kinase whose oncogenic actions are well-characterized, while Stat5a is a transcription factor whose activities are critical in attenuating the oncogenicity of Jak2. Following PRL stimulation, it was observed that hPRLrL/I co-expression induced approximately two-fold greater Jak2-Y1007/1008 phosphorylation (pJak2) compared to that induced by hPRLrL expression alone. Further, it was observed that hPRLrL/I co-expression induced ten-fold less Stat5a-Y694 phosphorylation (pY-Stat5a) than hPRLrL expression alone. These data indicate unchecked pJak2 activity may also be a contributing mechanism in the observed transformation. Overall, these results demonstrate that hPRLrI, alongside hPRLrL, is sufficient for transformation of normal breast tissue.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Liver Leptin Receptor Gene Network Moderates the Effects of Early Life Adversity on Anxiety and Depression Problems in Children and Adolescents

Randriely Merscher Sobreira de Lima, Ph.D. student[1], Barbara Barth, Ms, PhD student[2], Danusa Mar Arcego, PhD[2], Euclides José de Mendonça Filho, PhD student[1], Sachin Patel, Bachelor degree[3], Zihan Wang, Bachelor degree[3], Irina Pokhvisneva, Bachelor degree[3], Roberto Britto Sassi, PhD[4], Geoffrey B. C. Hall, PhD[5], Ana Paula Santana de Vasconcellos Bittencourt, PhD[6], Michael Joseph Meaney, PHD[7], Carla Dalmaz, PhD[1], Patricia Pelufo Silveira, MD,PHD[8].

[1]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [2]McGill, Montreal, QC, Canada, [3]Ludmer Centre for Neuroinformatics and Mental Health Douglas Hospital Research Centre, McGill University, Montreal, QC, Canada, [4]Mood Disorders Program, Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada, [5]Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, ON, Canada, [6]Universidade Federal do Espirito Santo, Vitória, Brazil, [7]McGill Univ, Verdun, QC, Canada, [8]McGill Univ, Montreal, QC, Canada.

SUN-722

Leptin is a hormone involved in the regulation of food intake, with receptors largely expressed centrally and peripherally, in structures like the hypothalamus and the liver. Beyond its well-known actions as an energy-balance regulator, leptin is linked to psychiatric disorders. Considering that the association between genetic and early environmental factors contributes to psychopathology, disruptions of leptin signaling could be a key mechanism in this interaction. To investigate this possibility, we created an expression-based polygenic risk score (ePRS) reflecting variations in the function of the LepR gene network in the liver and hypothalamus, and investigated its interaction with postnatal adversity on Child Behavior Checklist in 4 years old children (main cohort: MAVAN, N=137) and 17 years old teenagers (Replication Cohort: ALSPAC, N=2630). There is an interaction effect between adversity exposure and liver-based LepR-ePRS, increasing depressive and anxiety problems on the MAVAN cohort (β=78.16, p=0.02, β=83.77, p=0.01). In ALSPAC, the results were replicated, showing an interaction between adversity exposure and liver-based LepR-ePRS, increasing the depression score and somatic symptoms (β=24.65, p=0.005; β=33.51, p=0.009). No significant interactions were found using the hypothalamus-based LepR-ePRS (p>0.05), suggesting specificity for the liver LepR gene network to predict these behavioral outcomes. A parallel-independent component analysis showed relationships between the SNPs from the liver ePRS-LepR and gray matter density in cortical areas involved in emotion regulation (middle frontal gyrus, inferior parietal lobule and anterior cingulate). Finally, the relationship between gene and MRI components in this analysis is moderated by the history of early life adversity exposure. Enrichment analysis of the liver LepR co-expression network shows that these genes are related to biological processes including regulation of glucose transport, cholesterol metabolism and cellular glucose homeostasis, which indicates possible underlying mechanisms linking peripheral metabolism-related gene expression and the development of emotional symptoms. Our data supports the hypothesis that exposure to early adversity affects emotional behavior, and the liver LepR gene network is an important moderator of these effects. Further studies on development of emotional symptoms should consider metabolic markers to understand these complex phenotypes.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

STAT5A Regulation by Serine Phosphorylation in Breast Cancer

Alicia E. Woock, BS[1], Jacqueline M. Grible, BS[1], Patricija Zot, MD[2], J Chuck Harrell, PhD[1], Idowu Michael, MD-MPH[2], Charles V. Clevenger, MD,PHD[2].

[1]VIRGINIA COMMONWEALTH UNIV, Richmond, VA, USA, [2]VCUHS, Richmond, VA, USA.

SAT-139

The neuroendocrine hormone prolactin (PRL) and its cognate receptor (PRLr) have been implicated in the pathogenesis of breast cancer. PRL signaling relies on activating kinases such as the tyrosine kinase Jak2 and serine/threonine kinases ERK1/2, Nek3, PI3K, and AKT. In the canonical pathway of PRL signaling, Jak2 phosphorylates the transcription factor Stat5a at tyrosine residue 694 (pY694-Stat5a), preceding Stat5a nuclear translocation and transcriptional activity. However, Stat5a exists with functional duality as a transcription factor, having both pro-differentiative and pro-proliferative target genes. Other Stat family members (Stats 1, 3, and 6) have been shown to have transcriptional activity in the un-phosphorylated (upY) state, distinct from that of pY-Stat activity. This distinction (upY vs. pY) may underlie the duality of Stat5a, coupled with additional regulatory non-canonical post-translational modifications. Within this notion, Stat5a contains two serine residues, S726 and S780, whose phosphorylation are necessary for hematopoietic transformation. However, their functions in PRL-mediated breast cancer pathogenesis have not been examined. We hypothesize that