

enriched in high shear regions of healthy arteries and significantly reduced in plaque (Figure 1B).

Conclusions Endothelial cell responses to high shear are different in healthy and diseased arteries. Some shear stress related genes are different between healthy arteries and plaques could explain these differences. Future studies will focus on these shear stress related genes to identify their functions and pathways.

BS22

MATRIX STIFFNESS DRIVES INCREASED VASCULAR SMOOTH MUSCLE CELL VOLUME RESPONSE VIA AQUAPORIN MEDIATED WATER INFLUX

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Decreased aortic compliance is a major risk factor for the development of cardiovascular diseases including hypertension and atherosclerosis. Healthy aortae are compliant and can change shape in response changes in blood pressure. This ability arises because of the balance of collagen-I, that provides tensile strength, and elastic extracellular matrix (ECM) components in the medial layer of the aortic wall. Vascular smooth muscle cells (VSMC) are the predominant cell type in the aortic wall and their contraction decreases aortic compliance. Ageing triggers increased deposition of collagen and degradation of the elastic components. This drives stiffening of the aortic ECM. VSMCs are mechanosensitive and respond to this stiffening by generating increased actomyosin generated forces. These are known to contribute to the decreased aortic compliance associated with ageing and hypertension. However, the mechanisms driving the VSMC response remain unknown. In this study, we use polyacrylamide hydrogels of physiological and pathological stiffness. Angiotensin II stimulation of quiescent VSMCs on hydrogels resulted in decreased VSMC area but VSMC volume remained unaltered. In contrast, angiotensin II treatment resulted in increased VSMC area and volume on hydrogels of pathological stiffness. Aquaporins are a family of ubiquitous transmembrane proteins involved in the transport of water across membranes. They have been shown to play important roles in the regulation of cell volume in a range of tissues. Aquaporins 1 and 4 are both expressed in VSMCs, therefore, we hypothesised that aquaporins 1 and 4 permitted increased water influx when VSMCs are exposed to enhanced matrix stiffness. To test this, we utilised the aquaporin 1 inhibitor TCAQP1 and the aquaporin 4 inhibitor TGN020. Importantly, pretreatment of with either TCAQP1 or TGN020 blocked the increased VSMC area response of angiotensin II stimulated VSMCs on hydrogels of pathological stiffness. We next plan to investigate VSMC volume response. Our data suggests that aquaporin 1 and 4 mediated water influx increases volume of angiotensin II stimulated VSMCs in environments of pathological stiffness.

BS23

SPATIAL TRANSCRIPTOMICS PROVIDES A MECHANISTIC INSIGHT INTO SOX9 MEDIATED CARDIAC FIBROSIS

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Introduction Heart failure incidence has seen a 92% increase since 1990, with the majority of cases arising as a consequence of ischaemic and hypertensive heart disease. This is in part due to lack of effective treatments targeting the chronic additive remodelling within diseased hearts. Therefore, increased understanding of the underlying mechanisms is required to inform therapeutic development. Within our group we have identified ectopic expression of SRY-Box 9 (SOX9) as a key regulator of liver and kidney fibrosis. Recent studies have also implicated SOX9 in driving cardiac fibrosis. We aim to integrate spatial transcriptomics (ST) with single cell (sc) RNA sequencing and computational approaches to deconvolute intercellular populations and processes. These approaches will provide a mechanistic insight into the role of SOX9 in remodelling myocardial tissue. **Materials and Methods:** Fibrosis and hypertrophy were induced over 2 weeks using transverse aortic constriction (TAC) on wild type and SOX9-null mice. Echocardiography was used to analyse cardiac function. ST was performed using the 10X Genomics platform on cryosections of WT Sham, WT TAC and SOX9-null TAC hearts. The data was analysed by squidpy on python. Structural changes were evaluated with immunohistochemistry and immunofluorescence.

Results Following TAC, ectopic SOX9 expression was detected in myofibroblasts associated with interstitial fibrosis and in cardiomyocytes immediately adjacent. Significantly, Sox9-null mice improved TAC-induced hypertrophy and fibrosis. To uncover the functional role of SOX9 in heart fibrosis and provide novel mechanistic insight we carried out single cell ST. ST resolved the damaged heart tissue into discrete gene expression clusters that correlated with histological landmarks. We integrated published scRNA-seq data to increase the resolution of the ST data. Through Cell2location computational approaches we defined multi-cell type clusters to reveal disease associated molecular signatures. We identified various subtypes of cardiomyocytes and fibroblasts within and surrounding areas of high fibrosis that have a set of distinguished differentially expressed genes. Interestingly, the gene expression profile of the fibrosis associated cardiomyocyte subpopulations suggested a profibrotic non-canonical cardiomyocyte subtype, which was reduced in Sox9-null fibrotic hearts.

Conclusion In conclusion our study provides evidence to support a key role for SOX9 in the propagation of cardiac remodelling. Using cutting edge ST we have spatially resolved cell populations suggesting a SOX9-dependent role for profibrotic cardiomyocyte-fibroblast crosstalk in mediating disease progression.