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Understanding genetic basis of coronary artery disease using personalised vascular model

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The contribution of chromosome 9p21 risk interval to coronary artery disease (CAD) is well established across many independent patient cohorts. Lately, genome wide association studies reveal the androgen-dependent TFPI-regulating protein (ADTRP) as a novel susceptibility gene for CAD, especially in East Asian populations. Patients carrying ADTRP single nucleotide polymorphisms (SNPs) were found to have decreased ADTRP mRNA expression in their circulating leukocytes. Initial studies suggest a role of ADTRP in anticoagulant protection of the endothelium and inflammation. Nonetheless, there remain knowledge gaps in the functional relevance of ADTRP risk variants in the pathogenesis of CAD.

Our aim is to interrogate the mechanisms through which ADTRP risk variants influence on pathological processes of atherosclerosis. We have leveraged on induced pluripotent stem cell (iPSC) technology to generate relevant cell derivatives which would otherwise be inaccessible from patients (e.g. human coronary endothelial cells). The derivation of iPSC from patients with CAD risk genotypes provide the opportunity to analyse pathways associated with the presence of genetic risk determinants. We have generated iPSCs with and without ADTRP risk allele rs6903956 from age- and gender-matched CAD patients and normal individuals respectively. These CAD and normal iPSC lines successfully formed three germ layers in in vivo teratoma assay. Based on previously developed protocols, we differentiated the iPSC lines into endothelial cells via a precursor stage, lateral plate mesoderm, which is the developmental lineage from which the cardiovascular tissues originate. These endothelial cells were positive for PECAM1 and formed tube-like structures, with comparable tube formation capacity as the primary coronary artery endothelial cells. The CAD iPSC-derived endothelial cells (with rs6903956) express lower levels of ADTRP mRNA and protein than those from normal iPSCs (without rs6903956). We found heightened inflammatory activation (e.g. IL-8 secretion) in CAD endothelial cells than the normal endothelial cells. Cell cycle analysis demonstrated greater extent of apoptosis and less proliferation in the CAD endothelial cells.

The challenge with studying SNPs is that they are unlikely to be a causal factor, but rather act through complex biochemical network that impact on core genes with direct relevance to CAD. We are elucidating chromatin long range interactions between the ADTRP locus where rs6903956 resides, and the genes implicated in atherosclerosis. The advantage of our cellular system also extends to the understanding of crosstalk between ADTRP regulatory network and other susceptibility genomic loci such as the 9p21 risk interval. Our work will open up paths to obtain human perspective to vascular pathological mechanisms.