Abstract: 75O

Novel role for protein kinase D in cardiac extracellular matrix signalling

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Introduction: Protein Kinase D (PKD) encompasses a family of intracellular serine/threonine kinases that regulate cellular responses to chronic overnutrition (Renton et al. 2021). PKD has been implicated in the development of metabolic heart disease, a specific form of heart dysfunction observed in individuals with obesity and diabetes (Liu et al. 2015; Venardos et al. 2015). Our group has developed a novel genetically induced dominant negative mouse model of reduced protein kinase D activation (DNPKD). We have previously shown that DNPKD mice are protected from the high-fat diet (HFD) induced cardiac dysfunction observed in wild type (WT) mice (De Jong et al. 2021). However, the mechanisms by which PKD contributes to the development of obesity-related heart disease are currently unknown. **Methods:** Transcriptomics and protein expression analyses were performed on left ventricular tissue obtained from humanely killed WT and DNPKD mice (N=12 per group) following a 15-week HFD. To identify the predominant cardiac cell types involved, primary cardiomyocytes and fibroblasts were isolated from humanely killed adult WT and DNPKD mice and PKD protein expression was analysed via western blot. Gene sequencing and statistical overrepresentation were analysed using unpaired t-tests with false discovery rate multiple comparison testing and Fischer's exact test, respectively. Protein expression was analysed using a two-way ANOVA (genotype x diet). **Results:** DNPKD hearts displayed an overrepresentation of genes associated with Reactome pathways regulating the extracellular matrix (ECM), such as 'crosslinking of collagen fibrils', 'integrin cell surface interactions', 'collagen formation', 'collagen chain trimerisation', 'collagen degradation', and 'extracellular matrix organization'. The expression of ECM-related genes Thbs1, Thbs4, Nov, Spp1, Itga8, Prelp, Ltbp2, Cilp were significantly increased in DNPKD hearts. Reduced activation of the ECM regulatory protein, focal adhesion kinase (FAK, phosphorylated at Tyr397) was observed in DNPKD hearts. PKD protein was highly abundant in isolated adult cardiac fibroblasts when compared with isolated primary adult cardiomyocytes. **Discussion:** Cardiac ECM dysregulation is one proposed mechanism behind the development of obesity-related cardiac dysfunction. Our results show that PKD is mostly found in fibroblasts in the heart and plays an integral role in the dysregulation of the cardiac ECM in obesity. This previously unrecognised role for PKD in the heart could explain the cardio-protective effect previously observed in animal models of reduced PKD activation (De Jong et al. 2021).

References:

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