CLINICAL IMPLICATIONS OF BASIC RESEARCH

Periostin and Myocardial Repair, Regeneration, and Recovery

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Early reperfusion therapy for myocardial infarction has transformed the treatment of this disease. The restoration of blood flow to the heart within hours after thrombotic coronary occlusion reduces infarct size, maintains cardiac function, and minimizes the risk of late heart failure and lethal arrhythmias. However, high success rates of coronary reperfusion, coupled with aggressive efforts to shorten the time from the manifestation of symptoms to the restoration of arterial blood flow, have brought us close to the practical limits of acute revascularization therapy for myocardial infarction.

Recent work by Kuhn et al.[1] underscores the influence of postinfarction cellular and molecular events on adverse cardiac remodeling and heart failure. An understanding of these events may lead to new strategies to improve outcomes that offer a therapeutic window of weeks rather than hours.

Shortly after myocardial infarction, dead or severely damaged cardiomyocytes are eliminated through phagocytosis or programmed cell death (apoptosis) and are replaced by migratory interstitial fibroblasts. The fibroblasts lay down a dense extracellular matrix of collagen that, like any new scar, requires a robust vasculature. Concomitantly, surviving cardiomyocytes in the peri-infarct area, which are terminally differentiated and therefore normally incapable of proliferating, undergo pathologic hypertrophy to compensate for the lost contractile tissue. When scarification is insufficient or impaired, as in patients undergoing long-term treatment with glucocorticoids, intraventricular pressures can overwhelm the structural integrity of the damaged myocardium, causing potentially lethal ventricular rupture. Therefore, proper wound healing and cardiac scarring after myocardial infarction is essential for survival, and the risk of an adverse outcome after myocardial infarction has less to do with the size of the infarct than with whether there is abnormal cardiac dilatation, or remodeling.[2]

Remodeling that occurs over weeks or months after infarction is the result of dilation of the ventricular cavity, with pathologic hypertrophy and fibrosis of the noninfarcted myocardium, each of which further impairs cardiac function. Mechanistically, the noncontracting myocardial scar exerts biomechanical stress on the surrounding viable myocardium, which responds by releasing neurohormones and cytokines that stimulate apoptosis of cardiomyocytes and replacement fibrosis. These cellular events and processes are the same as those that are essential to infarct healing. The goal is therefore to support local infarct healing while limiting more generalized myocardial remodeling. To this end, the regeneration of normal myocardium — by means of either transforming undifferentiated precursor stem cells into cardiomyocytes and vascular cells or forcing the proliferation of terminally differentiated cardiomyocytes and the blood vessels that serve them — has become the holy grail of cardiac repair.

Adult cardiomyocytes are severely limited in their ability to proliferate. Indeed, only a handful of adult myocardial cells in a million have detectable nuclear-DNA synthesis, and since adult cardiomyocytes typically have two nuclei, the extent to which these rare nuclear divisions actually produce new cells is unknown. However, observations of dramatic increases in the synthesis of cardiomyocyte DNA after myocardial injury[3] suggest that proliferation can be conditionally induced. Kuhn et al. attempted this by co-opting a factor implicated in many cancers.

The key cellular events that result in cancer are increased proliferation of cells and tissues, accompanied by angiogenesis, precisely the critical processes that are needed for myocardial regeneration, if they can be targeted to the heart. Kuhn et al. examined the effects of periostin —

a protein involved in cell survival and angiogenesis that is secreted by many human tumors[4] — on cardiac repair. They observed that a truncated recombinant form of periostin increased the rate of DNA synthesis in adult cardiomyocytes in tissue culture by stimulating integrins to activate the phosphatidylinositol 3′-kinase–protein kinase B pathway. The injection of periostin into normal rat hearts increased the prevalence of markers of cardiomyocyte DNA synthesis and cytokinesis, confirming the in vitro findings. The long-term application of periostin to infarcted rat hearts with

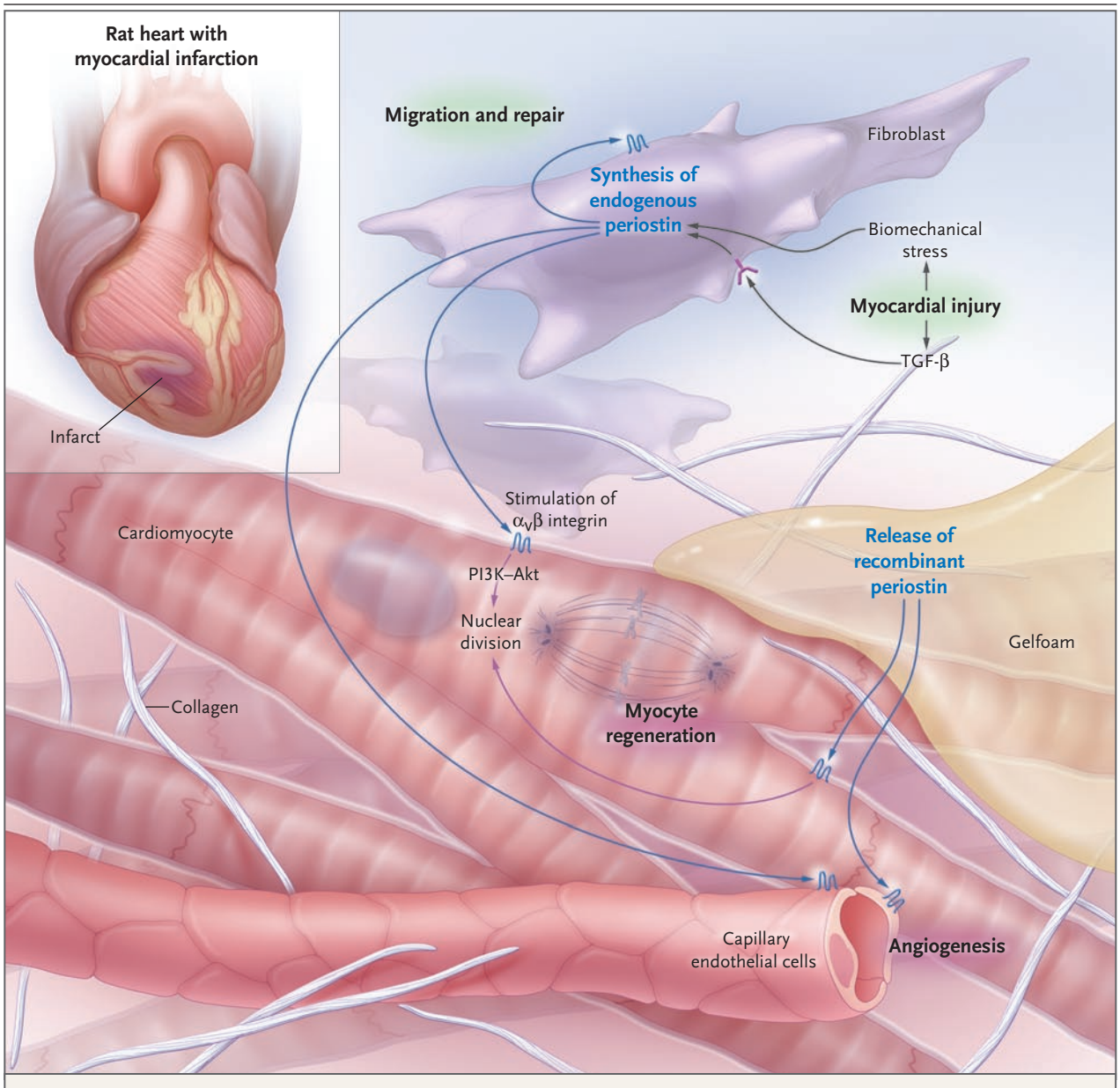

Figure 1. Periostin and Cardiac Remodeling.

A recent study by Kuhn et al.[1] suggests that the application of periostin can enhance cardiac repair after myocardial infarction in the rat. Whereas the endogenous production of periostin by myocardial fibroblasts is stimulated by cardiac injury and promotes healing by activating $\alpha_v\beta_1$, $\alpha_v\beta_3$, or $\alpha_v\beta_5$ integrins on myocytes and vascular endothelial cells, long-term release of recombinant periostin from a Gelfoam patch on the epicardium was found to stimulate the same pathways to promote cardiomyocyte regeneration and angiogenesis, thus minimizing remodeling. TGF-β denotes transforming growth factor β, and PI3K–Akt phosphatidylinositol 3′-kinase–protein kinase B.

the use of saturated Gelfoam patches attached to the epicardium did not affect the short-term infarct size or impair scarring but did enhance contractile performance and improve cardiac remodeling after 12 weeks, while decreasing myocardial fibrosis and cardiomyocyte hypertrophy. Hearts treated with periostin also had denser capillary beds than did control hearts, suggesting enhancement of myocardial angiogenesis (Fig. 1).

Periostin is normally secreted by cardiac fibroblasts in response to myocardial injury, and it interacts with integrin receptors on target cells to modulate cellular and matrix remodeling (Fig. 1). The potential for recombinant forms of periostin or other factors with similar activity profiles to improve cardiac repair and regeneration is tantalizing.

The data described by Kuhn et al. do not establish a causal relation between periostin-stimulated cardiomyocyte proliferation and improved cardiac remodeling after myocardial infarction, nor is it clear that the nuclear division in cardiomyocytes resulted in the production of new cardiomyocytes. Furthermore, the prevention of myocardial fibrosis and hypertrophy is not necessarily a primary effect of recombinant periostin but may be a by-product of the overall improvement in cardiac hemodynamic status. Indeed, periostin-knockout mice paradoxically show reduced fibrosis and better cardiac function, as compared with wild-type mice, after myocardial infarction.[5] Further studies are needed to clarify these issues. Meanwhile, the clinical application of periostin or conceptually similar therapies to target cardiac remodeling after myocardial infarction remains an exciting prospect.

No potential conflict of interest relevant to this article was reported.

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