Nature Reviews Drug Discovery | AOP, published online 16 October 2015; doi:10.1038/nrd4764

CARDIOVASCULAR DISEASE

Patching up the heart

The ability of adult mammalian heart tissue to regenerate is limited and insufficient to repair injury caused by myocardial infarction (MI). Although considerable efforts are currently being invested in the development of stem cell-based regeneration strategies, several challenges remain. Now, writing in *Nature*, Ruiz-Lozano and colleagues identify the epicardial protein follistatin-like protein 1 (FSTL1) as a cardiomyocyte regenerative factor that is lost upon MI. Restoration of epicardial FSTL1 levels improved cardiac function and survival in mouse and swine MI models.

The epicardium of the heart is an external epithelial layer that contributes to myocardial growth during development by providing progenitor cells and mitogens. Given this, Ruiz-Lozano and colleagues set out to identify whether epicardium-secreted factors might support adult myocardial regeneration.

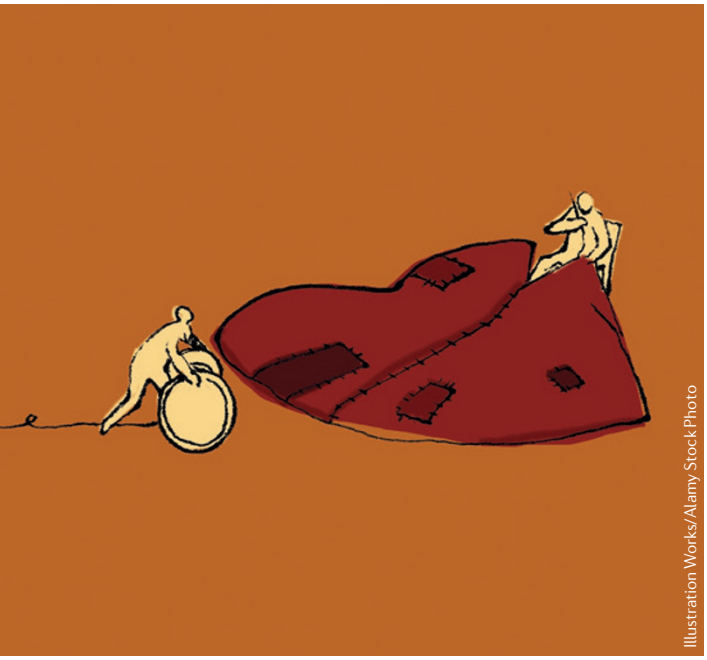

Illustration Works/Alamy Stock Photo

To do this, they first co-cultured mouse embryonic stem cell-derived cardiomyocytes ($mCMs^{ESC}$) with epicardial mesothelial cell (EMC) cultures, which stimulated $mCMs^{ESC}$ proliferation. This effect was recapitulated with conditioned media prepared from EMC cultures (EMC media) or from adult epicardium-derived cells. Furthermore, suturing collagen nano-fibrillar patches containing EMC media to the epicardium of adult mouse hearts immediately following surgically induced MI improved morphometric parameters and cardiac function after 2 weeks.

The authors then set out to identify specific factors that might mediate the beneficial effects of this patch on the injured heart. Mass-spectrometric analysis of EMC media identified FSTL1 — a known modulator of cardiac development — as one of the most abundant secreted proteins. Indeed, treatment of $mCMs^{ESC}$ with recombinant human FSTL1 for 8 days increased the number of functional cardiomyocytes.

Analysis of mouse FSTL1 expression revealed that although the protein is expressed throughout the myocardium during fetal development, expression is restricted to the epicardium during adulthood. However, following ischaemic injury, FSTL1 becomes abundant in the myocardium and absent from the epicardium and infarcted area.

The authors therefore next investigated the effects of preserving epicardial FSTL1 levels during MI *in vivo*. They sutured hFSTL1-loaded collagen patches to the epicardium of mouse hearts and simultaneously induced MI. Four weeks later, cardiomyocyte cell cycle entry and cytokinesis were observed, accompanied by attenuated fibrosis and increased vascularization. This resulted in significantly improved survival and sustained long-term recovery of cardiac function.

Similar cardiac recovery occurred when epicardial hFSTL1-loaded patches were grafted 1 week after ischaemia–reperfusion injury (IRI) in mice, when cardiac function had substantially decreased. In addition, delivery of epicardial FSTL1 in the swine model of IRI promoted stable recovery of contractile function and limited fibrosis.

Surprisingly, myocardial FSTL1 did not promote heart regeneration, either basally or following transgenic overexpression in cardiomyocytes, but instead seemed to have a cardioprotective role. Further studies indicated that the differences in proliferation-stimulating activity between the epicardial and myocardial forms of the protein may be due to post-translational modifications, such as cell-type specific glycosylation.

Epicardial FSTL1 therefore represents a regenerative factor that is normally present in healthy epicardium, but lost upon MI. Thus, restoring epicardial FSTL1 may represent a new approach to promoting cardiomyocyte regeneration following MI.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPER Wei, K. *et al.* Epicardial FSTL1 reconstitution regenerates the adult mammalian heart. *Nature* **525**, 479–485 (2015)