SCIENTIFIC SEMINAR

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Functional genomics for cardiometabolic traits: from GWAS to causal genes

A dramatic increase in obesity and type 2 diabetes (T2D) worldwide has already offset hard fought gains in life expectancy in many regions of the world, and the projections for the next 20 years are disheartening. Insulin resistance (IR) is associated with obesity and is essential to the development of cardiometabolic diseases like T2D, non-alcoholic fatty liver (NAFLD) and cardiovascular disease. Despite the advance human genetics and genome wide association studies (GWAS) have provided in identifying genetic loci for IR, T2D and cardiometabolic traits, the lack of progress towards defining the causal genes and molecular mechanisms within these loci has greatly hampered the advance in the field. For example, there are now over 300 loci associated with T2D but very few definitively identified causal genes.

Our laboratory focuses on understanding the genetic basis of insulin resistance and cardiometabolic traits through the combination of human genetics, iPSC-based models of human disease and functional screenings incorporating CRISPR-based gene modifications and single cell sequencing in relevant metabolic cell types. Over the past years we have: i) defined two novel cardiometabolic genes, NAT2 and FAM13A, ii) generated a unique large scale iPSC library (1000 iPSC lines from 200 individuals) with accurate measurements of insulin sensitivity which allowed us to define determinants of transcriptional variability in human iPSCs and to discover key drivers of insulin responsiveness and, iii) defined a high-priority list of cardiometabolic candidate causal genes through perturbation and colocalization analyses. Finally, we are currently performing CRISPR-based screens (perturb-seq,) to discover novel genes involved in adipogenesis and in NAFLD.

Through these different approaches we have started to gain a better understanding of the genetic architecture governing IR and cardiometabolic traits. Our ultimate goal is to find new therapeutic targets for IR, T2D and NAFLD to help ease the tremendous burden suffered by those affected by the worldwide epidemic of cardiometabolic diseases.

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