IL-10 targets myofibroblasts and dampens cardiac fibrosis

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Provenance: This is a Guest Editorial commissioned by the Section Editor Chunyu Li (Department of Emergency Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Comment on: Verma SK, Garikipati VN, Krishnamurthy P, *et al*. Interleukin-10 Inhibits Bone Marrow Fibroblast Progenitor Cell-Mediated Cardiac Fibrosis in Pressure-Overloaded Myocardium. Circulation 2017;136:940-53.

Received: 07 October 2017; Accepted: 19 October 2017; Published: 08 November 2017.

doi: 10.21037/jphe.2017.10.03

View this article at: http://dx.doi.org/10.21037/jphe.2017.10.03

In a recent issue of Circulation, Verma *et al.* (1) uncover a new interleukin-10 (IL-10)-dependent mechanism inhibiting fibrosis in pressure overloaded mouse myocardium. In this study, pressure overload was achieved in wild-type (WT) and IL-10 knockout (IL-10KO) mice by transverse aortic constriction (TAC), a widely used experimental mouse model that creates pressure overload-induced left ventricular hypertrophy, leading to heart failure. IL-10KO mice displayed more bone marrow (BM)-derived fibroblast progenitor cell mobilization and homing to the heart. Chimeric IL-10KO mice with WT BM were protected against TAC-induced cardiac fibrosis and presented improved heart function. Verma *et al.* (1) found out that IL-10 inhibits homing and trans-differentiation of BM-derived fibroblast progenitor cells (FPC) in myofibroblasts, major effector cells of cardiac fibrosis. In vitro experiments performed on FPC isolated from mouse BM (prominin 1^+ $CD45^+$ cells) indicated that IL-10 could suppress the expression of the fibrosis-associated miR-21 in response to transforming growth factor-β (TGF-)β.

Cardiac fibrosis is associated with nearly all forms of heart disease. It is a common feature of several pathological conditions including myocardial infarction, pressure overload, hypertrophic cardiomyopathy, viral infections, toxic insults, or metabolism disorders. In contrast to physiological cardiac remodeling necessary for post-injury tissue healing, pathological cardiac fibrosis is characterized by excessive deposition of extracellular matrix (ECM) proteins, which reduces ventricular compliance and cardiac function, leading to heart failure.

To date, there is no generally accepted therapy to treat or hinder cardiac fibrosis. The study of Verma *et al.* unravels potential therapeutic cellular and molecular targets, which can have broad clinical impact. Indeed, due to epidemics of diabetes, obesity, population aging, and medical advances (more people survive a heart attack), the number of people diagnosed with heart failure is steadily increasing and projected to rise by 46 percent by 2030, affecting more than 8 million people (American Heart Association's 2017 Heart Disease and Stroke Statistics Update) (2).

In a general manner, organ fibrosis is characterized by the destruction of normal organ architecture and consequent decline of its function. This is a common final stage of long-lasting tissue fibrosis, resulting from a sum of minor injuries over a life time, progressive disturbance of the balance between the synthesis and degradation of ECM components, and production of an excessive amount of ECM by activated myofibroblasts. Myofibroblasts are α-smooth muscle actin (α-SMA) positive, spindle, or stellate-shaped cells. Their origin is not clear, they may arise by the phenoconversion of permanent cellular constituents of the heart, including cardiac fibroblasts, myocytes, endothelial cells [via endothelial to mesenchymal transition (EndMT)], and vascular smooth muscle cells, from stem cells, or from BM-derived circulating progenitors. Activated myofibroblasts can be produced in response to profibrotic mediators, such as TGF-β, growth factors, and inflammatory cytokines that are produced by various cell

types, including myocytes, resident fibroblasts, endothelial cells, and infiltrating immune cells. However, the relative contribution of the recruited and resident cell types to the activation of myofibroblasts remains unclear.

Verma *et al.* (1) show that TAC induces homing of FPC to the heart and their trans-differentiation into myofibroblasts, which can be inhibited by IL-10. They identified a TGFβ-Smad2/3 signaling-mediated miRNA-21 maturation as a novel mechanism by which IL-10 might inhibit BM-FPC-mediated cardiac fibrosis in the pressure-overloaded myocardium.

TGF-β-mediated signaling pathways differentiate myofibroblast from their precursors. Although phosphorylation of Smad2/3 is the classical pathway activated downstream of TGF-β receptors I and II, TGF-β can also promote some non-canonical signaling pathways including the activation of extracellular signal-regulated kinase (ERK)/cJun/p38 mitogen activated protein kinases. Whether IL-10 can also inhibit this pathway has not been assessed in Verma *et al.* (1). Likewise, since growth factors including platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) also contribute to the activation of myofibroblasts, it would be interesting to study the effect of IL-10 on these pathways. Finally, it has recently been reported that myofibroblast phenoconversion may proceed through the activation of a CXCL12/CXCR4 axis, which promotes signaling through the EGFR and downstream MEK/ERK and PI3K/Akt pathways, independently of TGF-β or Smad signaling (3).

The recruitment of innate immune cells in injured tissues plays an important role in the fibrosis process. Macrophages can indeed produce TGF-β and other profibrotic cytokines, therefore participating in myofibroblast activation. Recent evidence indicate that neutrophils can also be involved in the scenario by playing both beneficial and detrimental effects. Neutrophils contribute to infarct healing by affecting monocyte/macrophage recruitment and polarization in the ischemic myocardium (4). Conversely, changes in circulating neutrophils predict negative post-ischemic ventricular remodeling (4). Chronic inflammation drives pathological cardiac remodeling (5). We can thus reason that a chronic low-grade inflammatory state is likely to promote pathological cardiac remodeling by direct effects of neutrophils and macrophages and pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α) on fibrosis (6). For instance, since elderly people are more susceptible to heart failure, this mechanistic link could be particularly relevant to the process of aging-related cardiac fibrosis. Indeed, aging is characterized by the progressive functional decline of many interrelated physiological systems. In particular, aging is associated with the development of a systemic state of low-grade inflammation, and with progressive deterioration of metabolic function. In fact, persistent expression of a NLRC4 inflammasome gene module in older individuals and subsequent expression of the pro-inflammatory cytokine IL-1β was found to be correlated with metabolic dysfunction, oxidative stress and a lack of familial longevity (7). In older person, the balance between innate immunity and adaptive immunity shifts toward innate immunity, with a decrease in lymphocytes that may be accompanied by an increase in neutrophil counts. Interestingly, a recent study demonstrated a role for neutrophil extracellular traps (NETs) in cardiac fibrosis. This phenomenon depends on the enzyme peptidylarginine deiminase 4 (PAD4) that citrullinates histones, leading to subsequent chromatin decondensation and NET formation (8). Mice deficient for PAD4 were protected against aging-related heart fibrosis and they maintained cardiac function longer than WT mice. Neutrophils from older mice were more prone for PAD4-mediated histone citrullination and NET formation compared with young mice. In addition, this study showed that NETing neutrophils are recruited to the heart upon ascending aortic constriction, with extracellular chromatin being injurious to the heart and detrimental to its function. Neutrophils are a major source of IL-10 upon tissue injury (9), and chronic inflammation induces a switch in neutrophil phenotype, potentially leading to the production of circulating IL-10 secreting neutrophils. However, whether neutrophils exert anti- or pro-fibrotic functions in the settings of pressure overload-induced cardiac fibrosis remains unclear. Importantly, the cellular source of IL-10 has not been identified in the study of Verma *et al.* (1). Assessing whether IL-10 secreting neutrophils are produced during acute and chronic cardiac fibrosis, and whether they could suppress FPC homing to the heart and their trans-differentiation into myofibroblasts requires further investigation.

In mice, the same team and others showed that IL-10 treatment attenuates both myocardial infarction and pressure overload-induced heart inflammation and improved cardiac function (10-12). Similarly, IL-10 administration to mice suffering from autoimmune myocarditis results in a significant decrease of myocardial inflammation and

fibrosis, as well as prevent the relapse of the left ventricular function and increased the ejection fraction (13). The study of Verma *et al.* (1) nicely indicates that IL-10 holds pertinent therapeutic potential for treatment of heart failure by its strong inhibitory role in BM-FPC-mediated fibrosis in pressure-overloaded myocardium. Clinical trials are in progress investigating the effect of the supplementation of IL-10 in Crohn's diseases (14). In heart disease, further preclinical and clinical studies are certainly needed to identify the cellular source and targets of IL-10, to elucidate its precise role in the suppression of cardiac inflammation and fibrosis, and to estimate its potential therapeutic effectiveness.

In Verma *et al.* (1), the analysis of miRNA expression profiles in BM-FPC isolated from IL-10KO mice revealed upregulation of the pro-fibrotic miR-21 (15). The authors then showed that IL-10 can reduce miR-21 levels by inhibiting TGF-β-Smad2/3 signaling. Several experimental studies in mice found an association between increased miR-21 levels and myocardial fibrosis, a process relying on TGF-β and EndMT of endothelial cells (16) or on osteopontin, through the fibrotic MAPK-SMAD7 and anti-apoptotic PDCD4-PTEN pathways (17). Interestingly, *in vivo* silencing of miR-21 could prevent both the development of angiotensin II and pressure overload-induced cardiac fibrosis (17,18). The study of Verma *et al.* (1) uncovers an upstream inhibitory mechanism of pathological miR-21 dysregulation with potential larger impact on the fibrotic process.

In the same line of research, using a rat model of chronic heart failure, a recent study showed that miR-487b ameliorates cell apoptosis, inflammatory reaction of myocarditis, and fibrosis through inhibiting the IL-33/ST2 pathway by suppressing IL-33 (19). This finding is of particular interest in view of the association of the IL-33/ST2 pathway with the severity of heart failure clinical course and decline of cardiac function in heart failure patients. Strong evidence indicates that intramyocardial IL-33/ST2 signaling plays a crucial cardioprotective role during mechanical overload (20). Cardiac fibroblasts are a major source of IL-33. Furthermore, it has been shown that endothelial-specific deletion of IL33 or cardiomyocyte-specific deletion of ST2 exacerbated pressure overload-induced cardiac hypertrophy (21). Although further studies are required to elucidate the mechanisms linking miR-487b, IL-33/ST2 to the fibrotic processes, we can anticipate that silencing miR-487b could represent another potential anti-fibrotic therapeutic approach with distinct mechanism of action. Also, detailed studies of intramyocardial functional interactions between IL-10 and IL-33-dependent pathways in specific cell types are awaited. Indeed, it is worth noting that broad inhibition of TGF-β early postinfarction has worsened post-myocardial infarction remodeling, while targeted suppression in the myocyte could be beneficial (22). Rather than by altering fibrosis, myocyte-selective TGF-β inhibition augments the synthesis of several protective cytokines, such as thrombospondin 4, IL-33, follistatin-like 1, and growth and differentiation factor 15, an inhibitor of neutrophil integrin activation and migration. It turned out that myocyte-expressed TGF-β regulates acute neutrophil inflammatory response in ischemic hearts. These findings highlight the importance of cell-specific targeting of signaling pathways, such as those driven by TGF-β in the search of a potent therapeutic strategy against maladaptive cardiac remodeling. The novel insight provided by the study of Verma *et al.* (1) is in accordance with this concept. Specific targeting of myofibroblasts using IL-10 or miR-21 antagomirs could be considered a valuable approach to counteract excessive ECM production and prevent heart failure.

Acknowledgements

Cécile Oury is Senior Research Associate at the National Funds for Scientific Research, Belgium (F.R.S.-FNRS).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/jphe.2017.10.03
Cite this article as: Lancellotti P, Oury C. IL-10 targets myofibroblasts and dampens cardiac fibrosis. J Public Health Emerg 2017;1:83.

