Results At day 1 and day 7 post-MI, Csf1r-expressing cells accumulated within the injured myocardium, consistent with a role in regeneration.[2] At day 1 post-MI, fractional area change (FAC) decreased from 40.9% ± 1.6 to 18.0% ± 2.4% ($p<0.0001$) and from 41.0% ± 1.3 to 16.5% ± 2.7% ($p<0.0001$) in *Porcn*$^{fl/}$Csf1r^{Cre-ve} and Porcnfl/Csf1rCre-ve mice respectively. By 21 days after MI, FAC had recovered to 47.4% ± 2.5% ($p<0.0001$) in *Porcn*$^{fl/}$Csf1r^{Cre-ve} and 45.8% ± 1.9% ($p<0.0001$) in *Porcn*$^{fl/}$Csf1r^{Cre-ve} littermates. Coronary vascularisation was restored in the infarct area by 21 days in both lines, but interstitial fibrosis was significantly higher in *Porcn*$^{fl/}$Csf1r^{Cre-ve} (6.0 ± 0.9% LV) compared to *Porcn*$^{fl/}$Csf1r^{Cre-ve} (3.8 ± 0.5% LV, $p<0.05$). In WT neonatal hearts, MI increased the expression of *Wnt5b* and *Fzd2*, genes associated with regulation of fibrosis.[8]

Conclusion Mϕ-derived WNTs are not required for re-vascularisation or restoration of myocardial function after neonatal myocardial injury, but are necessary for scar removal during regeneration.

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11 TARGETING 11β-HSD1 TO PROMOTE ANGIOGENESIS – CONSEQUENCES FOR SOLID TUMOUR GROWTH

[1]Callam Davidson*, [2]Morwenna Muir, [1]Natalie Homer, [1]Ruth Andrew, [2]Val Brunton, [1]Patrick WF Hadoke, [1]Brian R Walker. *[1]Centre for Cardiovascular Science, The Queen's Medical Research Institute, Edinburgh, UK; [2]Edinburgh Cancer Research Centre, Institute of Genetics and Molecular Medicine, Edinburgh, UK*

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11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), which generates active glucocorticoids from inactive precursors, is expressed in glucocorticoid target tissues, including the arterial wall. Since active glucocorticoids are anti-angiogenic 11β-HSD1 inhibitors enhance angiogenesis and may have therapeutic potential in ischaemia. However increased angiogenesis may be detrimental in tumours. This investigation tested the hypothesis that 11β-HSD1 inhibition promotes angiogenesis and tumour growth in mouse models of squamous cell carcinoma (SCC) and pancreatic ductal adenocarcinoma (PDA).

Murine tumour cells (1×10^6) were injected subcutaneously into mice (female, 10–12 weeks, FVB/C57Bl6/J) receiving RM-1 diet with, or without (Control), the 11β-HSD1 inhibitor UE2316 (175 mg/kg). Tumour size was measured every 2–3 days for 2–3 weeks. Sections of tumours were stained for vascular markers (CD31, alpha-smooth muscle actin) for quantification of vessel density. Steroid/drug levels were measured in plasma/tissues using liquid chromatography tandem mass spectrometry whilst 11β-HSD1 activity was assayed in tissue homogenates by high performance liquid chromatography. The effects of 11β-HSD1 inhibition on angiogenesis were examined *ex vivo* using an aortic ring assay. Data are mean±SEM.

11β-HSD1 inhibition increased SCC tumour growth in FVB mice ($p<0.01$) but did not affect the growth of PDA tumours in C57Bl6/J mice. Vessel density was unaffected in both tumour types. SCC tumours expressed more 11β-HSD1 mRNA and had higher ($p<0.001$) enzyme activity (0.291 ±0.054 nmoles product/mg/min) than PDA tumours (0.038 ±0.006). FVB mice had higher plasma UE2316 levels than C57Bl6/J mice (164.6±78.28 nM vs 14.4±6.23 nM), and reduced circulating corticosterone after UE2316 treatment. UE2316 reduced type 1 collagen in SCC tumours (9.8±0.8 vs 3.8%±0.6% area, $p<0.001$). Pharmacological inhibition of 11β-HSD1 did not alter steroid-mediated angiostasis in aortic rings.

11β-HSD1 inhibition does not promote angiogenesis in SCC or PDA tumours, but may increase SCC growth through a mechanism involving reduced fibrosis. Whether 11β-HSD1 inhibition increases angiogenesis in glucocorticoid-sensitive tumours remains to be established.

12 PREVENTION OF CONTRAST-MEDIA INDUCED RENOVASCULAR TOXICITY USING LIPID NANOPARTICLE ENCAPSULATION

Rachel Donaghey*, Alexander B Mullen, Paul A Coats. *Strathclyde's Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Scotland, UK*

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Introduction The primary goal of conventional lipid nanoparticles (LiNPs) is to target and release drugs at the site of disease. In comparison, this research aims to minimise drug interactions by entrapping the nephrotoxic contrast agent, iohexol (IOX), within protective particles. Susceptible patients, such as those with diabetes, suffer from pre-existing vascular dysfunction which is exacerbated by IOX.[1] Mechanisms of IOX-associated toxicity are unknown, therefore, cell-based assays will be used to examine toxicity and whether it may be prevented through LiNP encapsulation.

Method Human umbilical vein endothelial cells (HUVEC), vascular (VSMC) and kidney cells (HEK-293) and were treated with IOX or IOX-encapsulated LiNPs (n=3). A metabolic indicator assay were used to determine metabolic activity after treatment proliferation and toxicity. Cell counting and a dye exclusion assay were used to confirm toxicity.

Results Resazurin experiments showed a significant reduction in metabolic activity after 2 hour IOX incubation resulting in a 54%, 15% and 52% reduction in HUVEC, VSMC and HEK-293 metabolic activity respectively. These results were confirmed through cell counting analysis. Encapsulation of IOX within LiNPs was found to prevent IOX-associated renal toxicity as metabolic activity was comparable to non-treated cells (129%) ($p<0.05$).

Conclusions Treatment of HEK-293 and VSMCs with IOX led to a reduction in viable cells and an increase in toxicity which was mainly influenced by concentration rather than time. Encapsulation of IOX within LiNPs was found to prevent toxicity *in vitro*. Future work will be carried out to determine mechanisms behind contrast agent-associated toxicity with a focus on *ex vivo* kidney perfusion and vascular contractile experiments.

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