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EDITORIAL COMMENT

Platelet-Derived Growth Factors

A New Therapeutic Opportunity for Treating Cardiac Fibrosis?*

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Myocardial infarction (MI) is among the leading causes of morbidity and mortality worldwide.[1] MI is characterized by ischemic death of a substantial portion of the left ventricle, leading to a wound healing response that ultimately results in replacement of functional tissue with a collagenous scar. The development of the scar is mediated by cardiac fibroblasts, which differentiate to a myofibroblast phenotype capable of secreting large amounts of collagen and other extracellular matrix (ECM) components. Whereas this "reparative" fibrosis is required to replace necrotic tissue and prevent myocardial rupture, excessive "reactive" fibrosis that extends into the border and remote areas further impairs cardiac function and dramatically increases the risk of developing heart failure.[1,2] Although classical pharmaceutical approaches targeting neurohormonal heart failure pathways have some off-target antifibrotic properties, therapies specifically targeting fibroblasts and fibrosis have largely been unsuccessful. Thus, novel therapies specifically targeting these cells are of major interest in treating patients with MI.

In this issue of *JACC: Back to Translational Science,* Hume et al[3] investigated the therapeutic efficacy of platelet-derived growth factors (PDGFs) in treating MI, specifically PDGF-AB. PDGFs are a group of signaling proteins that affect cellular mitosis and migration and have been studied for their role in angiogenesis.[4] Recently, this group showed that PDGF-AB improved cardiac function, vascular remodeling, and scar alignment 28 days after MI in a pig model.[5] Studying human cardiac fibroblasts in vitro, Hume et al[3] found that of several PDGF isoforms, PDGF-AB was able to attenuate the myofibroblast phenotype as assessed by a more spindle-shaped structure and decreased α-smooth muscle actin expression. PDGF-AB exerted an antiproliferative effect, but promoted migration of human cardiac fibroblasts. Furthermore, PDGF-AB promoted a unique ECM profile in human cardiac fibroblasts and exerted a proangiogenic phenotype. Next, using a murine model of MI, Hume et al[3] investigated the mechanisms by which PDGF-AB improves scar remodeling, showing that PDGF-AB had a robust effect to decrease myofibroblast differentiation in the infarct and border zones, while increasing fibroblast interactions with other cell types. They next explored the mechanisms by which PDGF-AB improved cardiac function after myocardial ischemia-reperfusion in a pig model, which is considered the gold standard of translational models for MI. Reflecting their earlier results, PDGF-AB reduced myofibroblast differentiation without affecting proliferation in the post-MI pig heart. Using RNA-sequencing, they identified key ECM and inflammatory gene networks altered by PDGF-AB. They also found that PDGF-AB increased the proportion of proreparative M2 macrophages and increased scar anisotropy or alignment and organization of the collagen fibrils. Finally, they showed that PDGF-AB treatment altered hundreds of long noncoding RNAs. True to their earlier findings in fibroblast phenotypes, these long noncoding RNAs were predicted to down-regulate genes associated with cell cycle (ie, proliferation), ECM degradation and inflammation, while up-regulating genes for required for cell migration. These exciting results offer a promising new endogenously produced candidate for improving scar remodeling after MI.

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In addition to the exciting translational results presented in this study,[3] the novel methodology provides new insights into fibroblast interactions with the local microenvironment and geometric analysis of the scar tissue. For example, the team employed imaging mass cytometry, which uses machine-based learning to identify fibroblast subtypes and their spatial distribution in the heart (infarct, border, and remote zones). They were able to identify 19 distinct fibroblast clusters and found that PDGF-AB down-regulated a specific cluster that expressed proliferative markers (Ki67). They also calculated decreased overall differences between several sets of clusters, indicating that PDGF-AB enhanced fibroblast interactions with other cell types. This finding indicates that enhancing fibroblast interactions with other cells, such as immune or endothelial cells, may affect their ability to cross-talk with these cells to regulate inflammation and angiogenesis. This highlights the importance of assessing cell spatial distribution, in addition to more traditional measures of fibroblast activation, for fibrosis studies moving forward.

While this impressive study by Hume et al[3] offers much translational and methodological value, it raises several questions. One is the receptor mechanism by which PDGF-AB exerts its effects. Cardiac fibroblasts widely express PDGF-receptor α (PDGFRα), and is often used as a cardiac fibroblast marker.[4] Because PDGFRα is the only PDGFR expressed in these cells, it is assumed that it mediates the effects of PDGF-AB. Hume et al[3] did find that transforming growth factor β (TGF-β) treatment increased PDGFRα expression, bringing into question whether this is a negative feedback loop in which the profibrotic TGF-β sensitizes fibroblasts to PDGF-AB to prevent excessive myofibroblast activation. This was reflected in the results of Hume et al,[3] in which PDGF-AB partially attenuated the effects of TGF-β on myofibroblast phenotype. Loss of PDGFRα inhibits fibroblast activation to an extent large enough to disrupt appropriate healing after MI.[1,4] It would be informative to investigate whether a specific PDGFRα agonist exerts the same effects as PDGF-AB, as well as avoiding the pleiotropic effects of PDGF-AB on other cell types, such as anti-inflammatory/proreparative M2 macrophages. Hume et al[3] justifiably focused on PDGF-AB; however, it will be critical to understand the roles of other isoforms on PDGFRα signaling in fibroblasts. Another important factor to consider is the potential timing of the administration and its effect on remodeling and fibrosis of the remote (noninfarcted) area of the heart. Whereas PDGF-AB impressively accelerated scar maturation, the remodeling of the remote LV is arguably more important in terms of long-term outcomes in patients with MI.[1] Thus, it may be of more therapeutic value if PDGF-AB attenuates remote left ventricular fibrosis long term.

In summary, the study presented by Hume et al[3] offers much basic, translational, and methodological insight into improving cardiac remodeling and attenuating fibrosis after MI. The results highlight the necessity of further understanding the roles of PDGFs in cardiac fibroblasts, whereas the novel methods indicate the importance of assessing geometric and spatial characteristics of cardiac fibroblasts and adopting this as standard practice.

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