sensitivity was associated with a significant decrease in fatty acid oxidation rates in the BCATm-/- failing hearts compared to the WTCre+/+ failing hearts. This decrease in fatty acid oxidation in the BCATm-/- failing hearts was associated with a significant decrease in myocardial oxygen consumption rates. As a result, cardiac efficiency (cardiac work/myocardial oxygen consumption) was significantly increased in the BCATm-/- failing hearts compared to the WTCre+/+ failing hearts.

Conclusions/implications We conclude that the accumulation of BCKA, and not BCAA, is a major contributor to cardiac insulin resistance via abrogating mitochondrial translocation of Akt. Targeting BCKA may represent a potential therapeutic approach to improve cardiac insulin-stimulated glucose oxidation in the setting of heart failure, obesity and diabetes.

Conflict of Interest None

BS33 THE RAF 'PARADOX BREAKER' INHIBITOR, PLX8394, ACTIVATES ERK1/2 IN ENDOTHELIAL CELLS AND PROMOTES CARDIAC REMODELLING

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Introduction RAF kinases activate the ERK1/2 cascade, a key pathway involved in cardiac remodelling and cytoprotection. Since activating mutations in BRAF cause cancer, small molecule inhibitors of RAF have been developed. However, a paradoxical effect is observed with some inhibitors which activate rather than inhibit ERK1/2. Therefore, 'paradox breaker' inhibitors have been developed as new-generation cancer therapies void of this effect (e.g. PLX8394). Here, we determined the effects of PLX8394 on endothelial cell (EC) ERK1/2 signalling and the heart in vivo.

Methods Murine ECs were incubated with PLX8394 and effects on ERK1/2 activity determined by western blotting for the phosphorylated (i.e. activated) kinases. Effects on gene expression were determined by qPCR. The effects of PLX8394 on the heart in vivo were determined by infusing male wildtype C57Bl/6J mice (10-12wks, n= 6/group) with PLX8394 (5mg/kg/d, 7d) using osmotic minipumps. Cardiac function/dimensions were assessed using echocardiography; effects on cardiac morphology were assessed by histological staining. mRNA expression was assessed by qPCR. Statistical tests used 1-way ANOVA with Holm-Sidak's post-test (in vitro studies) and unpaired t-tests (in vivo studies).

Results PLX8394 activated ERK1/2 in ECs in a time (7.4 ±2.3-fold at 5 min; p=0.0365; n=5) and concentration (>1uM; p=0.0625; n=3) dependent manner. This was associated with significant increases in expression of mRNAs encoding the immediate early gene Fos (6.1±2.6-fold; p<0.0001; n=4) and the vasoconstrictor peptide endothelin-1 (Edn1) (2.7±0.9-fold; p=0.0038; n=4). In vivo, PLX8394 decreased cardiac output (p=0.0092), predominantly through reduced stroke volume (p=0.0103). Structurally, PLX8394 promoted cardiac hypertrophy, with increased diastolic left ventricular (LV) posterior wall thickness (p=0.0425) and decreased LV internal diameter (p=0.0463) at 7 d. Cardiac hypertrophy resulted from increased cardiomyocyte cross-sectional area (p=0.0002) despite no changes in Myh7, Nppa or Nppb mRNAs. Moreover, PLX8394-induced cardiac remodelling was not due to increased fibrosis, with no change in mRNA expression of collagens1-4 and using histological assessment.

Conclusion Despite being developed as a 'paradox breaker' for cancer, PLX8394 promoted ERK1/2 signalling in murine ECs and cardiac remodelling in vivo. These preliminary findings suggest that such inhibitors, currently in Phase 3 trials for RAF-mutant cancers, have potential to modulate cardiac function in patients.

Conflict of Interest N/A

BS34 TELOMERE DAMAGE PROMOTES VASCULAR SMOOTH MUSCLE CELL SENESCENCE AND IMMUNE CELL RECRUITMENT AFTER VESSEL INJURY

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Aim Vascular smooth muscle cells (VSMCs) accumulate in injury-induced neointimal lesions and atherosclerotic plaques in an oligoclonal fashion, yet plaque VSMCs show reduced proliferation and cell senescence. DNA damage leads to VSMC senescence and inflammation, and VSMC senescence promotes atherosclerosis; however, the exact mechanism by which VSMC senescence promotes lesion formation is not known. Here, we investigated telomere damage-induced VSMC senescence, the contribution of senescence-induced inflammation and the mechanisms involved, the consequences of VSMC senescence in vivo after injury, and whether it promotes clonality.

Methods Stress-induced premature senescence (SIPS) was induced by the chemotherapeutic doxorubicin (24h treatment + 21d recovery). Lentiviruses were used to stably overexpress a dysfunctional TRF2 mutant protein (TRF2T188A) in human VSMCs (hVSMCs). SM22aTRF2T188A mice were generated that express human TRF2T188A in VSMCs only, and crossed with Myh11-CreERT2 Rosa26-Confetti multicolour reporter mice, to study cell senescence and clonality in vivo. Arterial injury was induced in these mice by ligation of the left common carotid artery for 28 days.

Results Both SIPS and TRF2188A-induced VSMC senescence were characterised by persistent telomere damage, and associated with formation of micronuclei, activation of cGAS-STING cytoplasmic DNA sensing, and induction of multiple pro-inflammatory cytokines. Silencing of cGAS in TRF2T188A hVSMCs partially inhibited NFkB-dependent cytokine expression. In vivo, VSMC-specific TRF2T188A expression in a multicolour clonal VSMC-tracking model demonstrated no change in VSMC clonal patches after injury, but increased neointima formation (figure 1), outward remodelling and cellular senescence. Moreover, neointimal lesions of VSMC-specific TRF2T188A mice were characterised by increased ICAM1 expression and increased abundance of CD45+, CD3+ and CD68+ cells when compared to littermate controls, indicating increased immune/inflammatory cell infiltration and/or retention.

Conclusions Persistent telomere damage promotes VSMC senescence and inflammation, and exacerbates neointima formation after injury. Our data suggest that persistent telomere damage-induced VSMC senescence plays a major role in