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INVITED EDITORIAL

A dualistic approach to heart repair through FGF10

Tim Koopmans[1] and Eva van Rooij [1,2]*

[1]Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences (KNAW) and University Medical Center Utrecht, Utrecht, Netherlands; and [2]Department of Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

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This editorial refers to 'FGF10 promotes cardiac repair through a dual cellular mechanism increasing cardiomyocyte renewal and inhibiting fibrosis' by F. Hubert *et al.*, https://doi.org/10.1093/cvr/cvab340.

When oxygen demand outweighs its supply for prolonged periods the heart undergoes a myocardial infarction (MI), with a corresponding loss in heart muscle, pump function, and formation of a rigid scar. The acute loss in myocardial tissue and replacing scar drive a sequence of maladaptive remodelling responses that ultimately can overwhelm the coping mechanisms of the heart, paving the way for heart failure. Consequently, ischaemic heart disease kills more people than any other disease worldwide.[1]

Without an evolved mechanism for rapid renewal, remaining cardiomyocytes have little to offer to combat lost pump function. While the heart's capacity for cardiomyocyte regeneration is still present up to 1 week after birth, this response fades during adult stages in mammals.[2] Understanding the molecular biology involved, and how to control it, are key objectives of cardiovascular regenerative medicine. A recent study by Hubert *et al.*[3] shows that fibroblast growth factor 10 (FGF10) may be one of these.

Previous work from the Rochais lab demonstrated that FGF10, while absent in adult hearts, is specifically expressed in right ventricular cardiomyocytes during late stage development and neonatal growth, where it controls its own proliferation presumably through an autocrine loop.[4] In their most recent work discussed here, Hubert *et al.*[3] show that under injury conditions (permanent ligation of the left anterior descending coronary artery to model MI) FGF10 broadly recapitulates its developmental expression pattern in adult mice, albeit with low levels. By using

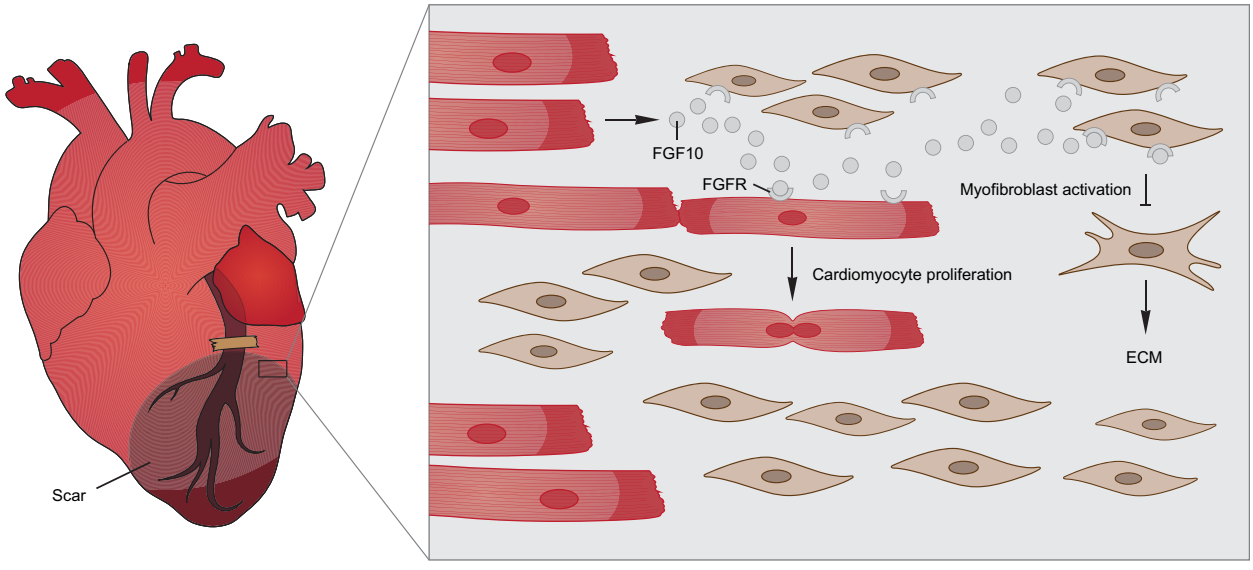

Figure 1 Proposed mode of action of FGF10 in the damaged adult mammalian heart.

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* Corresponding author. E-mail: e.vanrooij@hubrecht.eu

transgenic overexpression, they go on to show that increasing FGF10 beyond its native expression can partly alleviate the injury response by pushing the mitosis-refractory myocardium into a more proliferative state, presumably by acting on pre-existing adult mononucleated cardiomyocytes. Conversely, FGF10 haploinsufficiency disrupts this process, resulting in a worsening of pathological remodelling and a further decline in function. A follow-up analysis on failing human heart samples corroborated these results and revealed a strong correlation between FGF10 expression levels and cycling ($MKI67^{+}$), small-sized cardiomyocytes.

Although FGF10 expression is normally restricted to the cardiomyocyte in the infarcted adult mouse heart, its receptors (e.g. FGFR1 and FGFR2B) follow a more broad expression profile. Indeed, global elevation of FGF10 pleiotropically benefitted the heart beyond the proliferative capacity of the cardiomyocyte, with favourable effects on ejection fraction, left ventricular end systolic volume, and remodelling parameters, while reduced FGF10 levels showed the opposite effect. Although a detailed investigation on the supposed non-cell-autonomous mechanisms of FGF10 remains to be further clarified, the authors provide some initial groundwork that points to the cardiac fibroblast. Systemic elevation of FGF10 was associated with reduced infarct size and accompanying fibrosis, and decreased expression of myofibroblast target genes tailored towards its activation and the extracellular matrix (e.g. Pgdfra, Col1a1, and Col3a1). Follow-up bulk RNA sequencing experiments (21 days post-MI) confirmed the downregulation of extracellular matrix genes, and elevated FGF10 correlated with reduced fibrosis in human patient samples. With supporting *in vitro* experiments in human cardiac fibroblasts, it was proposed that FGF10 interferes with transforming growth factor beta 1 (TGF-β1) signalling (which plays a central role in cardiac fibrosis) to inhibit myofibroblast differentiation (*Figure 1*).

Post-MI fibrosis is a dynamic and complicated process, and anti-fibrotic drugs for cardiac disease have proven difficult in the clinic.[5] The evolving composition, collagen load, fiber orientation and degree of cross-linking, size, shape, and location of the scar are all important determinants of heart function, remodelling, and patient outcome. As such, understanding the functional implications of fibroblast biology *in vivo* requires a deep understanding on tissue mechanics and physiological interactions that take place in the heart (e.g. scar formation vs neurohormonal activation).[6] Future work on FGF10 as an anti-fibrotic agent should therefore emphasize on the molecular and cellular mechanisms underlying the complexity of cardiac fibrosis, making use of single-cell transcriptomics, epigenomics, and/or proteomics approaches to help chart the fibroblast landscape in more detail.

Despite the requirements for follow up mechanistic experiments, the clear cardioprotective potential of FGF10 supplementation provides sufficient rationale for exploring FGF10 as a therapeutic strategy. The apparent ease at which these mice tolerate high levels of systemic FGF10, at least up to 21 days post-MI, lends support to FGF10 as a clinically relevant candidate, yet long-term effects of chronic FGF10 exposure should first be carefully considered. Recombinant FGF10 (repimerfin) has already been tested clinically as a treatment option for ulcerative colitis and mucositis, but its development was terminated after it failed in several clinical trials.[7] Nevertheless, the drug was well tolerated and administered topically, which leaves room for exploring the ischaemic heart as a potential target organ. Some challenges remain to improve half-life, tissue retention and bio-availability of freely available proteins, prompting bio-engineering approaches (e.g. bio-compatible polymers) that can be co-administered along with FGF molecules.[8] As FGF10 normally is expressed in cardiomyocytes only, the use of adeno-associated virus (AAV)-mediated overexpression using a cardiotrophic vector could be explored to enhance local delivery and prevent at least some of the unwanted off-target effects.

Overall, the study by Hubert *et al.*[3] clearly shows a beneficial effect of FGF10 after ischaemic injury. While the effects of FGF10 on cardiomyocytes might be cell autonomous, its effects on cardiomyocyte regeneration might simultaneously reduce activation of nearby fibroblasts and hence cardiac fibrosis, which can further facilitate the pro-proliferative niche for cardiomyocytes. And while the exact cellular contribution in response to the FGF10 treatment still needs to be parsed out, the presented dual cellular mechanisms by which FGF10 acts upon the injured heart might mark the beginning for what could be a relevant heart-healing strategy to invest in going forward.

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