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EDITORIAL COMMENT

Quality Over Quantity

BMP-9 Regulation of Scar Formation After Myocardial Infarction*

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Myocardial infarction (MI) leads to death of heart muscle due to ischemic injury and replacement by a collagen-based scar. In the acute phase immediately after injury, cardiac inflammation and fibroblast activation contribute to scar formation and wound healing of the injured heart. In the short term, the fibrillar collagen-rich scar is essential to maintain the structural integrity of the heart and prevent cardiac rupture. However, prolonged fibroblast activation and collagen production can lead to pathologic fibrotic remodeling and heart failure. Current therapeutic approaches to treat MI are focused on improving the viability and function of cardiac muscle, but inhibition or reversal of cardiac fibrosis is essential to maintain cardiac output.[1] Therapeutic approaches targeting cardiac fibrotic remodeling must allow sufficient scarring for wound healing after MI while also limiting long-term fibrosis.

In the healthy heart, cardiomyocytes are surrounded by fibrillar collagen-rich extracellular matrix (ECM) produced predominantly by neighboring cardiac fibroblasts. The ECM acts as a mechanical scaffold for the heart as necessary for transmission of contractile force. Therefore, too much, too little, or disorganized collagen deposition compromises normal heart function. After MI, cardiac fibroblasts in the infarcted area become activated contractile myofibroblasts that secrete ECM proteins and remodeling enzymes, including matrix metalloproteinases (MMPs).[1] Myofibroblast activation and collagen production during cardiac wound healing and fibrosis is dependent on transforming growth factor (TGF)-β signaling through Smads2/3 and MMP activity. At the same time, antifibrotic pathways, including bone morphogenetic protein (BMP) signaling through Smad1, limit myofibroblast activation and collagen production.[1] Thus, the balance of profibrotic and antifibrotic pathways is essential for effective wound healing, while also being critical for prevention of pathologic remodeling and heart failure.

BMP-9 has recently been identified as an antifibrotic factor in the heart.[2] Although BMP-9 is upregulated in human heart failure, it also limits pathologic cardiac fibrosis in mice. BMP-9 null mice subjected to transverse aortic constriction (a pressure overload model) demonstrate increased cardiac fibrosis and decreased heart function. Treatment of wild-type mice with recombinant BMP-9 under conditions of pressure overload results in limited cardiac fibrosis, improved heart function, and increased Smad1 activation. Moreover, BMP-9 treatment of cultured human cardiac fibroblasts decreases TGF-β-mediated collagen I production. Increased fibrosis due to loss of BMP-9 is accompanied by increased Smad3 activation, whereas BMP-9 treatment leads to decreased activated Smad3, supporting an antagonistic relationship between BMP-9/Smad1 and TGF-β/Smad3 signaling during cardiac fibrosis.[2]

In this issue of *JACC: Basic to Translational Science*, Bhave et al[3] build on the role of BMP-9 in cardiac fibrosis by demonstrating the requirement for BMP-9 in cardiac wound healing and short-term survival of mice subjected to acute myocardial infarction (AMI)

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by permanent left anterior coronary artery ligation. In this study, BMP-9 null mice exhibited a significantly decreased survival by 7 days after MI, largely owing to transmural myocardial rupture, but at the same time had a much larger left ventricle fibrotic area compared with wild-type mice. Furthermore, BMP-9 null mice demonstrated other signs of a profibrotic cascade 2 weeks after MI, including significantly increased TGF-β1, collagen I, TGF-β coreceptor endoglin, myofibroblast marker α-smooth muscle actin, and phosphorylated Smad3, as well as significantly decreased antifibrotic phosphorylated Smad1/5. The predisposition of BMP-9 null hearts to rupture was unexpected, because the increase in collagen I is hypothesized to stabilize heart structure. To determine why BMP-9 null hearts were more likely to rupture after MI, the authors next looked at the activity of collagen remodeling enzyme MMP-9. MMP-9 was significantly increased in the infarcted area of BMP-9 null hearts after MI, suggesting that collagen I was being turned over faster than it was being produced. In support of this, the authors also found higher levels of circulating collagen degradation marker ICTP. Limiting BMP-9 in human cardiac fibroblasts in culture results in a similar profibrotic signaling cascade with increased collagen I, MMP-9, TGF-β signaling through phosphorylated Smad3, and myofibroblast activation.[3] Altogether, this study suggests that, in the absence of BMP-9, the quality of ECM, specifically collagen, is affected by the increased activity of MMPs. Moreover, while TGF-β/Smad3 signaling is required for initial scar formation, its activity must be balanced by BMP-9 signaling through phosphorylated Smad1 to limit pathologic remodeling and preserve cardiac function.

In humans, cardiac fibrosis is typically monitored by sophisticated imaging techniques that assess the amount of tissue damage and scarring. However, the striking observation that the loss of BMP-9 in mice leads to cardiac rupture after AMI, despite increased overall collagen, implies that collagen deposition is not sufficient to maintain cardiac output. Instead, for effective wound healing, collagen fibers need to be remodeled to optimize the quality of the collagen matrix. In humans after MI, higher levels of the biomarker of collagen degradation ICTP in serum are correlated with worse outcomes. Thus, the quality of the collagen matrix may also be important for cardiac wound healing as well as contributing to pathologic cardiac fibrosis after a heart attack. Therefore, additional noninvasive methods are needed to measure both the quantity and quality of fibrillar collagen as an indicator of cardiac disease progression.

Collagen remodeling during cardiac wound healing and pathologic fibrosis is known to be regulated by MMPs, which have been identified as therapeutic targets in cardiovascular disease. Just as elevated circulating ICTP is associated with worse outcomes in humans and mice, elevated MMP-9 also has been shown to predict mortality in patients with AMI as well as in BMP-9 null mice.[3,4] However, clinical trials of MMP-9 inhibitors after injury have not improved patient outcomes. More recent studies have implicated MMP-9 in cardiac inflammation and scarring during the acute phase after MI. Therefore, therapeutic targeting of MMPs, as well as BMP/TGF-β signaling, will need to take the timing and specific ECM remodeling stages into account to allow for effective cardiac wound healing while inhibiting pathologic fibrotic remodeling.[4]

Despite the clear requirement of BMP-9 for cardiac fibrosis after injury in mice,[3] many questions remain to be answered. In humans, BMP-9 is elevated in failing hearts with extensive fibrosis. Thus, its role as an antifibrotic agent in human heart disease is unclear. In mice lacking BMP-9, cardiac wound healing is compromised in the context of increased MMP-9 activity and indicators of collagen degradation. Although there is evidence for an antagonistic role in profibrotic signaling, it is uncertain whether BMP-9 directly or indirectly regulates TGF-β signaling. Furthermore, specific molecular interactions of TGF-β/Smad3 and BMP/Smad1 signaling pathways, as well as how they control the quality of collagen remodeling, potentially via MMP-9 activation, during scar formation are not fully defined. Furthermore, as in many mouse cardiac injury studies, only male mice were included in the analysis of BMP-9 function after AMI. It is assumed that female mice would not experience cardiac rupture, but female-specific cardioprotective mechanisms related to pro- and antifibrotic signaling in cardiac wound healing or pathologic fibrosis are yet to be defined. Further studies are also needed to determine the basis of poor-quality collagen found in a ruptured scar vs the longer-term fibrotic collagen deposition related to BMP-9 signaling and MMP-9 function.

Although cardiac rupture in humans is uncommon, antifibrotic BMP-9/Smad1 and profibrotic TGF-β/Smad3/MMP-9 pathways could potentially be leveraged to develop new methods to treat cardiac fibrosis. In mice, BMP-9 treatment via repeated injections inhibited cardiac fibrosis and improved cardiac function. However, the treatment protocol requires frequent injections owing to pharmacokinetics of the recombinant growth factor, and repeated BMP-9 exposure caused bone formation at the injection

sites.[2] Currently, BMP signaling is being targeted by injections of a neutralizing antibody for BMP receptor activity in clinical trials to treat pulmonary arterial hypertension.[3] Moreover, therapeutic approaches that target TGF-β signaling, BMP-9, and MMP-9 are currently being investigated for prevention of metastatic cancer progression. Therefore, efforts to promote cardiac wound healing or limit cardiac fibrosis through BMP-9 activation or MMP-9 inhibition in the heart could be detrimental to a cancer prognosis and vice versa, as has also been seen for cardiotoxic chemotherapeutic agents and chimeric antigen receptor T-cell therapies.[5] However, continuing to parse out the molecular mechanisms that balance cardiac profibrotic and antifibrotic pathways to support initial scar formation after MI, while limiting long-term fibrosis, should still lead to the development of novel therapies to prevent, or even reverse, cardiac fibrotic disease.

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