4cell, 8cell, morula, inner cell mass, trophoectoderm (TE) as well as six-week embryos by Nimble Gen Human DNA Methylation 3x729K CpG Island Plus RefSeq Promoter Array and compared the data with our published genome-wide DNA methylomes of human gametes and early embryos generated from in vivo maturation oocytes. We showed that IVM embryos show abnormal DNA methylation reprogramming pattern. By analyzing the abnormally reprogrammed promoters, we further found that IVM may affect the functions of demethylation related genes. Oocytes from IVM manipulation were tested with higher DNA methylation levels, and their abnormal methylated promoters mainly enriched in immune and metabolism pathways. Furthermore, we investigated the DNA methylation of TE, which was directly related with implantation process and revealed the abnormal methylated promoters were related with metabolism pathway too. Our data support that IVM may influence the DNA methylome of oocytes, which in turn affects the methylome of their embryos. However, due to the limited number of samples and the inability of the chip to cover all CpG sites, the results of this study require further research and validation.

Thyroid

THYROID DISORDERS CASE REPORTS I

Unplanned Pregnancy Post Thyroid RAI Ablation

Arpita Bhalodkar, MD1, Agustin Busta, MD2.
1Lenox Hill, Northwell, New York, NY, USA, 2Northwell Health, Inc., New York, NY, USA.

SUN-516

A patient’s pregnancy and fetus are at an increased risk for complications secondary to history of recent RAI ablation and maternal secondary hypothyroidism. A 31 year old female with a recent history of miscarriage presented with abnormal thyroid function tests and was history of low dose levothyroxine use. She complained of a 3 month history of extreme fatigue, palpitations and 18 pound weight loss at the time of presentation. Her thyroid stimulating immunoglobulin was 9.21 IU/L (0-0.55), free thyroxine 6.2ng/dL (0.9-1.8), free triiodothyronine 20.04 pg/mL (1.8-4.6) with a suppressed TSH 0.01 uIU/ml (0.27 - 4.2). She was started on methimazole. Her 24 hour radioactive iodine uptake was 60% and she subsequently underwent radioactive iodine-131 ablation in capsule form. She failed the ablation after 7 months and remained on methimazole during that duration. Her second radioactive iodine uptake was 58% and she underwent a second RAI ablation. Her TSH was 50 uIU/ml and her free thyroxine was 0.1 ng/dl. She was started on levothyroxine for replacement. Patient unexpectedly became pregnant approximately six weeks after her radioactive iodine treatment. Studies have shown that with the exception of miscarriages, there is no evidence that exposure to radioiodine affects the outcome of subsequent pregnancies and offspring. Although the number of children born of mothers exposed to radioiodine is relatively small, the present data indicates that there is no reason for patients exposed to radioiodine to avoid pregnancy. The only adverse effect observed in the study series is an increased incidence of miscarriages in women exposed to therapeutic radioiodine during the year which preceded conception. The fetus would be at risk due to maternal hypothyroidism.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

The Intermediate Prolactin Receptor Is a Breast Cancer Oncogene

Jacqueline M. Gripe1, BS1, Patricia Zat, MD2, J. Chuck Harrell, PhD2, Michael Idowu, MD, MPH2, Charles V. Clevenger, MD, PHD2.
1Virginia Commonwealth Univ, Richmond, VA, USA, 2VCUHS, Richmond, VA, USA.

SAT-130

Epidemiological, cellular, and genetic analyses indicate the hormone prolactin (PRL) and its cognate receptor in humans (hPRLr) are significantly involved in breast cancer pathogenesis. Recent evidence demonstrated that a truncated mouse PRLr (mPRLrT) is oncogenic when expressed with canonical long mPRLr (mPRLrL). mPRLrT shares significant sequence homology with a naturally-occurring and widely-expressed hPRLr isoform, the intermediate hPRLr (hPRLrI). As determined by tissue microarray (TMA), hPRLrI is expressed in >85% of breast cancer, with expression increasing as a function of both tumor grade and Ki67 status. To confirm the oncogenic potential of hPRLrI, isoform-specific hPRLrI knock-down (KD) was performed in breast cancer cell line MCF7. hPRLrI KD resulted in a significant decrease in proliferation, migration, and anchorage-independent growth. Given the homology between mPRLrT and hPRLrI, we hypothesized hPRLrI may similarly induce transformation, when expressed alongside wild-type long hPRLr (hPRLrL). hPRLrL/JI co-expression in the immortalized but not transformed human breast cell line MCF10A resulted in a significant increase in proliferation, migration, and anchorage-independent growth. These results were not observed following overexpression of either isoform alone, demonstrating that hPRLrL/JI co-expression is necessary to induce transformation of normal mammary epithelia. To test our hypothesis in vivo, we established MCF10A xenografts using female NSG mice. Following intraductal injection, we observed rapid tumor growth in the hPRLrL/JI cohort, significantly over that of expressing either isoform alone. To determine mechanisms of transformation, we examined both differential protein stability and altered signaling events. In analyzing receptor degradation, a cycloheximide assay revealed hPRLrL stability is increased when heterodimerized with hPRLrL. hPRLrL turnover is impaired in breast cancer, indicating this phenomenon may be involved in the observed hPRLrL-mediated transformation. Regarding differential signaling, we examined the Jak2/Stat5a pathway. Jak2 is a promiscuous
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 (pJák2) 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 hPRLrL, 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. student1, Barbara Barth, Ms, PhD student2, Danusa Mar Arcego, PhD3, Euclides José de Mendoça Filho, PhD student1, Sachin Patel, Bachelor degree1, Zihan Wang, Bachelor degree1, Irina Pokhvisneva, Bachelor degree3, Roberto Britto Sassi, PhD1, Geoffrey B. C. Hall, PhD2, Ana Paula Santana de Vasconcelos Bittencourt, PhD4, Michael Joseph Meaney, PhD5, Carla Dalmaz, PhD3, Patricia Pelufo Silveira, MD, PHD6.

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

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

STAT5A Regulation by Serine Phosphorylation in Breast Cancer

Alicia E. Wook, BS1, Jacqueline M. Gruble, BS2, Patricija Zot, MD2, J Chuck Harrell, PhD3, Idowu Michael, MD-MPH2, Charles V. Cleveenger, MD, PHD2.

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