Review Article

The role of transforming growth factor (TGF)-β in the infarcted myocardium

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Abstract: The adult mammalian heart has negligible regenerative capacity. Following myocardial infarction, sudden necrosis of cardiomyocytes triggers an intense inflammatory reaction that clears the wound from dead cells and matrix debris, while activating a reparative program. A growing body of evidence suggests that members of the transforming growth factor (TGF)-β family critically regulate the inflammatory and reparative response following infarction. Although all three TGF-β isoforms (TGF-β1, -β2 and -β3) are markedly upregulated in the infarcted myocardium, information on isoform-specific actions is limited. Experimental studies have suggested that TGF-β exerts a wide range of actions on cardiomyocytes, fibroblasts, immune cells, and vascular cells. The findings are often conflicting, reflecting the context-dependence of TGF-β-mediated effects; conclusions are often based exclusively on *in vitro* studies and on associative evidence. TGF-β has been reported to modulate cardiomyocyte survival responses, promote monocyte recruitment, inhibit macrophage pro-inflammatory gene expression, suppress adhesion molecule synthesis by endothelial cells, promote myofibroblast conversion and extracellular matrix synthesis, and mediate both angiogenic and angiostatic effects. This review manuscript discusses our understanding of the cell biological effects of TGF-β in myocardial infarction. We discuss the relative significance of downstream TGF-β-mediated Smad-dependent and -independent pathways, and the risks and challenges of therapeutic TGF-β targeting. Considering the high significance of TGF-β-mediated actions *in vivo*, study of cell-specific effects and dissection of downstream signaling pathways are needed in order to design safe and effective therapeutic approaches.

Keywords: Transforming growth factor-beta (TGF-β); cardiac remodeling; myocardial infarction; fibroblast; cardiomyocyte; inflammation

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Introduction

Transforming growth factor (TGF)-β is the prototypical member of a large family of secreted growth factors; in mammals, the TGF-β family is comprised of 33 members (1). Originally identified as a cytokine that induces cellular "transformation" *in vitro*, promoting anchorage-independent growth (2-5), TGF-β is now recognized as a pleiotropic and multifunctional growth factor that regulates a wide range of cellular responses, and may play a critical role in development, and in the pathogenesis of many diseases (1,6,7). In mammals, three TGF-β isoforms (β1, β2 and β3) have been identified; these isoforms are encoded by different genes. Although *in vitro* studies suggest that the three isoforms have similar actions, the distinct phenotypes of mice with isoform-specific genetic disruption indicate numerous non-compensated functions of the three TGF-βs in organ development and in tissue homeostasis (8-11). Despite a large body of evidence demonstrating induction, release and activation of TGF-βs following tissue injury, understanding of their *in vivo* functions in repair and remodeling has been hampered by the complexity of their

context-dependent actions and downstream signaling cascades.

The adult mammalian heart has negligible regenerative capacity. Following myocardial infarction up to one billion cardiomyocytes become necrotic; this massive sudden loss of cardiomyocytes overwhelms any existing regenerative reserve, resulting in replacement of dead cells with collagen-based scar. The cellular events involved in repair of the infarcted heart can be divided in three distinct, but overlapping phases: the inflammatory phase, the proliferative phase and the maturation phase (12,13). During the inflammatory phase, release of alarmins by necrotic cardiomyocytes activates innate immune pathways, leading to recruitment of leukocytes in the infarcted myocardium (14). Clearance of the infarct from dead cells and matrix debris by professional phagocytes activates anti-inflammatory cascades leading to suppression of the inflammatory response and transition to the proliferative phase of infarct healing (15). During the proliferative phase, activated myofibroblasts deposit large amounts of extracellular matrix proteins in the infarcted area, while activation of angiogenesis ensures perfusion of the highly cellular and metabolically active wound. The maturation phase follows, as activation of anti-fibrotic pathways limits the fibrogenic response, leading to formation of a mature scar with low cellular content that contains cross-linked collagenous matrix. Healing of the infarcted heart is associated with adverse remodeling of the ventricle, a constellation of cellular events that involve both infarcted and non-infarcted segments and are associated with the development of heart failure (16).

A growing body of evidence suggests that TGF-β signaling pathways play an important role in regulation of the cellular events associated with cardiac repair, by modulating injurious, inflammatory, reparative, angiogenic, and fibrogenic responses. This manuscript reviews our current understanding of the role of TGF-β in the infarcted heart, focusing on its diverse cellular actions, discussing molecular cascades modulated by TGF-β, and identifying potential therapeutic targets.

Expression of TGF-β in normal myocardium

High levels of myocardial TGF-β expression have been observed during embryonic development and in adult life, predominantly localized in cardiomyocytes and in the extracellular matrix (17). TGF-βs have been implicated in cardiac development and in valve morphogenesis (18,19). In adult mammals, TGF-β is stored in the myocardium in a latent form; whether low-level constitutive TGF-β activity is important for cardiac function remains unknown. In neonatal rat cardiac cardiomyocytes, exogenous TGF-β sustained spontaneous rhythmic beating in serum-free conditions (20); however, the *in vivo* relevance of these observations is unclear.

Regulation of TGF-β isoforms in myocardial infarction

Induction of TGF-β isoforms has been extensively documented in both mouse and large animal models of myocardial infarction (17,21-26). In reperfused mouse infarcts, TGF-β1 and β2 mRNA levels show an early peak after 6–72 h of reperfusion; in contrast, TGF-β3 upregulation exhibits a prolonged time course with persistently elevated expression after 7 days of reperfusion (21). Most cell types involved in cardiac repair are capable of synthesizing and secreting large amounts of TGF-β; the relative contributions of various cell types in infarction-related upregulation remains poorly defined. Whether different cell types and distinct molecular pathways are responsible for upregulation of each TGF-β isoform is unknown. Studies in a porcine model of chronic coronary constriction suggested that cardiomyocytes are a major source of TGF-β following cardiac injury (22). On the other hand, experiments in a mouse model of myocardial infarction suggested that TGF-β is localized in infarct macrophages (27). Genetic disruption of monocyte chemoattractant protein (MCP)-1/CCL2, a chemokine with a crucial role in recruitment of monocytes/macrophages in the infarcted myocardium attenuated TGF-β2 and β3 mRNA expression, suggesting that mononuclear cells may be an important source of TGF-β isoforms in reperfused infarcts (28). The contributions of other cell types have not been convincingly documented. Platelets have been suggested to be an important source of TGF-β1 in the pressure-overloaded myocardium (29); however, their role as a source of growth factors in the infarcted myocardium has not been systematically investigated. Lymphocyte subsets and mast cells infiltrate the infarcted heart (30-33) and are capable of producing TGF-βs. Moreover, much like most tissues, the normal myocardium may contain constitutive stores of matrix-bound latent TGF-β that can be activated following injury (34), initiating a response even in the absence of *de novo* synthesis.

The biology of TGF-β activation

TGF-βs are secreted as latent complexes, consisting of the TGF-β dimer, the latency-associated peptide (LAP), and a latent TGF-β-binding protein (LTBP). Current concepts suggest that while the LAP confers latency to TGF-β (35,36), the LTBP contributes to sequestration into the extracellular matrix (34). Although the LAP is cleaved intracellularly from the mature TGF-β dimer through furin-mediated actions, TGF-β and LAP remain bound after secretion through non-covalent interactions, forming the small latent complex. Activation of TGF-β signaling cascades requires release of the TGF-β dimer from the latent complex and requires the co-operation of several distinct mediators, including integrins, proteases, reactive oxygen species (ROS) and matricellular proteins.

In the infarcted heart, evidence suggesting the presence of bioactive TGF-β in cardiac extracellular fluids (37), and activation of downstream Smad-dependent signaling (38) suggest rapid activation of TGF-β. The mechanisms responsible for TGF-β activation following infarction remain poorly understood. ROS activation is a hallmark of the ischemic response and may be involved in TGF-β activation in the infarcted myocardium. Cell surface integrins interact with LAP and have been directly implicated in TGF-β activation in many tissues (39); however, whether integrins play an important role in activating TGF-β in the infarcted heart remains unknown. Although *in vitro*, αvβ5 and αvβ3 integrins contributed to latent TGF-β activation and subsequent cardiac myofibroblast differentiation (40); the *in vivo* significance of these interactions has not been directly tested. Proteases of various classes (including serine proteases, cathepsins, metalloproteinases, and cysteine proteases) are capable of activating TGF-β *in vitro*. Although protease release and activation during the inflammatory phase of infarct healing may contribute to TGF-β activation; the *in vivo* significance of these effects has not been investigated. Matricellular proteins are markedly upregulated in the infarcted heart (41-43) and may play an important role in TGF-β activation. The prototypical matricellular protein thrombospondin (TSP)-1 interacts with LAP, promoting release of the TGF-β dimer from the latent complex (44). In both mouse and canine infarcts, a strikingly selective upregulation of TSP-1 in the infarct border zone is associated with activation of TGF-β signaling. TSP-1 loss attenuates activation of Smad-dependent pathways following myocardial infarction, suggesting an important role for this matricellular protein in activation of TGF-β cascades (41). Finally, exposure to an acidic environment has been implicated in activation of latent TGF-β. It has been suggested that lactic acid may trigger pH-dependent TGF-β activation in patients with idiopathic pulmonary fibrosis (45). Whether the abundant lactic acid generated in the ischemic myocardium is involved in local activation of TGF-β remains unknown.

Cellular actions of TGF-β in the infarcted myocardium

TGF-βs are capable of regulating phenotype and function of all cell types involved in cardiac injury and repair (*Figure 1*). Although TGF-β1, β2 and β3 exhibit distinct patterns of regulation following myocardial infarction, information on isoform-specific actions in the infarcted myocardium is lacking. Most *in vitro* studies have investigated TGF-β1-mediated actions. *In vivo* experiments on the other hand, have focused on the role of TGF-β receptor-activated signaling, exploring pathways common to all three isoforms and to other members of the TGF-β superfamily. Thus, our current knowledge precludes conclusions regarding cellular actions of specific isoforms.

Effects of TGF-β on ischemic cardiomyocytes

Early studies suggested that injection of exogenous TGF-β in isolated perfused hearts undergoing brief myocardial ischemia followed by reperfusion exerts protective actions, attenuating oxidative stress and reducing release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α (46). In a model of reperfused feline myocardial infarction, TGF-β1 administration reduced cardiomyocyte death; these protective actions were associated with attenuated neutrophil recruitment in the infarcted myocardium (47). Whether TGF-β-mediated protection in these studies is due to activation of direct pro-survival pathways in cardiomyocytes, or reflects suppression of injurious inflammatory signaling, remains unknown. Regarding the effects of TGF-β on cardiomyocyte survival, *ex vivo* and *in vitro* experiments have produced conflicting results. In isolated perfused hearts, TGF-β1 infusion during early reperfusion protected cardiomyocytes from apoptosis through actions involving p42/p44 mitogen-activated protein kinase (MAPK) signaling (48). In contrast, in rat cardiomyocytes the pro-apoptotic effects of angiotensin II were attributed to activation of TGF-β signaling (49).

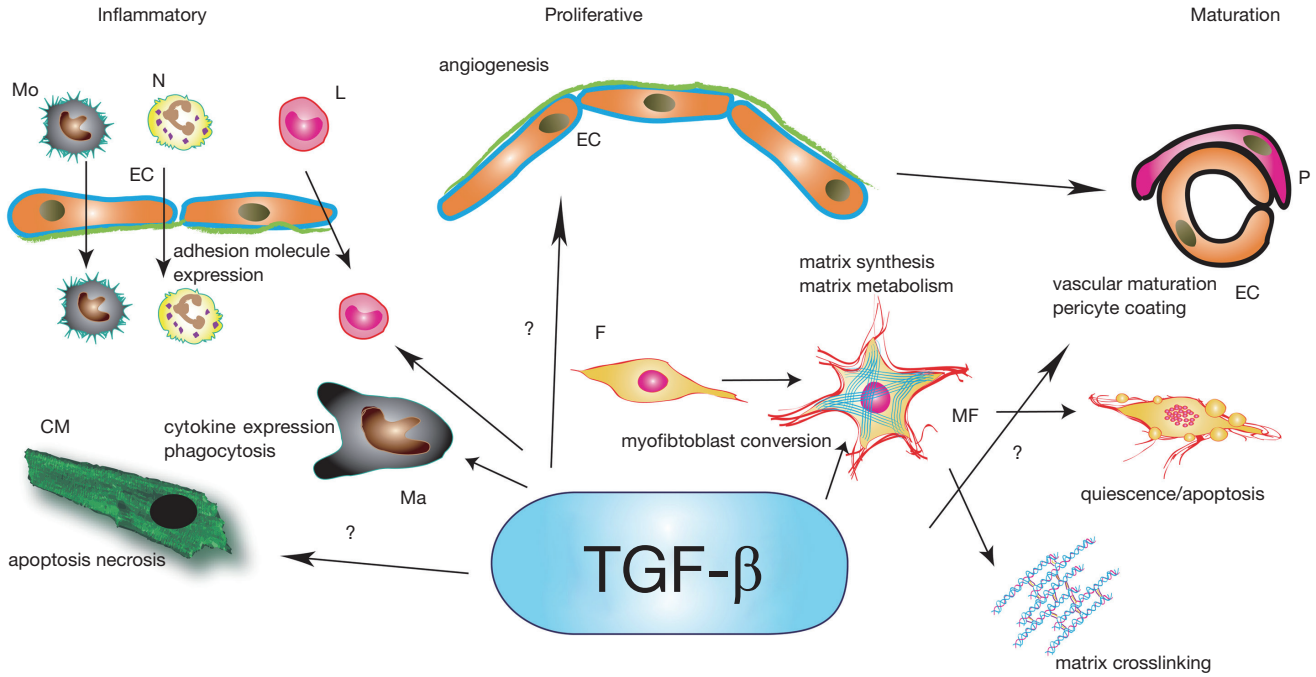

Figure 1 The cell biological actions of TGF-β in the infarcted myocardium. TGF-β may exert a wide range of actions on all cell types involved in injury, repair and remodeling of the infarcted heart. TGF-β may modulate survival pathways in cardiomyocytes, promote mononuclear cell chemotaxis, exert anti-inflammatory actions on macrophages, suppress endothelial cell adhesion molecule synthesis, modulate lymphocyte phenotype, promote myofibroblast conversion and activation, and regulate angiogenesis and vascular maturation symbols. Mo, monocyte; N, neutrophil; L, lymphocyte; Ma, macrophage; CM, cardiomyocyte; EC, endothelial cell; F, fibroblast; MF, myofibroblast; P, pericyte; TGF-β, transforming growth factor-beta.

Moreover, *in vitro* studies have demonstrated direct actions of TGF-β on cardiomyocyte function, mediated through upregulation of the laminin receptor 37/67 (50). Considering its notoriously pleiotropic and context-dependent actions, the effects of exogenous administration of TGF-β are likely dependent on the dose, route and timing of administration, and the specific characteristics of the experimental model.

Endogenous cardiomyocyte-specific TGF-β actions have been recently investigated using genetic models of cell-specific TGF-β receptor disruption (51). In a model of non-reperfused myocardial infarction, mice with cardiomyocyte-specific disruption of TGF-β signaling were protected from death due to cardiac rupture. The mechanism of protection remains poorly defined. It was suggested that TGF-β signaling in cardiomyocytes may suppress synthesis of cardioprotective genes, such as interleukin (IL)-33, growth differentiation factor (GDF)-15 and TSP-4.

Effects of TGF-β on immune cells

A large body of *in vitro* and *in vivo* evidence suggests that TGF-βs modulate phenotype and function of immune cells, critically regulating inflammatory responses (52). *In vitro*, femtomolar concentrations of TGF-β promote neutrophil (53) and monocyte (54) chemotaxis; this effect may be important for recruitment of leukocytes in inflamed tissues. Picomolar TGF-β concentrations stimulate synthesis of a variety of pro-inflammatory cytokines and chemokines by monocytes (54,55). In contrast to its pro-inflammatory actions in monocytes, TGF-β is known to deactivate macrophages, suppressing MCP-1/CCL2, IL-1β and TNF-α synthesis (56-58). It should be emphasized that effects of TGF-β on immune cells can be either pro- or anti-inflammatory depending on the cytokine milieu, the tissue origin of the cells, and the experimental context (59). For example, despite its potent chemotactic actions for monocytes and neutrophils in single-cell assays, TGF-β may attenuate leukocyte migration across an endothelial layer by reducing surface expression of adhesion molecules (60). Thus, attribution of pro- or anti-inflammatory properties to TGF-βs should be based on robust *in vivo* evidence, rather than on *in vitro* experiments.

In vivo, TGF-β1 plays an essential role in preventing spontaneous inflammation in mammalian tissues.

Approximately 50% of TGF-β1 null mice develop normally and show no gross developmental abnormalities. However, 2–4 weeks after birth, these mice develop massive multi-organ inflammation, predominantly affecting the heart and lungs (9). Mice with T cell-specific loss of the type II TGF-β receptor TβRII exhibited an inflammatory disease with striking similarities to TGF-β1 KO animals, suggesting that TGF-β may act by suppressing T cell-mediated inflammation (61).

Repair of the infarcted heart is dependent on timely recruitment of inflammatory leukocytes, and subsequent activation of reparative macrophages that stimulate myofibroblast activation and angiogenesis (15,62). Evidence from *in vitro* studies and *in vivo* neutralization experiments suggest that, in healing infarcts, TGF-β may regulate inflammatory leukocyte function. Experiments in a canine model of myocardial infarction demonstrated that TGF-β bioactivity is markedly increased in the post-ischemic cardiac lymph (reflecting release of active TGF-β in the cardiac extracellular space), and contributes to monocyte chemoattractant activity during the first five hours of reperfusion (37). In a mouse model of non-reperfused myocardial infarction, early systemic inhibition of TGF-β signaling through transfection with the extracellular domain of TβRII increased mortality, accentuating neutrophil recruitment, and increasing expression of TNF-α, IL-1, and MCP-1/CCL2 (63). These observations are consistent with an important role for TGF-β in negative regulation of the post-infarction inflammatory response. In addition, mice with genetic loss of TSP-1, a crucial TGF-β activator, had defective containment of the post-infarction inflammatory response, associated with evidence of attenuated Smad2 activation (41). These effects may reflect a crucial role for localized TSP-1-mediated activation of TGF-β in the infarct border zone as a "barrier" preventing expansion of the inflammatory reaction into the non-infarcted area. In the absence of TSP-1, expansion of inflammatory activation increases fibrosis and accentuates adverse remodeling (41). However, it should be emphasized that TSP-1 has multiple cellular targets and several functional domains and may regulate inflammation and fibrosis through TGF-β-independent effects (64).

The specific effects of TGF-β on the phenotype of immune cells in the infarcted myocardium remain poorly understood. *In vitro*, TGF-β has been shown to modulate macrophage phenotype, promoting M2 polarization (65), enhancing macrophage-colony stimulating factor (M-CSF)-induced proliferation (59), inhibiting nitrite release (66), reducing cytotoxic activity (67), and suppressing release of inflammatory mediators (68). However, the potential involvement of TGF-β in mediating the dynamic phenotypic alterations of infarct macrophage subpopulations remains unknown. TGF-β also serves as a central mediator in T lymphocyte differentiation and activation, critically regulating phenotype and function of all subpopulations (69-71). Although activated subsets of T lymphocytes have been implicated in repair and remodeling of the infarcted heart (30,32,72), the relative role of TGF-β signaling in their recruitment and activation has not been investigated.

TGF-β in regulation of fibroblast phenotype and function

The central role of TGF-β in cardiac fibroblast activation is well-documented by a wide range of *in vitro* studies and by extensive associative *in vivo* evidence (73). TGF-β mediates conversion of fibroblasts into myofibroblasts (74), a phenotypic transformation associated with reparative and fibrotic responses. Moreover, TGF-β markedly and consistently stimulates synthesis of extracellular matrix proteins (such as collagen I, collagen III and fibronectin) (75,76) and promotes a matrix-preserving program by decreasing collagenase expression and by accentuating tissue inhibitor of metalloproteinases (TIMP)1 expression (38,77). In contrast, effects of TGF-β on cardiac fibroblast proliferation are less consistent: both proliferative and anti-proliferative effects have been reported (76,78). Differences in TGF-β concentration, and in the experimental context may account for the conflicting observations.

During the proliferative phase of infarct healing, abundant myofibroblasts infiltrate the infarct border zone (79,80) and serve as the main source of collagen (81), while participating in extracellular matrix metabolism by secreting matrix metalloproteinases (MMPs). Most infarct myofibroblasts originate from resident fibroblast populations (82,83); TGF-β may play a crucial role in conversion of these highly plastic interstitial cells into myofibroblasts. TGF-β may also stimulate extracellular matrix synthesis and modulate the protease expression profile of these cells. Unfortunately, this concept is only supported by systemic TGF-β inhibition experiments; *in vivo* effects of fibroblast-specific loss of TGF-β signaling have not been studied. In a model of non-reperfused infarction, TGF-β inhibition through administration of a neutralizing antibody had detrimental effects, accentuating chamber dilation, increasing myocardial MMP expression, and reducing collagen synthesis (84). Two independent investigations

inhibiting TGF-β by using gene transfer of the extracellular domain of TβRII suggested that TGF-β may play a key role in fibrosis of the infarcted heart (63,85). TGF-β inhibition after the inflammatory phase of cardiac repair attenuated deposition of fibrous tissue in the infarcted region (85). These investigations support the critical role of TGF-β as a regulator of extracellular matrix deposition and metabolism following myocardial infarction. However, whether fibroblasts are the main cellular targets responsible for these actions of TGF-β remains unknown.

Effects of TGF-β on endothelial cell phenotype and on infarct angiogenesis

Vascular endothelial cells are the most abundant non-cardiomyocytes in the adult mammalian myocardium (86), and play an important role in repair of the infarcted heart. During the inflammatory phase, endothelial cells serve as a source of chemokines (87,88); interactions between activated endothelial cells and leukocytes are critical for recruitment of neutrophils and monocytes in the infarcted myocardium (89). During the proliferative phase, endothelial cells proliferate and generate neovessels (90), important for perfusion of the healing infarct and for supply of granulation tissue cells with oxygen and nutrients. Finally, during the maturation phase, neovessels acquire a coat comprised of mural cells (91,92); this process restrains angiogenesis, suppresses inflammatory activation, and may contribute to stabilization of the scar (93).

TGF-β is critically involved in vascular development through effects on both endothelial cells and pericytes (94) and modulates endothelial cell gene expression and activity. The actions of TGF-β on endothelial cells may be either angiogenic or angiostatic, depending on the context, the differentiation of the cells, and the presence or absence of other mediators (94,95). Very limited information is available on the effects of TGF-β on vascular cells in the infarcted myocardium. *In vitro*, TGF-β stimulation attenuates chemokine synthesis by cytokine-stimulated endothelial cells (96); such actions may contribute to suppression of the inflammatory response following myocardial infarction. TGF-β may also be implicated in infarct angiogenesis and vascular maturation; however, information on specific cellular actions is lacking.

TGF-β and cardiac regeneration

Enhancement of the extremely limited regenerative capacity of the infarcted heart is a major goal in cardiovascular research (97,98). Because of their broad effects on differentiation and fate of progenitor cells (99), several members of the TGF-β family have been suggested as potential activators of the regenerative response. Fish and amphibians exhibit robust myocardial regenerative responses; in zebrafish, TGF-β has been implicated in myocardial regeneration (100). *In vitro*, TGF-β stimulation increased the expression of cardiac transcription factors in embryonic stem cells, directing them towards cardiomyocyte differentiation (101). *In vivo*, implantation of TGF-β pre-programmed CD117+ stem cells into the infarcted myocardium induced angiogenesis and was reported to promote a regenerative response (102). However, in other studies, TGF-β appeared to act as a suppressor of cardiac regeneration. TGF-β inhibition enhanced differentiation of stem cell-derived mesoderm to cardiomyocytes (103). Moreover, in a model of cardiac injury, TGF-β inhibition improved cardiomyoblast-mediated regeneration (104). The conflicting findings may reflect distinct effects of TGF-β on various cell types used to promote myocardial remuscularization.

TGF-β signaling pathways in the infarcted myocardium

Active TGF-β signals by binding to the TGF-β receptor complex at the cell surface. TGF-β binds to the constitutively active TβRII; this complex recruits and transphosphorylates the type I receptor (TβRI) (105,106). TβRI activation propagates downstream signaling involving a family of intracellular effectors, the Smad proteins (106,107). The receptor activated Smad proteins (R-Smads), Smad2 and Smad3 are phosphorylated upon activation of the cytoplasmic domain of TβRI; then form a trimeric complex with the common Smad, Smad4. Subsequently, the activated Smad complex translocates to the nucleus, recruits coactivators or corepressors into transcriptional complexes (108), and regulates gene transcription. Although TGF-βs typically activate Smad2/3 cascades, it has been recognized that Smad1 and Smad5 may also be activated by TGF-β in certain cell types, providing an alternative Smad-dependent pathway for signal transduction (109). The structurally divergent inhibitory Smads (i-Smads), Smad6 and Smad7, are induced by TGF-βs as part of a negative feedback loop that inhibits TGF-β signaling by interfering with phosphorylation of R-Smads (110). In addition to Smad-dependent signaling, TGF-β also activates a wide

range of non-canonical cascades, including p38 MAPK, Erk, JNK, TAK-1, and Rho GTPase pathways (111-113).

Activation of both Smad2/3 and Smad1/5 pathways has been reported in infarcted hearts (38,114). Although TGF-βs are likely important activators of the Smad2/3 cascade, other members of the TGF-β family, angiotensin II, or matricellular proteins may also contribute to Smad activation. Our knowledge on the role of Smad3 signaling in myocardial infarction is based on *in vitro* experiments and on investigations using mice with global loss of Smad3. Smad3 KO animals had no significant defects in resolution of inflammation; but exhibited attenuated leukocyte recruitment in the infarcted area. Moreover, global Smad3 loss reduced fibrosis in the infarct border zone and in the remodeling myocardium, resulting in improved diastolic function (38). *In vitro* experiments showed that Smad3 null cardiac fibroblasts were hyperproliferative, but exhibited impaired function. Smad3 was critically involved in myofibroblast transdifferentiation and mediated TGF-β-induced extracellular matrix synthesis and TIMP upregulation (38,76). Considering the broad effects of Smad3 on all cell types, it is unclear whether the improved remodeling exhibited by mice with global loss of Smad3 is due to fibroblast-mediated actions. Understanding the role of Smad-dependent signaling in myocardial infarction requires cell-specific loss-of function strategies.

The role of Smad-independent TGF-β signaling pathways in the infarcted heart has not been systematically investigated. TGF-β-activated kinase (TAK)-1, a member of the MAPK family, is activated in the pressure-overloaded myocardium, and is involved in cardiac hypertrophy and fibrosis (115). The potential role of TAK-1 following infarction has not been studied. Experimental studies in models of renal and pulmonary injury have suggested an important role for non-Smad pathways [such as p-21-activated kinase 2 (PAK2) and c-Abl] in fibrotic diseases (116,117). However, the involvement of these pathways in repair and fibrosis of the infarcted heart remains unknown.

It has been proposed that, in addition to its direct effects on the cells responsible for cardiac repair, TGF-β may also act by inducing expression of downstream effectors, such as the matricellular protein connective tissue growth factor (CTGF)/CCN2, or endothelin (118). CCN2 may synergize with TGF-β to stimulate cardiomyocyte hypertrophy (119) and enhance fibrosis (76). Although transgenic overexpression studies have suggested protective effects of CCN2 on the size of the infarct (120), actions of endogenous CCN2 in the infarcted myocardium have not been dissected. It is unclear, whether any of the effects of TGF-β on the cellular response to myocardial infarction are mediated through CCN2. A recent study suggested that in a model of myocardial TGF-β overactivation, induced through cardiac-specific expression of an active TGF-β mutant, CCN2 did not play an important role in cardiac pathology (121).

Targeting TGF-β in myocardial infarction

Because of its critical role in repair, remodeling, fibrosis and regeneration, TGF-β is considered an attractive therapeutic target in myocardial infarction and cardiac remodeling (118). Unfortunately, the pleiotropic and context-dependent actions of the TGF-β isoforms, and the complexity of TGF-β-activated signaling cascades have hampered therapeutic application. Clearly, in the infarcted myocardium, TGF-β has both beneficial and detrimental actions. Identification of safe and effective therapeutic strategies will require understanding of the cellular basis for these effects, and dissection of the distinct actions of Smad-dependent and Smad-independent TGF-β signaling. Unfortunately, expansion of our knowledge on the pathophysiological role of TGF-β in myocardial infarction may not be sufficient for implementation of effective strategies in human patients. In the clinic, post-infarction remodeling and heart failure is pathophysiologically heterogeneous. For the same amount of cardiomyocyte loss, some patients develop dilative remodeling and systolic dysfunction, while others may have extensive fibrosis, accompanied by diastolic heart failure (122). Differences in TGF-β responses between patients may account for the distinct patterns of post-infarction remodeling in various subpopulations. Identification of patients with overactive TGF-β responses through the use of carefully validated biomarkers, or imaging studies, will be important in order to design personalized treatment strategies. Moreover, it should be emphasized that, because of its broad effects on many cell types, targeting TGF-β may carry significant risks (123). A large body of evidence suggests that disruption of the TGF-β/Smad axis promotes aortic aneurysm formation and rupture (124-126). Thus attempts for clinical translation of TGF-β/Smad inhibition strategies should exclude patients vulnerable to the potentially adverse consequences of Smad3 disruption on vascular remodeling. Temporal considerations are also highly significant: early inhibition of the TGF-β response may perturb reparative responses essential to maintain the structural integrity of the ventricle.

Successful translation will require a combination of animal studies to understand the cellular targets and functions of TGF-β, and human investigations to identify patients likely to benefit from specific therapeutic interventions.

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Footnote

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