SCIENCE AT THE EDGE

2016 SEMINAR SERIES

Quantitative Biology Graduate Program | Gene Expression in Development and Disease

Stephen Parker

Department of Computational Medicine and Bioinformatics
Department of Human Genetics
University of Michigan

"Genetic Regulatory Signatures Underlying Islet and Muscle Gene Expression and Type 2 Diabetes"

Genome wide association studies (GWAS) have identified >100 single nucleotide polymorphisms (SNPs) that encode type 2 diabetes (T2D) and related trait susceptibility. However, the pathogenic mechanisms for most of these SNPs remain elusive. We examined genomic, epigenomic, and transcriptomic profiles in disease-relevant human pancreatic islets and skeletal muscle biopsies to understand the links between genetic variation, chromatin landscape, and gene expression in the context of T2D. *cis*-eQTLs for tissue-specific genes are enriched in target tissue enhancers.

We identified specific transcription factor (TF) footprints embedded in active regulatory elements with ATAC-seq, and found T2D GWAS loci to be significantly enriched in islet Regulatory Factor X (RFX) footprints. Remarkably, risk alleles that overlap with RFX footprints uniformly disrupt the RFX motifs at high information content positions. This finding indicates that RFX function underlies these T2D mutations; *RFX6* maintains beta cell identity and controls glucose homeostasis, and beta cell specific deletion of *RFX6* results in impaired insulin secretion. Indeed, autosomal recessive mutations in *RFX6* result in Mitchell-Riley syndrome, which is characterized by neonatal diabetes.

Our findings may represent a novel connection between rare coding variation in the islet master regulatory TF *RFX6* and common non-coding variation in multiple target sites for this TF. Together, these results suggest that common regulatory variations impact islet TF footprints and the transcriptome, and that a confluent RFX regulatory grammar plays a significant role in the genetic component of T2D predisposition.

REFERENCES

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FRIDAY, DECEMBER 9, 2016

11:30 AM, ROOM 1400 BPS

Refreshments at 11:15

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