Macrophage-Mediated Cardiac Fibrosis

P. Christian Schulze, Richard T. Lee

Both clinicians and investigators have long tended to consider cardiac fibrosis as a hopelessly unavoidable “final common pathway” of tissue injury. We are painfully familiar with the serious consequences of myocardial fibrosis, including diastolic dysfunction and promoting reentry dysrhythmias, but we seem to accept that diseased myocardium eventually develops fibrosis. However, only the most advanced fibrotic tissues are lifeless; in fact, dynamic matrix turnover in fibrosing tissues is easily demonstrated, whereas the matrix of normal tissues is, in comparison, remarkably quiescent. That we can potentially steer matrix metabolism beneficially to reduce dysrhythmias or improve ventricular function is reason enough to try to understand cardiac fibrosis. In addition, as we will briefly touch on here, recent excitement in cardiac regeneration offers us yet another important reason to unravel fibrosis, because myocardial scarring may be standing in the way of successfully repairing the heart.

Treatment options to prevent cardiac fibrosis are limited and include angiotensin converting enzyme inhibitors and aldosterone blockade. Matrix metalloproteinase inhibition may also reduce fibrosis. The effects of metalloproteinase inhibition on cardiac fibrosis do not appear to be attributable to changes in collagen degradation, and there has been little recent progress on using metalloproteinase inhibition clinically. With so few weapons against cardiac fibrosis, it is therefore important to develop new strategies through understanding basic molecular pathways of matrix metabolism.

There are different types of cardiac fibrosis, and some forms of fibrosis are probably at least transiently beneficial. The fibrosis of the healing infarct in the days after myocardial infarction prevents cardiac rupture, but eventually dense regions of fibrosis may be arrhythmogenic. Pressure overloaded myocardium causes fibrosis within weeks that is initially perivascular; this is so reproducible that sham-operated mice can be easily distinguished from pressure-overloaded mice by the dramatic deposition of collagen around intramyocardial arterioles. Eventually, hypertensive myocardium develops a more diffuse interstitial fibrosis, as the cardiac fibroblasts react to a cascade of myocardial factors including connective tissue growth factor, transforming growth factor-β1, endothelin-1, and angiotensin II.

Cardiac fibrosis may be an integral factor in the inability of mammals to regenerate myocardium. Whereas injured mammalian hearts develop myocardial scarring, zebrafish regenerate cardiac tissue with remarkably little fibrosis. When cardiac myocyte division is impaired by mutation in the mitotic checkpoint kinase mps1, zebrafish cardiac regeneration is limited and scarring develops instead. Thus, as proposed by Mark Keating and colleagues, fibrosis and regeneration may be complementary “ying and yang” processes of injured myocardium. In their model, if regeneration occurs vigorously, fibrosis is inhibited; if regeneration is negligible, fibrosis fills in. It is then attractive to speculate that encouraging cardiac regeneration in mammals through activating endogenous cells or through cell therapy will inhibit fibrosis. Similarly, fibrosis and scarring may impair our ability to achieve truly functional regenerated myocardium.

The concept of a balance between fibrosis and regeneration is supported by the intriguing parallel of wound healing in the embryo, the ultimate tissue engineer. Wound healing is fast and remarkably scar-free in early embryos compared with adults. Healing embryos lack the invading myofibroblasts typical of adult wounds, and early embryonic wounds are largely devoid of macrophages. Interestingly, until relatively late in mouse development (day E14.5), macrophages are generally not recruited to embryo wounds. This time corresponds to the time when scarring begins to occur in the mouse embryo, raising the possibility that an important distinction between scar-free healing in the early embryo and fibrosis in adult wound healing arises from the contribution of macrophages.

Might the macrophage also play a crucial role in cardiac fibrosis? Macrophages are poised to tip the balance of matrix synthesis and degradation, both through direct secretion of proteases and through cytokine-mediated stimulation of fibroblasts and other cells. Given this background, we are fortunate to have new data provided by Moriwaki et al in this issue of Circulation Research. Their study suggests an important role of macrophages in cardiac fibrosis and that the balance of urokinase plasminogen activator (uPA) and its inhibitor PAI-1 may mediate this effect.

It’s worth noting that, like many important scientific contributions, this study was based initially on keen observations from other experiments rather than from straightforward hypothesis-testing. Dichek and colleagues generated transgenic mice with macrophage-targeted overexpression of uPA (using the scavenger receptor promoter) initially to explore the role of macrophages in atherosclerosis. In the course of these experiments using mice bred into the apolipoprotein E (ApoE) null background, they noted a pattern of cardiac

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**References**


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Myocardial injury such as infarction and inflammation as well as specific homing factors lead to migration and infiltration of macrophages and leukocytes. Selective cardiac infiltration by macrophages is revealed by macrophage-specific overexpression of uPA, as indicated by the study by Moriwaki et al. Increased myocardial uPA activity, which can be inhibited by PAI, 1 leads to myocardial fibrosis, possibly through deranged matrix metabolism. Ultimately, as suggested by Poss, Keating, and colleagues, fibrosis and regeneration may be complementary. Therefore, stimulation of regenerative pathways might inhibit fibrosis, as it seems to do in the wounded early embryo; similarly, fibrosis may limit our attempts at cardiac regeneration.

Fibrosis that did not appear to be attributable to epicardial coronary disease. This raised the possibility that the macrophages themselves, and not arterial disease, caused cardiac fibrosis. This was demonstrated by breeding the macrophage-specific uPA transgene with ApoE<sup>−/−</sup> mice, which led to cardiac fibrosis but, as expected, no atherosclerosis. Furthermore, bone marrow from these transgenic mice enhanced cardiac fibrosis in ApoE<sup>−/−</sup> mice with cardiac-selective accumulation of macrophages in the heart.

As noted by the authors, perhaps the most fascinating finding of this report is that the heart is so susceptible to macrophage infiltration. uPA compared with other organs. Other tissues in these transgenic mice had more uPA, but they were resistant to macrophage infiltration and fibrosis. Identifying the pathways responsible for the selective infiltration of these macrophages could yield cardiac-specific therapies. In addition, this report will hopefully stimulate new experiments on the roles of macrophages and uPA in other nontransgenic models of cardiac fibrosis, because the effect of transgenic overexpression of a protein does not necessarily reflect the effect of that protein at physiological levels.

The study by Moriwaki et al provides an interesting piece in the puzzle of cardiac fibrosis by implicating the macrophage and uPA (Figure). Although the cardiovascular community is feverishly pursuing cell therapy and other attempts in cardiac regeneration, we should remember that it is difficult for one myocyte to perform coordinated and efficient cardiac work with another myocyte through a dense band of collagenous tissue. Ultimately, if we can prevent excessive fibrosis at the same time as stimulating regenerative pathways, we may be able to mimic the early embryo’s enviable combination of healing without scarring.
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