administré aux femmes enceintes lors de leur première visite prénatale. Le questionnaire a été adapté du PPAQ auquel ont été ajoutées des questions sur leur dossier obstétrique et de nature sociodémographique et ethnoculturelle.

Résultats: À ce jour, 138 femmes suivies au CHUM ont été recrutées. Nos résultats préliminaires suggèrent que 60 % d’entre elles ne discutent pas d'AP avec leurs professionnels de la santé. Parmi celles qui en ont discuté, 31 % n'ont pas reçu d’informations sur les bénéfices de l’AP et 65 % n'ont reçu aucune recommandation quant à la pratique d'AP. En ce qui a trait au niveau d'activité physique de nos participantes, une dépense énergétique hebdomadaire moyenne d'environ 270 MET.h/semaine a été calculée.

Discussion / Conclusion: L'AP n'est pas systématiquement abordée lors de la première visite prénatale et, lorsque les professionnels de la santé discutent du sujet, ils donnent souvent aucune recommandation. Il est nécessaire d'améliorer la pratique clinique concernant les recommandations d'AP afin d'améliorer les issues de la grossesse.

Financement : EKSAP, CRRF, CRDM, Diabète Québec

RÉSUMÉ 162 - Le risque de décollement de la rétine après l'implantation d'une kératoprothèse Boston de type I : aperçus d'une revue de cas rétrospective

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Introduction: La kératoprothèse Boston type 1 (KPro1) est une cornée synthétique utilisée en cas de cécité cornéenne pour restaurer la vision. Bien que KPro1 puisse atteindre une acuité visuelle supérieure à 20/200, il est associé à des événements indésirables connus. Cette étude vise à examiner l'incidence du décollement de rétine (DR) suite à l'implantation de KPro1 et à identifier les facteurs de risque conduisant à cette complication.

Méthodologie: Cette étude rétrospective a analysé les données de 122 patients (140 yeux) ayant subi une implantation KPro1, avec une période de suivi moyenne de 7,58 ± 4,72 ans. L'intervention examinée était l'implantation de KPro1, le critère principal étant l'incidence de DR suivant l'implantation d'un KPro1 par rapport à des facteurs de risque tels que les données démographiques du patient, les données cliniques ou d'autres événements indésirables.

Résultats: L'indication la plus courante de KPro1 était l'aniridie (24,29%), et elle était également la plus associée aux DR (OR de 4,340 ; p=0,0022**). 5,33% des patients avaient un DR 12 mois après KPro1 et 20,10 % à 7,5 ans de suivi. Il n'y avait aucune différence en taux de DR entre les patients âgés de plus ou moins de 65 ans.

Discussion / Conclusion: L'aniridie était la plus associée au DR. Sinon, environ 80% des patients ne développent pas de décollement de rétine 7,5 ans après KPro1. Une plus grande prudence doit être accordée aux patients présentant une aniridie lorsqu'on envisage KPro1 en ce qui concerne le DR.



PRIX DE CONTRIBUTION À LA RECHERCHE PAVEL HAMET

1. Émile Lemoine

Machine-learning for the prediction of one-year seizure recurrence based on routine electroencephalography.
https://pubmed.ncbi.nlm.nih.gov/37542101/

2. Pedro De Oliveira Vianna

Comparison of Radiologists and Deep Learning for US Grading of Hepatic Steatosis.
https://pubmed.ncbi.nlm.nih.gov/37787678/

3. Alexia Piché

Assessing real-world implementability of a multimodal group-based tele-prehabilitation program in cancer care: a pragmatic feasibility study.
https://pubmed.ncbi.nlm.nih.gov/37965450/