RMB CVRC Seminar

The Robert M. Berne Cardiovascular Research Center Presents

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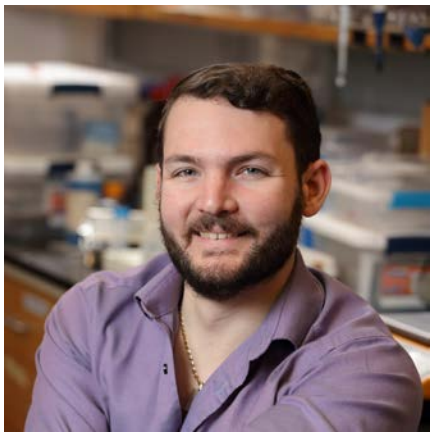

Identifying and characterizing causal coronary artery disease-associated variants regulating gene expression in vascular smooth muscle cells

Coronary artery disease (CAD) is a complex disorder with genetic and environmental influences. Genome-wide association studies (GWAS) have identified >300 loci associated with disease risk. Vascular smooth muscle cells (SMCs) play a critical role in the initiation and progression of atherosclerosis, the precursor to coronary artery disease. As part of this progression, SMCs undergo phenotypic changes mediated by changes in gene expression. We previously isolated SMCs from the ascending aortas of a cohort of 151 human heart transplant donors and found a subset of CAD-associated loci that regulate phenotypic changes relevant to the progression of atherosclerosis by altering gene expression in SMCs. However while these loci were identified, the specific causal SNPs within these loci remain unknown. We performed a series of orthogonal experimental approaches on our primary SMCs to identify CAD-associated SNPs regulating SMC gene expression in an allele-specific manner: (1) lentivirus-based massively parallel reporter assays (lentiMPRAs) and (2) Cleavage Under Targets & Release Using Nuclease (CUT&RUN) assays in donor-matched SMCs along with (3) assay for transposase-accessible chromatin with sequencing (ATAC-seq). We integrated the results of these three experiments and compared them with our previously obtained expression quantitative trait loci (eQTL) data to identify CAD-relevant variant-gene pairs in SMCs. Finally we used CRISPRi experiments to confirm their allele-specificity of the identified SNPs. We identified dozens of CAD-associated SNPs within functionally relevant regions of SMCs showing allele-specific expression in our lentiMPRAs. By comparing these identified variants with our previously obtained expression quantitative trait loci (eQTL) data, we identified 13 putative disease-relevant variant-gene pairs, which were confirmed with CRISPRi experiments.

Thursday March 7th, 2024
11:00 AM-12:00 PM
MR5 Room 3005

Refreshments served

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