±1.5 (% viability) CF vs PANC-1, n=3). A lower IC_{50} value for sunitinib was required to exert the same effects on CF (IC_{50}5.2 μM) vs PANC-1 (IC_{50}13.5 μM) cell viability.

These results suggest sunitinib can cause lethal effects in cardiac cells at lower doses than those required to induce pancreatic cancer cell death. Future work will aim to identify cellular mechanisms responsible for these toxic effects. Parallel studies in cardiac and cancer cells will be beneficial in distinguishing how focused anti-cancer drug delivery could be improved to avoid CTX.

7 NOX4 NADPH OXIDASE IS A KEY REGULATOR OF ENDOTHELIAL CELL FUNCTION IN EXPERIMENTAL DIABETES

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Introduction The characteristic hyperglycaemia of diabetes drives reactive oxygen species (ROS) production in endothelial cells (ECs), leading to microvascular dysfunction and cardiovascular complications. NADPH oxidases are enzymes whose primary function is to generate ROS, and which contribute to development and progression of cardiovascular disease. This study aimed to investigate the role of the NOX4 isoform, which is highly expressed in ECs, under hyperglycaemic conditions, in EC signalling and paracrine communication with fibroblasts, as a major determinant of diabetic cardiovascular remodelling.

Methods Human aortic endothelial cells (HAoECs) were treated with normal (NG, 5.5 mM) or high (HG, 25 mM) glucose for up to 5 days with or without NOX4 siRNA knockdown (KD) prior to assessment of mRNA expression (real-time RT-PCR; relative to β-actin) and superoxide generation (DHE fluorescence). NIH 3 T3 fibroblasts were treated with conditioned media from NOX4-modified HAoECs for 24 hour to interrogate effects on paracrine signalling.

Results HG treatment of HAoECs for 5 days increased mRNA expression of NOX4 (NG 1.01±0.06, HG 1.27±0.06; n=9, p<0.05) and associated antioxidant and proinflammatory genes (e.g. NRF2: 0.91±0.04 vs 1.22±0.04; IL-6: 1.03±0.13 vs 2.59±0.58; n=6, p<0.05). This was associated with increased superoxide production (262±12 vs 338±11 arbitrary units; n=4, p<0.05) at 2 but not 5 days. Interestingly, NOX4 KD under HG conditions increased mRNA expression of endogenous antioxidant enzymes after 2 days (e.g. NRF2: 1.90±0.06 vs 2.21±0.06; n=3, p<0.05) whilst normalising increased superoxide production. Furthermore, increased TGFβ-induced differentiation of NIH 3 T3 fibroblasts observed in the presence of conditioned media from HG-treated HAoECs was ablated by NOX4 KD (e.g. α-SMA: scrambled control 1.31 ±0.04, NOX4 KD 0.94±0.07; n=3, p<0.05).

Conclusions HG-induced NOX4 signalling regulates ROS production and endogenous antioxidant expression in ECs, driving paracrine stimulation of fibroblast differentiation. It therefore seems likely that EC NOX4 NADPH oxidase signalling contributes significantly to adverse diabetic cardiovascular remodelling.

8 HEDGEHOG RESPONSIVE STEM CELL ANTIGEN-1/S100β RESIDENT VASCULAR STEM CELLS CONTRIBUTE TO NEOINTIMAL FORMATION

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Intimal medial thickening (IMT) and vascular remodelling are hallmarks of arteriosclerotic disease. The origin of neointimal cells and the signalling molecules that direct their fate and function is controversial. Here, we demonstrate that Hedgehog (Hh) responsive $S100\beta^+/Sca1^+$ perivascular stem cells substantially contribute to IMT within carotid arteries of transgenic mice following ligation-induced injury *in vivo*. Genetic lineage tracing analysis using S100β-eGFP/Cre/ERT2 transgenic mice to mark resident vascular stem cells before injury demonstrated that Hh responsive $S100\beta^+/Sca1^+$ cells substantially contribute to IMT, an effect significantly attenuated following treatment with the Hh smoothened inhibitor, cylopamine. *In vitro*, recombinant SHh (rSHh) treatment of multipotent $S100\beta^+/Sca1^+$ resident stem cells increased target gene Gli expression, decreased telomerase activity, and promoted myogenic differentiation and cell growth; effects significantly attenuated following Hh inhibition. These findings suggest that perivascular $S100\beta^+/Sca1^+$ stem cells are a major source of neointimal cells contributing to IMT and suggest that this cohort may be a relevant therapeutic target to prevent arteriosclerosis.

9 ENDOTHELIAL NOX4 NADPH OXIDASE PROTECTS AGAINST ADVERSE CARDIAC REMODELLING ASSOCIATED WITH EXPERIMENTAL DIABETES

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Background Chronic heart failure (CHF) is a major cause of mortality in diabetes due to characteristic alterations in cardiac structure and function. The diabetic heart is typified by increased fibrosis, inflammation and microvascular remodelling together with hyperglycaemia-induced endothelial dysfunction and reactive oxygen species (ROS) generation, which may predispose to cardiovascular stress. The aim of this study was to investigate the specific contribution of endothelial Nox4 NADPH oxidase, a major source of cardiovascular ROS, to cardiac remodelling in experimental diabetes.

Methods Diabetes was induced in endothelial-specific Nox4 transgenic (Tg) mice and WT littermate controls (10–12 weeks of age; n=8–12/group) by streptozotocin (STZ) injection. After 6 months, echocardiography was performed and blood and cardiac tissue collected for metabolic and gene expression analyses, respectively.

Results Endothelial Nox4 overexpression did not affect blood glucose or HbA1c levels in control or diabetic animals.