Abstract 167 Figure 1

reduce length of attendance and improve patient flow and experience through the AMU.

REFERENCE

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax J, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology, European Society of Cardiology, European Heart Journal January 2016;37(3):267–315.

Conflict of Interest None

Basic Science

BS1 INVESTIGATING THE ROLE OF ENDOCARDIAL NOTCH SIGNALLING IN NEOVASCULARISATION OF THE HEART AFTER MYOCARDIAL INFARCTION

Tonia Thomas*. University of Oxford

10.1136/heartjnl-2019-BCS.165

Introduction Restoring blood flow after myocardial infarction (MI) is essential for the oxygenation of existing and newly regenerated tissue. Proangiogenic therapies have been previously investigated in an attempt to target existing coronary vessels, but with limited success. Endogenous vascular repair processes are poorly understood, therefore we sought to determine whether coronary vessel developmental mechanisms are intrinsically reactivated following injury in the adult mouse heart. During development, the endocardium contributes 60% of coronary vessels, in large part via compaction of the trabeculated endocardial surface perinatally. We therefore extended consideration to the endocardium as a source of de novo vessels in the adult MI setting.

Methods MI was induced in mice using LAD ligation, and pulse-chase genetic lineage tracing was utilised to investigate the source of sub-endocardial vessels in the ischemic adult heart. In order to gain insight into the mechanisms that regulate endocardium-derived vessel formation, we investigated candidate signalling pathways which orchestrate trabeculation and compaction during development. Following these preliminary analyses, a Notch1 loss-of-function model was generated to interrogate a potential role for Notch1 in endocardial remodelling and neovascularisation post-MI.

Abstract 167 Figure 2

Abstract B51 Figure 1

Results We demonstrated that the adult heart reverts to a hypertrabeculated state between 1 and 5 days post-MI and repeats the process of endocardial compaction from 7–14 days. This process appears to facilitate endocardium-derived neovascularization, leading to formation of mature sub-endocardial vessels after infarction. We observed reactivation of the Notch pathway in the endocardium following MI, in keeping with its role as a key regulator of these processes in development. Using a Notch1 loss-of-function mouse model targeted by an endothelial-specific Cre, we observed impaired trabeculation with reduced sub-endocardial vessel count after disruption of Notch activity. (Figure 1)

Conclusion We established that de novo vessel formation constitutes a significant component of the neovascular response and revealed that the endocardium is a major contributory source. Notch1 was identified as a key driver in this remodeling process and, moreover, our data suggest a role for Notch in driving endothelial-mesenchymal transition (EndMT) to provide smooth muscle support to newly formed vessels. Ongoing work seeks to determine whether targeting trabeculation in the adult heart will contribute to improved neovascularisation post-MI.

Conflict of interest N/A

B52

STX18-AS1 IS A LONG NONCODING RNA GOVERNING IN VITRO CARDIOMYOCYTE DIFFERENTIATION AND PREDISPOSING TO ATRIAL SEPTAL DEFECT VIA DOWNREGULATION OF NKX2-5

¹Yingjuan Liu*, ¹Mun-kit Choy, ¹Gennadiy Tenin, ¹Sabu Abraham, ¹Graeme Black, ²Bernard Keavney. ¹University of Manchester; ²Faculty of Biology, Medicine and Health, University of Manchester

10.1136/heartjnl-2019-BCS.166

Objectives A number of risk variants have been identified from Genome-wide association studies (GWAS) of Congenital Heart Disease (CHD). However, none of them has been functionally confirmed as yet. We sought to identify the gene and mechanism responsible for the GWAS signal (OR=1.46; $p=2.61 \times 10^{-10}$) which we previously identified at chromosome 4p16 for atrial septal defect (ASD).

Methods and results Exploration of the linkage disequilibrium pattern between SNPs in the region indicated association was restricted to the interval spanning the long noncoding RNA STX18-AS1. Since no homolog of STX18-AS1 is found beyond primates, all experiments were conducted in human tissues and cell lines. With RNA from 108 Right Atrial Appendages and corresponding blood DNA, we confirmed the risk SNPs (rs870142 and rs16835979) were eQTLs for STX18-AS1 in human cardiac tissues. In RNA expression analyses using qPCR on embryonic heart samples, the transcription of STX18-AS1 was detected to be the highest at CS14-CS18, the critical time for atrial septation during human heart development. With in situ hybridization on whole embryonic hearts of CS17-CS19, the expression of STX18-AS1 was also determined in the myocardium of Atrial Septum.

We next identified STX18-AS1 as a regulator of the key cardiac transcriptional factor NKX2-5 using CRISPR/Cas9 knockdown of STX18-AS1 in HepG2 cells. Mutations in NKX2-5 cause septal defects in humans. Reduced STX18-AS1 transcription inhibited the expression of NKX2-5 accompanied by decreased H3K4me3 at its promoter region. We demonstrated the interaction between STX18-AS1 RNA and WDR5 protein, which supported the epigenetic regulation effects of STX18-AS1. Using in vitro cardiomyocyte differentiation from human embryonic stem cells, we demonstrated that the knockdown of STX18-AS1 depleted the potential of human embryonic stem cells in differentiating into beating cardiomyocytes without changes in cell viability and pluripotency.