


CARDIOVASCULAR DISEASES

Periostin regenerates broken heart

DOI:
10.1038/nrd2406

Myocardial infarction, which results in scar formation rather than regeneration of the lost cardiomyocytes responsible for the 'pump' function of the heart, is a major cause of heart failure. Kühn and colleagues, writing in *Nature Medicine*, now show that following myocardial infarction, cardiomyocytes can be induced to proliferate by a recombinant protein known as periostin, resulting in improved cardiac function. Periostin and the pathway it induces could thus represent a novel therapeutic target for heart failure.

Following observations that cardiomyocytes in the border zone of a myocardial infarction have transiently increased cell-cycle activity, the authors hypothesized that

it may be possible to apply extracellular factors to induce cardiomyocyte proliferation. The authors identified periostin — a protein normally expressed during cardiac development but also re-expressed following injury to adult tissue including the myocardium — as a potential factor for inducing proliferation.

In vitro studies showed that periostin induces the full mitotic cell cycle of differentiated mononucleated rat cardiomyocytes. Further examinations showed that periostin requires integrin α_v and a β_1 , β_3 or β_5 subunit to induce cell-cycle re-entry via the phosphatidylinositol-3 kinase (PI3K) pathway. Inhibition of AKT signalling, an important downstream target of PI3K, also reduced periostin-induced cell-cycle re-entry. To confirm these results, adenoviral transduction of the bifunctional phosphatase PTEN, known to regulate the PI3K pathway, abolished periostin-stimulated DNA synthesis in cardiomyocytes. Also, transduction of a constitutively active form of PI3K increased cardiomyocyte DNA synthesis in the absence of periostin, indicating that PI3K signalling is sufficient for cell-cycle re-entry in the absence of periostin.

To determine whether periostin stimulates cardiomyocyte cell-cycle re-entry *in vivo*, recombinant periostin was injected into the myocardium of rats, resulting in cycling mononucleated cardiomyocytes with periostin-induced DNA synthesis and cytokinesis near the injection site.

As it had been previously suggested that sustained cardiomyocyte cell-cycle activity may decrease infarct size following myocardial infarction, Kühn and colleagues developed a long-term delivery system in which periostin is associated with Gelfoam, a biodegradable extracellular matrix.

In a rat model of myocardial infarction, periostin bound to Gelfoam was administered epicardially at the time of heart injury. Twelve weeks later, the periostin-treated rats had improved ventricular remodelling, better myocardial function and reduced infarct size. In periostin-treated hearts, these improvements were attributed to the 100-fold higher proportion of cycling cardiomyocytes compared with apoptotic cardiomyocytes 12 weeks after the myocardial infarction. Also, compared with the control hearts, the periostin-treated hearts had ~6 million more cardiomyocyte nuclei. Based on this, the authors concluded that cell-cycle re-entry and division of differentiated cardiomyocytes can account for the periostin-induced functional and structural improvements, which may provide an approach to induce myocardial repair.

Bethan Hughes



ORIGINAL RESEARCH PAPER Kühn, B. *et al.* Periostin induces proliferation of differentiated cardiomyocytes and promotes cardiac repair. *Nature Med.* **13**, 962–969 (2007)

FURTHER READING Kaye, D. M. *et al.* Drug discovery for heart failure: a new era or the end of the pipeline? *Nature Rev. Drug Discov.* **6**, 127–139 (2007)