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EDITORIAL COMMENT

A Potential New Therapeutic Direction for Fibrosis in the Injured Heart Orchestrated by Cardiac MSCs*

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Each year more than 800 thousand people in the United States alone experience myocardial infarction (MI). Some of these patients will develop heart failure, and currently, more than 6 million people only in the United States are diagnosed with heart failure. These alarming statistics illustrate the urgent need to better understand the cellular and molecular mechanisms leading to heart failure with a clear purpose of identifying the druggable target(s).

One of the recent approaches to improving heart function was stem cell-based therapy. Initially, it was hypothesized that stem cells (using autologous mesenchymal stem cells [MSCs]) of the umbilical cord or bone marrow origin might replace the damaged myocardium, and therefore, adverse remodeling would be reduced as well. Because it was demonstrated that these stem cells do not differentiate into cardiomyocytes, the paracrine effects that MSCs can exert on the neighboring cells were considered as a rationale for subsequent clinical studies. Recent meta-analyses of clinical trials in which MSC therapy was applied indicate that the long-term clinical benefits are small,[1] suggesting that other approaches should be considered.

The failing heart displays an array of dysregulations on cellular and molecular levels. Among them, 2 intertwined processes, fibrosis and inflammation, are hallmarks of the failing heart. Although it is clear that the fibroblast/myofibroblast population is expanded and produces excessive extracellular matrix proteins, the origin of these cells may not be fully understood. The fibroblast population has a high level of phenotypic and functional heterogeneity,[2] suggesting that different developmental origins may contribute to various fibroblast subtypes in steady-state and after injury.

Cardiac endogenous mesenchymal stem cells (cMSCs) have been identified as one of the fibroblast progenitors in the embryonic and adult heart.[3] CMSCs can contribute to homeostasis and repair after MI but also can cause overactive fibrosis, as discussed in the following text. Highlights from the recent literature show that endogenous MSCs in bone marrow, skeletal muscle, and heart undergo phenotypic and functional changes with aging and diseases in both human and rodent tissues.

In this issue of *JACC: Basic to Translational Science*, Hamid et al[4] elegantly delineate the mechanism by which cMSCs contribute to heart failure in a mouse model of permanent left coronary artery ligation. This study determined that after infarct, there is more than a 5-fold increase in the number of cMSC, which were characterized as $Sca1^{+}Lin^{-}CD45^{-}CD31^{-}DDR2^{-}$. These cMSCs, when isolated 8 weeks post-MI, release a plethora of cytokines and chemokines. Via the paracrine effect, therefore, cMSCs can influence leukocyte infiltration and macrophage polarization. Hamid et al[4] demonstrated that cMSCs could skew macrophage polarization into both M1 proinflammatory and M2 anti-inflammatory phenotypes, with a clear preference toward M1 polarity. Interestingly, coculture experiments revealed that M1 macrophages facilitate the cMSC differentiation into

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myofibroblasts in a reciprocal manner. Likewise, the myofibroblast population in the failing hearts was amplified 20-fold. The further analysis of cMSCs in the failing hearts reveals that they preferentially respond to PDGF-B and -D and express predominantly PDGFRβ, whereas PDGFRα^{+} cMSCs populate uninjured hearts. Three weeks of daily injections of imatinib, a nonspecific PDGFRβ inhibitor, stopped the decline of systolic function, reduced overactive fibrosis, and limited the number of monocyte-derived macrophages.

The current study introduces the notion that the PDGFRβ may be a therapeutic target for heart failure (or prevention of heart failure after injury). Imatinib is a nonspecific inhibitor, but the authors, by genetically silencing PDGFRβ, were brought to the same conclusion as for the imatinib study, which increases confidence in these data. The use of imatinib in other experimental models of heart diseases (hypertension, myocarditis, or chronic catecholamine stimulation) or other organ diseases (lungs) demonstrates significant overall improvement and fibrosis reduction. What is even more attractive in this work is the fact that imatinib is already used clinically, which can significantly simplify a potential drug approval process. Although the use of tyrosine kinase inhibitors is associated with cardiotoxicity,[5] the study uses a lower dose than the ones used to treat leukemias, suggesting that it can have positive outcomes without adverse effects in cardiac patients.

Given the fact that, as of today, there are no FDA-approved drugs treating cardiac fibrosis either by stopping the progression of the disease or reversing it, the recent study gives new insights into the biology of cMSCs and their response to pharmacological inhibition of PDGRFβ signaling, opening a possibility to a new therapy.

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