Epigenetic gene regulation has been increasingly established as a pivotal molecular mechanism driving heart development and its aberrant regulation has been implicated in congenital heart diseases. KMT2C is a histone methyltransferase enzyme that mediates the Histone 3 lysine 4 (H3K4) methylation that denotes active promoters and enhancers. Our previous work identified a number of de novo variants in KMT2C gene in nonsyndromic Tetralogy of Fallot patients. Global deletion of delta SET domain region of Kmt2c gene that harbour methyltransferase enzymatic activity resulted in neonatal lethality in mice. Histological analysis of knockout mice embryonic heart revealed ventricular septal defect (with and without an overriding aorta) with a low penetrance but also displayed a consistent phenotype resembling ventricular non-compaction. Embryonic hearts from the knockout mice at the e16.5 stage of development displayed a significantly thinner (p<0.05) compact myocardium of the left ventricle compared to the wild-type littermates. In order to get insights into the molecular mechanism for this phenotype, we carried out RNA sequencing experiments in ventricles of e16.5 embryonic hearts from mice with a homozygous deletion and wild type littermates. A significant decrease in gene expression is observed in many of the extracellular matrix (ECM) genes, especially elastin (p<1.0E-6), various subtypes of collagens, fibronectin, and integrins. We also found an altered expression of genes important for ECM homeostasis, e.g. MMPs, and ventricular trabeculation/compaction, e.g. Notch1. ECM is known to play important role in heart development, including trabeculation and formation of compacted myocardium. Our data suggest an important role played by Kmt2c in regulating ECM homeostasis and the formation of compacted myocardium.

Conclusions

We demonstrate, for the first time, that sEVs isolated from the PF of CAD patients induce a proinflammatory profile of human macrophages and that target crucial lipid metabolism pathways. These clinically relevant results could drive to decipher improved therapeutics able modulate the epicardial/myocardial immune response in CAD patients.

BS27 ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION AND MYOCARDIAL DEFORMATION IN A REPERFUSED MOUSE MODEL OF MYOCARDIAL INFARCTION

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We evaluated the feasibility and accuracy of four-dimensional preclinical ultrasound (4D-US) and speckle-tracking imaging (STI) for monitoring changes in function post reperfused myocardial infarction (MI).

Methods Seventeen female mice (age = 10–12 wk) underwent ligation of the left anterior descending coronary artery. Cardiac MRI (Varian 9.4T) and echocardiographic images (Visualsonics 3100) were acquired at 2weeks (n=6) or8weeks (n=11) post-surgery. Ejection fraction was calculated and then compared between 4D-US, MRI, M-mode and Simpson’s multi slice at each time point. Eight healthy mice and seventeen MI mice were used for STI strain analysis.

Results All ultrasound methods calculated ejection fractions that correlated with MRI. However, 4D-US provided the strongest agreement, outperforming M-mode and Simpson’s multi slice (4D-US: R2= 0.81, M-mode: R2= 0.55, Simpson’s: R2= 0.73) (table 1). STI-derived measures of global strain were significantly lower in the MI group in all dimensions (P < 0.005). (Figure 1 A) For regional strain analysis, circumferential strain values in MI were significantly lower in antero-lateral and septal regions compared with control mice (P < 0.001). (Figure 1 B). The longitudinal strain and radial deformation in MI were significantly decreased compared to the control groups. A, Differences in global strain between MI and control. B, Differences in regional strain in circumferential between MI and control. ns: not statistically significant; *P < 0.05; **P < 0.005; ***P < 0.001.

Abstract BS27 Figure 1 A-B, Differences in regional strain in circumferential between MI and control groups. A, Differences in global strain between MI and control groups. B, Differences in regional strain in circumferential between MI and control groups. ns: not statistically significant; *P < 0.05; **P < 0.005; ***P < 0.001.
strain were decreased in all segments of MI hearts compared with control mice except for one basal segment (P < 0.001) (figure 2 A-B). These reductions in regional contractility reflect the territory of the occluded coronary artery. **Conclusion** This study demonstrates that 4D-US performs well against MRI and better than M-mode and Simpson’s multi slice for left ventricle function analysis after MI. STI offers global and regional assessment of myocardium deformation in MI models and can be used to evaluate global and regional functional improvement from experimental treatments for MI.