HEALTHY AORTA (WILD-TYPE)

PLAQUE (APOE^{-/-})

Abstract BS30 Figure 1

of the plaque compared to distal (downstream) suggesting a potential correlation with WSS (figure 1C).

Conflict of Interest Atherosclerosis

BS31 VSMC CONTRIBUTION TO NEOINTIMAL LESIONS ARISES FROM THE CLONAL EXPANSION OF FEW PRIMED CELLS

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In healthy blood vessels, vascular smooth muscle cells (VSMCs) exist in a contractile, quiescent state but can switch phenotype to activate proliferation, migration and remodelling of the extracellular matrix. Phenotypically switched VSMCs contribute most cells within neointimal lesions, characteristic of atherosclerosis and in-stent restenosis, diseases that underlie heart attack and stroke. Using multicolour 'Confetti' VSMC-specific lineage tracing in animal models of vascular disease, we showed that the extensive VSMC contribution to these lesions results from the clonal expansion of few cells.

To understand how oligoclonal VSMC lesion contribution arises and to identify the signals activating VSMC proliferation *in vivo*, we used confocal microscopy to quantify VSMC clonal development over time in two models of vascular disease. We observed that the number and sizes of patches of clonally expanded VSMCs steadily increased, then plateaued post-injury. This suggests VSMC investment results from activation of a small number of VSMCs, rather than clonal competition following general VSMC activation. Selective VSMC activation in plaques was evidenced by the absence of plaques with high numbers of colours at any stage of plaque development.

In both models, VSMC activation was associated with vascular regions displaying elastic lamina alterations, medial acellularity and immune cell recruitment, implicating these as proliferation-triggering cues. However, not all VSMCs in these regions formed patches, suggesting that VSMCs must be primed to respond. In culture, few VSMCs gave rise to patches, suggesting cell-autonomous activation. This work supports the targeting of primed VSMCs in the healthy vessel as a therapeutic strategy against vascular lesion development.

Conflict of Interest None

BS32 THE ROLE OF BRANCHED-CHAIN KETO ACIDS IN MEDIATING INSULIN RESISTANCE IN THE FAILING HEART

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Brief introduction: Perturbed branched-chain amino acids (BCAA) oxidation positively correlates with the severity of cardiac insulin resistance in heart failure. We previously demonstrated that cardiac-specific deletion of the BCAA oxidative enzyme mitochondrial branched-chain aminotransferase (BCATm) increases cardiac BCAA levels and decreases branched-chain keto acids (BCKA) levels, enhances insulin-stimulated cardiac glucose oxidation rates. This increased cardiac insulin sensitivity is associated with an increase in the phosphorylation of protein kinase B (Akt) and activation of pyruvate dehydrogenase (PDH), the rate-limiting enzyme of glucose oxidation. However, whether it is the accumulation of BCAA or BCKA that is critical in mediating cardiac insulin resistance is unknown. How perturbed BCAA oxidation may mediate cardiac insulin resistance in heart failure is also unknown.

Explanation of basic Methods To address these questions, we first examined the effects of selectively enhancing cardiac BCKA levels on cardiac insulin-stimulated glucose oxidation. We perfused isolated working mice hearts (male and female C57BL/6N, n=8-10) with high levels of BCKA (α -keto-isocaproate 80 μ M, α -keto- β -methylvalerate 100 μ M, α -keto-isovalerate 70 μ M), levels that can be seen in diabetes and obesity.

Results High levels of BCKA completely blunted insulin-stimulated glucose oxidation rates and increased fatty acid oxidation rates. We also found that BCKA abolished insulin-stimulated mitochondrial Akt, an effect that was associated with PDH deactivation. We next determined the potential protective effect of reducing cardiac BCKA levels in the failing heart. We randomized WTcre^{+/+} and cardiac-specific BCATm^{-/-} mice (male, 25-30g, n=6-8) to undergo either sham surgery or transverse aortic constriction surgery to induce heart failure. Five weeks post-surgery, there was a marked increase in insulin-stimulated glucose oxidation rates in the BCATm^{-/-} failing hearts compared to the WTcre^{+/+} failing hearts, with no significant effect on glycolysis rates. Enhanced cardiac insulin