Editorial

Targeting selected extracellular matrix components to attenuate cardiac fibrosis

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Progressive fibrosis is a hallmark of heart failure and remains a central challenge in managing patients who have suffered from myocardial infarction (MI). Following ischemic injury to the heart, structural remodeling of the infarcted myocardium ensues. Structural cardiac remodeling, while initially adaptive, leads to irreversible heart failure due to the progressive loss of cardiac function resulting from myocardial fibrosis, wall thinning, and left ventricular (LV) dilatation (1). While surgical revascularization of the myocardium via coronary artery bypass graft (CABG) surgery and/or percutaneous coronary intervention (PCI) is beneficial, these interventions alone are unable to prevent progressive fibrotic remodeling and loss of cardiac function leading to clinical heart failure.

Cardiac fibroblasts are key mediators of the cardiac remodeling process. Following ischemic injury to the heart, activation of cardiac fibroblasts to a myofibroblast state drives progressive cardiac fibrosis (2). Myofibroblast activity leads to dysregulation of the cardiac extracellular matrix (ECM) environment, including net deposition of collagen types I and III and fibronectin (FN), and systolic and diastolic dysfunction (1,2). The ability to attenuate activation of cardiac fibroblasts presents an opportunity by which maladaptive fibrotic cardiac remodelling post-ischemic injury and progressive heart failure may be managed.

The recent findings of Valiente-Alandi *et al.* published in *Circulation*, characterize targeting FN polymerization as a promising therapeutic strategy for treating cardiac fibrosis. This study has been well designed and executed. By using two methods to interfere with FN polymerization, either a novel recombinant peptide inhibitor (pUR4) of FN polymerization or genetic ablation, Valiente-Alandi *et al.* provide rigorous evidence of this strategy's therapeutic potential. The authors present robust in-vitro evidence of the attenuation of myofibroblast activity. The use of human cardiac fibroblasts is an important step that brings their findings one step closer to clinical translation. In vivo findings presented by Valiente-Alandi *et al.* provide clear evidence of the therapeutic potential of targeting FN polymerization using a relevant ischemia-reperfusion (I/R) injury murine model. Relevant statistical models were used for the interpretation of the findings. The authors acknowledge the need for further investigation into the therapeutic window for FN polymerization interference post-I/R injury. Future work should be guided by considerations of a clinically relevant window of opportunity for treatment and the route of administration for a recombinant peptide. In summary, this work provides valuable insight into the management of progressive cardiac fibrosis and highlights the potential of leveraging the ECM. Valiente-Alandi *et al.* characterize targeting FN polymerization as a promising strategy by which maladaptive fibrotic cardiac remodelling post-ischemic injury and progressive heart failure may be addressed.

Our research group also aims to leverage the potential of the ECM in managing progressive cardiac fibrosis. We have shown that ECM bio-scaffolds are a new and

innovative solution for use as an adjunctive therapy to surgical revascularization of the myocardium post-ischemic injury. Our research demonstrates that ECM bio-scaffold is an active reservoir for bioactive components. We have provided evidence that restoring an optimal ECM environment is capable of attenuating cardiac fibroblast activation, promoting a pro-vasculogenic response, and leading to functional recovery post-ischemic injury to the heart in a pre-clinical porcine model (3-5). Ultimately, an ideal therapy will be directed at the attenuation of myofibroblast activity to prevent progressive cardiac fibrosis and promote functional recovery in patients post-MI.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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