including regulated exocytosis, secretion, vesicle mediated transport, antibacterial humoral response, and neutrophil degranulation. 4 molecular functions- fibrinogen binding, fibronectin binding, lipopolysaccharide binding, and Extracellular matrix binding; and 38 cellular components, including secretory vesicle, endomembrane system, and adherens junction were significant. The PPI network was highly significant (p-value < 0.001) at medium confidence (0.400) with 88 nodes, 140 edges, and an average node degree of 3.18. The MCODE plugin revealed two clusters, the former with 14 nodes, 73 edges, and a score of 9.733, and the latter with 6 nodes, 14 edges, and a score of 4.000. 9 candidate genes: ELANE, DEFA4, BPI, MPO, LTF, CAMP, OLFM4, LCN2, and VCL were identified, amongst which ELANE, LCN2, and MPO are associated with T2DM pathogenesis, while BPI and LTF have protective effects. OLFM4 deletion has been observed to improve glucose tolerance in mice models. **Conclusion:** This study provides a comprehensive analysis of genes, pathways, and functions which may be pivotal in T2DM pathogenesis and may represent potential therapeutic targets.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Inherited Human XY Sex Reversal and Gonadal Neoplasia Due to Enhanced Formation of Non-Specific Enhanceosomes by an Architectural Transcription Factor

Yen-Shan Chen, PhD[1], Joseph D. Racca, PhD[1], Alicia Belgorosky, MD, PhD[2], Michael Aaron Weiss, MD, PhD, MBA[1].
[1]Indiana University School of Medicine, Indianapolis, IN, USA, [2]Hospital de Pediatria Garrahan, Buenos Aires, Argentina.

The development of organisms is regulated by a fine-tuned gene-regulatory network, which is driven by transcription factors (TFs). In the embryogenesis, these TFs control diverse cell fates and final body plan. This is precisely regulated by a specific DNA-binding process and enhanceosome formation. A model is provided by testis determination in mammals, which is initiated by a Y-encoded architectural transcription factor, SRY. Mutations in SRY cause gonadal dysgenesis leading to various developmental defects. Such mutations cluster in SRY's high mobility group (HMG) box, a sequence-specific DNA-binding domain shared by a conserved family of TFs. Here, we have characterized several mutations at the same position in HMG box, which are compatible with either male or female phenotypes as observed in an XY father and XY daughter, respectively. These mutations, at a function-unknown motif in the SRY HMG box, markedly disturb the specific DNA affinity. On transient transfection of human and rodent cell lines, the SRY variants exhibit decreased specific DNA-binding activity (relative to wild type) are associated with mis-formed enhanceosomes. The variants' gene regulatory activities were reduced by 2-fold relative to wild-type SRY at similar levels of mRNA expression. When engineered

mutations that functions to increase the DNA-binding specificity were deployed to SRY variants, the transcriptional activity was in association with restored occupancy of sex-specific enhancer elements in principal downstream gene *Sox9*. Our findings define a novel mechanism of impaired organogenesis, disturbed specific DNA-binding activity of a master transcription factor, leading to a developmental decision poised at the edge of ambiguity.

Genetics and Development (including Gene Regulation)

FROM BENCH TO BEDSIDE: GENETICS, DEVELOPMENT AND CELL SIGNALING IN ENDOCRINOLOGY

Investigation of Epigenetic Control of DAX-1 Expression in Human Cell Lines

Caroline P. Riedstra, BA, Christina Tzagarakis-Foster, PhD.
UNIVERSITY OF SAN FRANCISCO, San Francisco, CA, USA.

Dosage-Sensitive Sex Reversal, Adrenal Hypoplasia Congenita, Critical Region on the X chromosome, gene 1 (*DAX-1* or *NR0B1*) is an orphan nuclear hormone receptor implicated in Adrenal Hypoplasia Congenita (AHC) and Dosage Sensitive Sex Reversal (DSS). In both instances, DAX-1 plays a key role in growth and development by modulating hormone function. In DSS, mutations on the X-chromosome lead to duplication of the region containing *DAX-1*, resulting in sex reversal, and in AHC, mutations in the *DAX-1* gene diminish development of adrenal tissue which leads to a reduction in adrenal hormone production. Expressed predominantly in tissues such as the testes, ovaries, breast, adrenal cortex, and lung, DAX-1 may serve as an indicator of aberrant growth. Here we hypothesize that *DAX-1* is epigenetically regulated, specifically in cancer cells, thereby reducing its expression. We surveyed various human cancer cells in order to determine whether inhibiting DNA methylating enzymes released epigenetic control of the *DAX-1* gene, resulting in an increase in expression. By implementing molecular techniques, such as bisulfite sequencing, we determined the precise methylation sites in the *DAX-1* gene. Additionally, we carried out methylation specific restriction enzyme analysis to differentiate degrees of methylation between lung, breast, liver, cervical, and adrenal carcinoma cell lines. Following confirmation of the precise methylation sites, we utilized chromatin immunoprecipitation (ChIP) in order to identify the modifying proteins present on the *DAX-1* CpG islands. In conjunction with these experimental techniques, we implemented a bioinformatics approach to analyze methylation in the promoter region of the *DAX-1* gene across tissue sample data acquired from The Cancer Genome Atlas Program. The results of this research could lead to a translational application of understanding where this orphan NHR fits into the development and progression of cancer. As a quickly growing field, cancer epigenetics is a key player in the ongoing pursuit for identifying biomarkers that may be pertinent in future therapeutic applications.