mitochondria was examined in the endothelium in intact blood vessels. In controls, TRPV4 activation with GSK1016790A(GSK) generated repetitive Ca^{2+} oscillations that required Ca^{2+} influx. When the $\Delta\psi_m$ was depolarised, by the uncoupler carbonyl cyanide m-chlorophenyl hydrazine (CCCP) or the complex I inhibitor rotenone, TRPV4 activation generated a much larger Ca^{2+} rise and propagating multicellular Ca^{2+} waves. The ATP synthase inhibitor oligomycin did not potentiate TRPV4 mediated Ca^{2+} influx. GSK-evoked Ca^{2+} waves, that occurred when mitochondria were depolarised, persisted in a Ca^{2+} free extracellular solution i.e. were independent of Ca^{2+} influx. These signals were blocked by the TRPV4 channel blocker HC067047 (HC067), the SERCA inhibitor cyclopiazonic acid, the phospholipase C (PLC) blocker U73122 and the inositol triphosphate receptor (IP3R) blocker caffeine. These observations suggest that TRPV4 may directly activate Ca^{2+} release from the internal store. The large propagating waves were inhibited by the pannexin blocker probenecid and the extracellular ATP blockers suramin and apyrase. These results highlight a previously unknown role of mitochondria in shaping TRPV4 mediated Ca^{2+} signalling and show that TRPV4 may trigger ATP release via a pannexin hemichannel when mitochondria are depolarised.

Conflict of Interest n/a

BS23

MRNA EXPRESSION PROFILING OF DUAL SPECIFICITY PHOSPHATASES (DUSPs) IN THE HYPERTENSIVE HEART

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Introduction DUSPs dephosphorylate Ser/Thr and Tyr residues, most notably in the mitogen-activated protein kinases (MAPKs) that are activated by dual phosphorylation in a T-X-Y motif. Whereas some DUSPs preferentially dephosphorylate nuclear MAPKs (DUSP1/2/4/5), others dephosphorylate cytoplasmic MAPKs, including growth-promoting ERK1/2 (DUSP6/7/9) and stress-responsive p38-MAPKs or JNKs (DUSP8/10/16). MAPKs regulate cell growth/survival/death and are implicated in hypertensive heart disease. DUSPs may fine-tune these pathways and influence cardiac remodelling. Here, we assessed expression profiles of cardiac DUSP mRNAs in human heart failure and hypertensive rodents.

Methods Cardiac DUSP (DUSPs 1, 2, 4, 5, 6, 7, 8, 9, 10 and 16) mRNA expression was assessed in an archive of human left ventricular tissue from control (n=12) and non-ischemic heart failure (n=12) individuals. Rodent hypertension models were also studied: spontaneously hypertensive rats (SHRs; 11-13 weeks, n=8) were compared to age-matched WKY controls (n=8), and C57BL/6J male mice (10 wks) were infused with vehicle (acidified-PBS, n=16) or 0.8 mg/kg/d angiotensin II (AngII) for 24h (n=11) or 7d (n=12) using osmotic minipumps. In all studies, cardiac DUSP mRNA expression was assessed by qPCR relative to GAPDH. Statistical tests used a 1-way ANOVA with Holm-Sidak post-test (mouse studies) and unpaired t-tests (human and rat studies).

Results All DUSPs were detected in human hearts except DUSP5; DUSP7 was significantly suppressed (0.53 ± 0.045 -fold, $p=0.0065$) in failing hearts. All DUSPs were detected in rat or mouse hearts. With chronic hypertension in SHRs, Dusp2

(1.39 ± 0.10 -fold, $p=0.0090$), Dusp4 (1.90 ± 0.17 -fold, $p=0.0004$), Dusp6 (1.31 ± 0.15 -fold, $p=0.0190$), Dusp7 (1.48 ± 0.05 -fold, $p<0.0001$), Dusp8 (2.01 ± 0.15 -fold, $p=0.0024$) and Dusp16 (1.22 ± 0.05 -fold, $p=0.0295$) were all upregulated relative to WKY controls, whilst Dusp9 was decreased (0.33 ± 0.08 -fold, $p=0.0232$). In contrast, in the acute model of murine hypertension with AngII-treatment, there were significant increases in Dusp8 (1.48 ± 0.12 fold, $p=0.0003$), Dusp10 (1.54 ± 0.08 -fold, $p<0.0001$) and Dusp16 (1.37 ± 0.06 -fold, $p=0.0306$) abundance at 24h, whilst only Dusp6 (1.47 ± 0.11 -fold, $p=0.0013$) was elevated at 7 days relative to vehicle controls.

Conclusion DUSPs are expressed in human and rodent hearts. With acute adaptation to hypertension, changes in DUSP profiles potentially modulate activities of stress-responsive MAPKs. However, in established hypertension and human heart failure, changes in DUSP profiles potentially modulate activities of cytoplasmic ERKs. Thus, DUSPs are likely to contribute to development of hypertensive heart disease.

Conflict of Interest None

BS24

INVESTIGATING THE ROLE OF SALT-INDUCIBLE KINASE 2 (SIK2) IN HEART

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Introduction Heart failure (HF) is characterised by an inadequate cardiac pumping ability and is one of the major causes of death worldwide. Numerous conditions lead to HF, such as myocardial infarction (MI). After MI, an extensive death of cardiac cells combined with limited regenerative capacity causes a pathological remodelling of the left ventricle, characterized by substantial fibrosis and hypertrophy. Replacement of damaged tissue or limitation of pathological progression are not achievable with current treatments. Thus, novel therapeutic approaches to address this unmet medical need are still required.

We decided to explore the unknown role of Salt-inducible kinase 2 (SIK2) in cardiac cells to potentially identify a novel target for HF therapy. Recently, this kinase has been identified as a key modulator of Hippo pathway-mediated stimulation of cell proliferation in *Drosophila* and a putative mediator of cardiac hypertrophy progression in response to chronic high-salt intake.

Methods and Results Firstly, we demonstrated that SIK2 protein is expressed in both fibroblasts and cardiomyocytes. We also identified a variation of its expression during the different developmental stages of the organism, displaying a greater level during the neonatal phase, and an elevated expression during HF progression, underlining the decisive importance of this kinase in myocardial tissue organization and remodelling.

We performed an in-silico analysis to unroll the mediators of this effect, which suggested that SIK2 activity is mainly mediated by either Hippo or Akt pathway. Exploiting an adenovirus overexpression system, we observed evidence of increased Akt phosphorylation levels. We also found that SIK2 overexpression in primary neonatal rat cardiomyocytes causes activation of LATS, one of the main components of the Hippo pathway, suggesting a potential SIK2-mediated regulation of the Hippo pathway. These alterations did not cause