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Speaker Introduction

Bio

Tai-Yi (Diana) Kuo, PhD, is an Associate Research Scientist in the Division of Endocrinology at Columbia University. She received her PhD from the University of California, Berkeley, and is a senior postdoctoral fellow in the laboratory of Domenico Accili, MD in the Naomi Berrie iabetes Center. Dr. Kuo is a recipient of a competitive NIH K01 career development award, and her research was recognized through the Chouinard Award for Excellence in Research as well as the Russ Berrie Foundation Scholars Award. Her current research focuses on pancreatic beta cell dedifferentiation and dysfunction in type 2 diabetes, and leverages next-generation sequencing to probe the genome and the epigenome of healthy and dedifferentiating beta cells, to identify potential targets for diabetes treatment.

Abstract

To this day, intergenic single nucleotide polymorphisms (SNPs) identified from genome-wide association studies (GWAS) are still a geneticist's nightmare,

because these SNPs are steps away from revealing the disease causative gene, relevant tissue(s), and the mechanism of action. For instance, fine mapping and validation of genes causing β cell failure from susceptibility loci identified in type 2 diabetes GWAS poses a significant challenge. The VPS13C-C2CD4A-C2CD4B locus on chromosome 15 confers diabetes susceptibility in every ethnic group studied to date. However, the causative gene is unknown. FoxO1, a transcription factor, is involved in the pathogenesis of β cell dysfunction, but its link to human diabetes GWAS has not been explored. To this end, we generated a genome-wide map of FoxO1 super-enhancers in chemically identified β cells using 2-photon live-cell imaging to monitor FoxO1 localization (i.e. nuclear FoxO1 is required for downstream ChIPseq experiment). Super-enhancers mark genes underpinning β cell identity, and comparing super-enhancers in mouse and human was our way to bridge the mouse data to human relevance. When parsed against human super-enhancers and GWAS-derived diabetes susceptibility alleles, this map revealed a conserved super-enhancer in C2CD4A, a gene encoding a β cell/stomach-enriched nuclear protein of unknown function. Genetic ablation of C2cd4a in β cells of mice phenocopied the metabolic abnormalities of human carriers of C2CD4A-linked polymorphisms, resulting in impaired insulin secretion during glucose tolerance tests as well as hyperglycemic clamps.

C2cd4a regulates glycolytic genes, and notably represses key β cell “disallowed” genes, such as lactate dehydrogenase A, Aldolase B, and monocarboxylate transporter. We propose that C2CD4A is a transcriptional coregulator of the glycolytic pathway whose dysfunction accounts for the diabetes susceptibility associated with the chromosome 15 GWAS locus.side effects. Furthermore, accumulating evidence revealed the interplay of gut microbiota and immune system in orchestrating neuroinflammation, autoimmunity, and neurogenesis. Here we highlight new insights in translational therapies of inflammatory diseases stemming from research on host-microbiota interactions.