

EDITORIAL COMMENT

New Insight Into Healing Mechanisms of the Infarcted Heart*

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Myocardial infarction (MI) leads to rapid necrosis of cardiac myocytes in the ischemic heart. Despite aggressive primary therapies to reconstitute blood supply and intense pharmacological approaches, prognosis remains poor, especially in patients with large MI and severe left ventricular dysfunction. Mechanistically, large myocardial infarcts induce a process termed “cardiac remodeling” that consists of morphologic, histological, and molecular changes of both the infarcted and the non-infarcted myocardium (1). Ventricular remodelling is a strong prognostic determinant and closely related to the incidence of arrhythmias and sudden cardiac death (2). There is an extremely narrow time window to rescue viable myocardium, and in contrast to some rare exceptions in nature (3), activation of endogenous healing mechanisms is insufficient to maintain tissue integrity and function. Thus, therapeutic approaches targeting healing mechanisms to prevent infarct expansion would be of great value. An understanding of such mechanisms is scarce but important to develop novel strategies to prevent development of heart failure after MI.

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The transforming growth factor (TGF)- β superfamily and MI. The TGF- β superfamily of cytokines exerts important functions in tissue homeostasis and adaptation by regulating cell survival, proliferation, and differentiation. Members include bone morphogenetic proteins, growth differentiation factors (Gdf), anti-muellerian hormone, activin, nodal, and TGF- β . A variety of those members have been described as playing a role in the development of cardiac diseases; for instance, it is well known that TGF- β plays an important role in extracellular matrix formation,

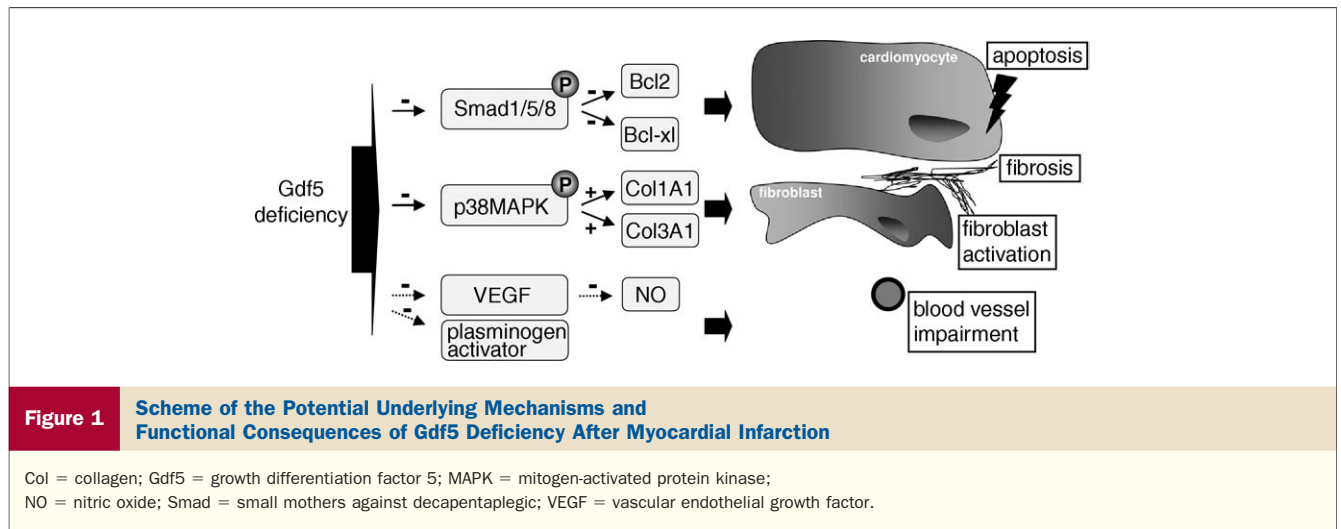
especially collagen production. Animals with targeted deletion of TGF- β display reduced collagen deposition (4), whereas an increase of TGF- β in the heart results in cardiac hypertrophy, interstitial fibrosis, and delayed wound-healing (5,6). Further TGF superfamily members are increased during heart failure and contribute to cardiac remodelling, including activin (7) and Gdf8 (myostatin) (8). The distant member Gdf15 protects the heart from ischemia/reperfusion injury, and consequently Gdf15-deficient mice develop greater infarct sizes and display more cardiomyocyte apoptosis in the infarct border zone (9).

In this issue of the *Journal*, Zaidi et al. (10) demonstrate a novel role for another member of the TGF- β superfamily, the growth Gdf5, for cardiac repair after MI. An important finding of the authors is that Gdf5 exerts functional effects in several different cells of the myocardium, including cardiomyocytes, cardiac fibroblasts, and potentially cardiac endothelial cells. Loss of Gdf5 substantially increases collagen production and fibrosis in post-infarction hearts, demonstrating key effects on cardiac fibroblasts. In addition, Gdf5 knockout (KO) mice show an increased rate of cardiomyocyte apoptosis, a further hallmark of heart failure. Finally, the authors found a reduced vascular density in animals lacking Gdf5 after MI, although this was not studied in detail. Thus, Gdf5 might target at least 3 important cellular compartments of the heart, all of considerable importance for ventricular remodelling processes. Cell type-specific KO strategies might further contribute an understanding on the individual roles in selected cardiac cell types. The authors detected Gdf5 expression in cardiomyocytes and myofibroblasts but did not analyze its expression in cardiac endothelial cells. This is surprising because Gdf5 was the first family member reported to may have a role in angiogenesis, and it was found that the addition of Gdf5 accelerated the migration of endothelial cells, whereas it did not affect their proliferation. Additional effects of the lack of Gdf5 in cardiac endothelium might result in angiogenesis defects after MI that would further contribute to impaired cardiac healing. One might speculate whether alterations in vascular density are mediated by direct Gdf5 effects on endothelial cells or whether potentially secondary paracrine effects are mediated by alterations of cardiomyocytes and/or fibroblasts. Whether further cells important for cardiac healing such as cardiovascular progenitor/stem cells or inflammatory cells are affected by Gdf5 also remains to be determined.

Mechanism of action of Gdf5. Usually, a TGF- β superfamily ligand binds to a TGF- β type II receptor, which functions as a serine/threonine receptor kinase. Upon receptor activation, certain small mothers against decapentaplegic (Smads) are activated. The underlying molecular mechanisms that drive such phenotypic alterations by Gdf5 deficiency seem to be different in cardiomyocytes, cardiac fibroblasts, and potentially endothelial cells. The Gdf5 induces p38-mitogen-activated protein kinase (MAPK)

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phosphorylation in cardiac fibroblasts and thus limits collagen production, whereas no effects are observed in cardiomyocytes. In contrast, Gdf5 has anti-apoptotic effects in cardiomyocytes that are mediated by endogenous Smad4 (and secondarily Smad1/5/8) but not p38-MAPK (Fig. 1). Only low numbers of p-Smad1/5/8-positive cells are detectable both in the scar tissue and viable myocardium after MI, implicating bone morphogenetic protein signaling as not playing a crucial role in remodeling (11). In contrast, the authors observed a sustained increase of p-Smad1/5/8 expression in Gdf5-KO mice after MI, suggesting a superior role of Gdf5 in regulation of this group of Smad factors. In aortic endothelial cells Gdf5 is pro-angiogenic at least in part by plasminogen activator activity (12). However, the upstream events that lead to different effects in different cardiac cells are unclear and need further mechanistic analyses. In addition, it is unclear whether there is crosstalk between various members of the TGF- β superfamily that drive molecular and morphological changes after MI. In addition, information about the role of TGF- β superfamily antagonists during infarct healing is missing. For instance, members of the DAN family of proteins (Ceberus, DAN, Gremlin) might antagonize TGF- β family members, and DAN indeed interacts with Gdf5 (13).

The authors' findings of reduced blood pressure of Gdf5-KO mice are interesting but warrant further detailed analysis. The Gdf5 increases vascular endothelial growth factor-A production (14), which augments nitric oxide release from the endothelium (15). This might contribute to the strong differences in overall blood pressure between wild-type and Gdf5-KO animals.

Gdf5: potential therapeutic approaches. The idea to use Gdf5 for therapeutic approaches is not entirely new and has been applied to induce formation and healing of tendons or bones (16,17), protect neurons in Parkinson's disease (18), or improve erectile dysfunction (19). The detrimental effects of the lack of Gdf5 on outcome after MI suggest therapeutic beneficial effects with this factor for cardiac healing. Future

studies need to test transgenic overexpression or pharmacological strategies that increase Gdf5 concentration in the heart after MI for therapeutic use. This would be of considerable interest, because the authors identified Gdf5 to confer anti-apoptotic effects on cardiomyocytes, and further data suggest angiogenic and anti-fibrotic characteristics, important to prevent ventricular remodeling. In conclusion, Zaidi et al. (10) provided new insight in healing mechanisms of the infarcted heart; approaches using Gdf5 might translate into new clinical translational strategies for post-MI treatment.

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