but this is decidedly more well-studied in the murine context. The role of SASP in myocardial remodelling clinically, and the capacity of the human myocardial SASP to serve as a biomarker for age-related cardiac remodelling and associated CVD, is still unclear. We aimed to evaluate this by marrying in vitro studies with clinical data from a large, older (> 85 years-old) patient cohort, and clinical data from small cohort of human donor hearts spanning a range of normalcy.

**Methods and Results** In human donor hearts, left ventricular p16 protein expression correlated with donor age (Pearson’s correlation=0.631, p<0.01), indicating that senescence is associated with increased donor age. To identify the mechanisms by which myocardial senescence may drive age-related dysfunction, we employed an in vitro model, AC16 cardiomyocytes were induced to senescence using doxorubicin (shown by transcript- and protein-level induction of classical senescence markers p16 (figure 1A) and p21), demonstrating the utility of this in vitro model for recapitulating cardiac senescence. Suggesting that cardiomyocyte senescence contributes to clinical age-related cardiac dysfunction through paracrine mechanisms, senescent human cardiomyocytes expressed a functional SASP which induced phenotypic changes in cardiac fibroblasts (formation of smooth muscle actin-positive stress fibres). Subsequent molecular analysis identified that this SASP contained emergent biomarkers of clinical CVD including GDF15 (figure 1B) and fractalkine. Fractalkine has previously been associated with poorer outcomes in clinical CVD but GDF15 is currently not well-understood. Therefore, GDF15 was analysed in clinical data from a large, older patient cohort (Newcastle 85+ study, n = 774) and was found to significantly elevated in patients with cardiac dysfunction (figure 2A, p<0.005), alongside the gold-standard clinical biomarker of cardiac dysfunction, NT-proBNP (figure 2B).

**Conclusions** Cardiomyocyte senescence is associated with a functional SASP which is capable of inducing remodelling phenotypes in non-cardiomyocyte cell types. Selected SASP factors such as GDF15 appear to show utility as clinical biomarkers of an aged, diseased cardiac phenotype. These may be useful additions to current biomarkers to form a signature which may aid prognosis and monitoring of CVD, even outside an ageing context.

**Conflict of Interest** None to declare

### Abstract BS31

**SNHG18 CONTROLS VASCULAR SMOOTH MUSCLE CELL PHENOTYPIC MODULATION AND NEOINTIMAL HYPERPLASIA**

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**Background** Emerging evidence has pinpointed a critical role for regulatory RNAs including long non-coding RNAs (LncRNAs) in vascular smooth muscle cell (VSMC) phenotypic modulation and cardiovascular diseases. One LncRNA, small nucleolar RNA host gene 18 (snhg18), has been widely implicated in cancers. However, little is known about its functional involvement in VSMC phenotypic modulation as well as neointimal hyperplasia. Herein, we attempted to explore the functional implication of snhg18 in VSMC phenotypic modulation and injury-induced neointima formation, and uncover its underlying molecular mechanisms.

**Methods and Results** Snhg18 expression was closely regulated during VSMC phenotypic modulation, and in remodelled arteries upon injury. Transforming growth factor beta-1 up-regulated snhg18 gene expression in VSMCs through modulating transcription factor Sp1. Snhg18 gene gain/loss-of-function studies in VSMCs revealed that VSMC contractile gene expression was positively, but VSMC proliferation and migration were negatively regulated by snhg18. Moreover, functional and mechanistic studies showed that snhg18 promotes a contractile VSMC phenotype by up-regulating miR-22-3p. Further mechanistic studies revealed that snhg18 up-regulates miR-22 biogenesis and miR-22-3p production by competitive binding with the A-to-I RNA editing enzyme, adenosine deaminase acting on RNA-2 (ADAR2), and that ADAR2 is a negative regulator in miR-22 biogenesis. Surprisingly, we observed that ADAR2 inhibited miR-22 biogenesis not through increasing A-to-I editing within primary miR-22, but by interfering the binding of the microprocessor complex subunit DGCR8 to primary miR-22. Importantly, perivascular snhg18 overexpression in the injured vessels dramatically up-regulated the expression levels of miR-22-3p and VSMC contractile genes, down-regulated the expression levels of the target genes of miR-22-3p, and prevented neointimal hyperplasia in wire-injured femoral arteries. Such modulatory effects were reverted by miR-22-3p inhibition in the injured arteries. Finally, we
observed a similar regulator role for SNHG18 in human VSMCs, and a decreased expression level for both SNHG18 and miR-22-3p in diseased human arteries; and we found that the expression level of SNHG18 was positively associated with that of miR-22-3p in both healthy and diseased human arteries.

Conclusion We demonstrates that snhg18 is a novel regulator of VSMC phenotypic modulation and injury-induced neointimal hyperplasia. Our findings have important implications for therapeutic targeting snhg18/miR-22-3p signalling in vascular diseases.

Key words: Long non-coding RNAs; Small Nucleolar RNA Host Gene 18 (SNHG18); Adenosine Deaminase RNA Specific B1; Adenosine deaminase acting on RNA-2; Vascular smooth muscle cells; Neointima; post-angioplasty restenosis; cell proliferation; cell migration.

Conflict of Interest N/A