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JACC Focus Seminar: Extracellular Matrix in Cardiovascular Health and Disease Extracellular Matrix in Ischemic Heart Disease, Part 4/4: *JACC* Focus Seminar

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Abstract

Myocardial ischemia and infarction, both in the acute and chronic phases, are associated with cardiomyocyte loss and dramatic changes in the cardiac extracellular matrix (ECM). It has long been appreciated that these changes in the cardiac ECM result in altered mechanical properties of ischemic or infarcted myocardial segments. However, a growing body of evidence now clearly demonstrates that these alterations of the ECM not only affect the structural properties of the ischemic and post-infarct heart, but that they play a crucial and sometimes direct role in mediating a range of biological pathways, including the orchestration of inflammatory and reparative processes, as well as the pathogenesis of adverse remodeling. In this final part of a 4-part review series, we review the evidence on the role of the ECM in relation to the ischemic and infarcted heart, as well as its contribution to cardiac dysfunction and adverse clinical outcomes.

Condensed Abstract:

Myocardial ischemia and infarction are associated with dramatic changes in the cardiac extracellular matrix (ECM). It has long been appreciated that these changes result in altered mechanical properties of affected myocardial segments. However, these changes to the ECM not only affect the structural properties of the ischemic and post-infarct heart, but they also mediate a range of important biological processes, such as inflammation and adverse remodeling. In this

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final of a 4-part review series, we focus on the role of the ECM in relation to the ischemic and infarcted heart, including its contribution to cardiac dysfunction and adverse clinical outcomes.

Keywords

Biomarker; collagen; fibroblast; heart failure; ischemic heart disease

So far in this review series we have covered basic extracellular matrix (ECM) biology in Part 1, the role of ECM in vascular disease in Part 2, and the involvement of ECM in myocardial interstitial fibrosis (MIF) in non-ischemic heart disease in Part 3. Here in Part 4 we address the role of ECM in ischemic heart disease.

In the majority of patients, ischemic heart disease is caused by atherosclerosis of the epicardial coronary arteries, which leads to an imbalance between oxygen supply and demand. Typically, a coronary luminal narrowing of greater than 75% does not cause a reduction in resting blood flow, but precludes an increase in oxygen supply when myocardial demand is increased (upon exercise, during tachy-arrhythmia, etc.), resulting in ischemia. When atherosclerotic disease is complicated by superimposed thrombosis, acute coronary occlusion results in myocardial infarction (MI). Complete and prolonged interruption of blood flow to the area subserved by the vessel leads to cessation of oxidative phosphorylation, depletion of high energy phosphates, and increased accumulation of metabolites in the ischemic myocardium. After 15-20 minutes of occlusion, disruption of aerobic metabolism in cardiomyocytes results in irreversible changes that eventually lead to cardiomyocyte death. As we review in this article, both chronic ischemia and acute MI are associated with profound changes in the ECM network. Furthermore, mounting evidence suggests that in ischemic and infarcted hearts, ECM alterations not only accompany the pathologic changes in cardiomyocytes, but play a crucial role in mediating injurious pathways, orchestrating inflammatory and reparative processes, and contributing to the pathogenesis of adverse remodeling.

The ECM in the infarcted heart

In adult mammals with MI, massive loss of cardiomyocytes overwhelms the extremely limited endogenous regenerative capacity of the heart (1). Thus, the infarcted myocardium heals through replacement of dead myocardium with a matrix-based scar. The myocardial reparative response can be divided into 3 distinct, but overlapping phases: inflammatory, proliferative and maturation. As the infarcted myocardial segments heal, non-infarcted areas remodel in response to hemodynamic loading and to the effects of immune cells and fibroblasts accumulating in the infarct border zone. The dynamic changes in ECM composition not only affect the structure and mechanics of the heart, but also play a critical role in regulation of the cellular responses in the infarcted and remodeling myocardium. During the inflammatory phase, fragments of ECM generated through early activation of proteases may serve as damage-associated molecular patterns (DAMPs) that activate immune cells, triggering an inflammatory reaction. Moreover, extravasated plasma proteins enrich the ECM, generating a plastic network of provisional matrix that serves as a conduit for immune and reparative cells. Phagocytosis of dead cells and matrix debris by

professional phagocytes inhibits inflammation, leading to the proliferative phase of infarct healing, characterized by activation of myofibroblasts and neovessel formation. Enrichment of the cardiac ECM through deposition of matricellular proteins plays a critical role in spatial regulation of growth factor signaling cascades, restricting the fibrotic response to areas of injury. In addition, activated fibroblasts secrete large amounts of structural ECM proteins, forming a scar. As the infarct matures, cross-linking of the ECM provides structural stability, while increasing ventricular stiffness. In viable myocardial segments, pressure and volume loads cooperate to induce chronic progressive deposition of collagen in the interstitium, thus contributing to the pathogenesis of post-infarction heart failure.

The role of ECM in the inflammatory phase of infarct healing

Activation of matrix-degrading proteases and generation of matrix fragments are the earliest ECM perturbations in infarcted hearts. In some studies, ischemic changes in the interstitial matrix have been reported to precede irreversible cardiomyocyte injury. In a porcine model, matrix metalloproteinase (MMP) activation was first detected in the cardiac interstitium after 10 minutes of coronary occlusion (2). Early MMP activation is followed by fragmentation of fibrillar collagens and other structural ECM proteins. In a pig MI model, release of type I collagen fragments in the serum was documented after 30 minutes of coronary occlusion (3). In ultrastructural studies, the earliest alterations in collagen morphology, described as “irregular arrangement” of collagen fibers, were noted after 40 min of coronary occlusion and were followed by a reduction in the density of collagen fibrils 2h after the acute event (4). Early increases in MMP activity in the ischemic myocardium reflect activation of latent stores, presumably through reactive oxygen species-mediated pathways (5). At a later stage, ischemic cardiomyocytes, fibroblasts, vascular cells and immune cells synthesize and release large amounts of proteases in the infarcted myocardium (6). Members of the collagenase family (such as MMP1), gelatinases (including MMP2 and MMP9) and cathepsins are upregulated in the infarcted heart (7,8) and also contribute to ECM fragmentation.

ECM fragments as regulators of the inflammatory and reparative response

Protease-mediated ECM fragmentation generates bioactive peptides that can modulate inflammatory, fibrogenic or angiogenic responses (9,10) (Figure 1). The terms “matrikines” and “matricryptins”, have been used to describe these biologically active matrix fragments. Although universally accepted definitions are lacking, the term “matrikine” is typically used to describe any fragment of an ECM molecule with biological properties distinct from those of the full-length molecule. On the other hand, the term “matricryptin” refers to a subtype of matrikines that require proteolytic processing to expose a functional domain and exert their biological actions (11). Although the rapid and prolonged activation of proteases may release a wide range of matrix fragments in the cardiac interstitium, their profile, time course of release, and potential involvement in regulation of myocardial inflammation and repair remain poorly understood. In the infarcted myocardium, all constituents of the cardiac ECM, (including fibrillar collagens, elastin, basement membrane proteins, fibronectin, hyaluronan, and newly-secreted matricellular macromolecules) (12-15) may be targeted by proteases to generate fragments (Table 1). Peptides derived from fibrillar collagens and elastin have been implicated in activation of immune cells in models of inflammation and tissue injury (10,16). Extensive evidence in models of pulmonary inflammation suggests that the

tripeptide proline-glycine-proline (PGP) and its acetylated form ac-PGP are generated from collagen through a multistep proteolytic cascade that involves MMP8, MMP9 and prolyl endopeptidase (17), and may act as a potent neutrophil chemoattractant signaling through activation of the chemokine receptor CXCR2 (18). Although PGP generation has been demonstrated in pressure-overloaded hearts (19), evidence implicating this pro-inflammatory matrikine in post-MI inflammation is lacking. Low molecular weight hyaluronan fragments may also exert potent pro-inflammatory actions in injured tissues, by activating toll-like receptor signaling pathways (20). Interestingly, it has been suggested that impaired clearance of these fragments may prolong and accentuate pro-inflammatory signaling in leukocytes and vascular cells (21,22), thus accentuating adverse remodeling after MI. Proteolytic processing of laminins by MMP2 and MMP14 has also been demonstrated to yield neutrophil chemoattractant peptides (23), while fibronectin fragments have been identified in the infarcted heart and are suggested to reduce monocyte migratory capacity in response to chemokines (15).

It should be emphasized that the effects of matrikines and matricryptins are not limited to the inflammatory phase of infarct healing. Prolonged activation of proteases in the infarcted myocardium generates ECM fragments for several days after MI. In addition to their effects on immune cells, matrix fragments may also modulate the fibroblast and vascular cell phenotype (24). Endostatin, a 20kDa fragment of collagen XVIII, may stimulate fibroblast proliferation (25), while exerting potent angiostatic actions (26). MMP9-mediated cleavage of collagen IV generates tumstatin, a fragment with angiostatic properties (27) that can be further degraded to produce fragments that promote a proliferative and migratory phenotype in cardiac fibroblasts (28). Canstatin, another collagen IV-derived fragment, may also activate fibroblasts, stimulating their proliferation and enhancing fibroblast-derived MMP synthesis (29,30).

Broad effects of MMPs in regulation of the inflammatory response

In addition to their role in ECM remodeling, MMPs regulate inflammatory and reparative cascades through proteolytic processing of cytokines, chemokines and growth factors. Several members of the MMP family can process the cell membrane-anchored precursor of tumor necrosis factor (TNF)-α to generate the active cytokine (31). MMP3 and the gelatinases MMP2 and MMP9 can also process pro-Interleukin (IL)-1β, generating the biologically active form of the cytokine in a caspase 1-independent manner (32). Furthermore, MMPs are implicated in the complex multistep cascade that leads to generation of mature transforming growth factor (TGF)-β from secreted latent complexes (33). MMPs also process several members of the chemokine family, including CXCL12/ stromal cell-derived factor (SDF)-1 and CCL2/monocyte chemoattractant protein (MCP)-1, exerting diverse and often conflicting actions that may either potentiate or inactivate the effects of the chemokine (34-38). Furthermore, MMPs may disperse chemokine gradients by degrading glycosaminoglycan binding sites that are critical for chemokine immobilization on the endothelial cell surface and subsequent interaction with activated leukocytes (39). Considering the critical involvement of chemokines and cytokines in leukocyte recruitment, repair and remodeling of the infarcted myocardium (40-42), MMP-dependent processing of inflammatory mediators may be a central regulatory mechanism in the post-infarct heart.

Discoveries suggesting subcellular localizations of some MMP family members in the cytosol, mitochondria or the nucleus have added complexity to our understanding of the role of MMPs in cardiac repair. It has been suggested that intracellular MMPs may have a wide range of substrates, including cytoskeletal proteins, signal transducers, enzymes, and transcriptional regulators (43). MMP-mediated degradation of contractile proteins, such as myosin and actinin, has been implicated in the pathogenesis of ischemic myocardial dysfunction (44,45). In vitro studies demonstrated that MMPs may also function in a non-proteolytic manner, regulating signal transduction or transcription (46). The *in vivo* significance of these functions remains to be fully defined.

The deposition of a plasma-derived provisional matrix regulates the post-infarction inflammatory response

Proteolytic degradation of the native myocardial ECM is accompanied by the formation of a highly plastic provisional matrix network that supports migration and differentiation of immune, vascular and reparative cells, contributing to scar formation (13,47). In models of vascular injury and of cutaneous repair, progressive changes in the composition of the provisional matrix have been described (48). Early provisional matrix is comprised predominantly of extravasated proteins (such as fibrinogen-derived fibrin and plasma fibronectin) (49). As immune cells and fibroblasts migrate into the injured tissue, the provisional matrix is enriched with a cell-derived component, comprised of cellular fibronectin and proteoglycans (50). Studies describing the cellular events in infarcted mammalian hearts suggest a similar transition ECM composition (13,51). Rapid induction and release of cytokines and growth factors, such as TNF-α and vascular endothelial growth factor (VEGF), may be responsible for increased vascular permeability (52,53), leading to extravasation of fibrinogen and fibronectin in the infarct zone (13,54). The role of the components of the provisional matrix in regulation of the inflammatory response following MI remains poorly supported by experimental *in vivo* evidence. In a mouse model of reperfused MI, fibrin-mediated pro-inflammatory actions were suggested to extend ischemic injury (55). Both fibrinogen and fibronectin contain integrin binding sites that may play a crucial role in adhesion and migration of leukocytes in the infarcted heart (56,57), and which may transduce signals that modulate cytokine and chemokine expression by macrophages (58-60). In addition to the direct effects of its components on inflammatory cells, the provisional matrix may also serve as a reservoir for cytokines and growth factors that mediate the transition to the proliferative phase of cardiac repair.

The role of ECM in the proliferative phase of infarct healing

The clearance of dead cells and matrix debris from the infarcted myocardium triggers a series of anti-inflammatory cascades that suppress leukocyte recruitment and generate a reparative environment. Infarct macrophages undergo phenotypic transitions, expressing and releasing mediators (like TGF-β and IL-10) that suppress inflammation, while promoting myofibroblast activation (61-63). Resident cardiac fibroblasts undergo myofibroblast conversion (64), expressing contractile proteins such as α-smooth muscle actin, and secreting collagens and other structural ECM proteins that are necessary for protection of the infarcted myocardium from catastrophic rupture (65). Although other cell types such as macrophages may produce collagen following myocardial injury (66), their relative

contribution as a source of structural ECM proteins is limited, and activated myofibroblasts represent the main collagen-synthesizing cells in the healing infarct. Myofibroblast activation requires the cooperation of several different cell types, including macrophages, lymphocytes, vascular cells and border zone cardiomyocytes, which secrete growth factors and matricellular proteins, converting the ECM into a signaling hub that localizes fibroblast-activating mediators into the infarct zone.

Transition to the proliferative phase of cardiac repair is marked by dramatic changes in the composition of the provisional matrix. The fibrin-based plasma-derived provisional network is lysed by fibrinolytic enzymes (67). *In vivo* studies suggest that the timely clearance of the fibrin-based provisional matrix by the plasminogen/plasmin system plays a crucial role in regulation of the reparative response. Plasminogen null mice exhibit marked defects in infarct healing, associated with impaired recruitment of reparative cells and perturbed replacement of dead cardiomyocytes with granulation tissue (68,69). As the fibrin network is lysed, activated macrophages and interstitial cells generate a cell-derived ECM that contains cellular fibronectin, hyaluronan, and proteoglycans (51,70). The cell-derived provisional matrix is further enriched with a range of matricellular macromolecules (13,71) and transduces key activating signals in fibroblasts, immune cells, vascular cells, and surviving border zone cardiomyocytes (Central Illustration).

The conversion of fibroblasts to activated myofibroblasts also occurs, which requires a close association with TGF-β-secreting macrophages (72) and local activation of latent TGF-β in the infarcted area. The deposition of specialized components of the matrix network plays a critical role in spatially-restricted TGF-β activation in the healing infarct. *In vitro* and *in vivo* evidence suggest that the ED-A splice variant of fibronectin mediates TGF-β1-induced myofibroblast conversion (73,74). However, the interactions between ED-A fibronectin and the TGF-β signaling cascade remain poorly understood. It has been suggested that ED-A fibronectin may act by immobilizing the large latent TGF-β complex within the ECM (75), thus localizing this growth factor in the area of fibroblast accumulation. Proteases, cell surface integrins and matricellular proteins may then cooperate to liberate the active TGF-β dimer from latent stores, triggering downstream fibrogenic signaling pathways (76). In addition to its role in stimulating TGF-β-driven fibroblast-activating responses, fibronectin may also play an important role in angiogenesis. The heparin II domain of fibronectin binds to VEGF (77) and may promote angiogenic activation of endothelial cells, thus stimulating neovessel formation in the infarct.

The modulation of interactions between growth factors and proteoglycans has profound effects on reparative, fibrogenic and angiogenic cascades. Induction of sulfatases in the infarcted heart can remove 6-*O*-sulfate groups from heparan sulfate in the extracellular compartment, thus perturbing interactions between VEGF-A and heparan sulfate, and increasing responsiveness to the angiogenic effects of VEGF (78). Inhibition of heparin sulfate sulfation may also affect bioactivity of several other cytokines, chemokines and growth factors, including CXCL12 and TGF-βs.

The effects of matricellular proteins

The term “matricellular protein” was coined to highlight the effects of structurally unrelated, injury-associated ECM components that regulate cellular functions by modulating signaling cascades (79,80). Prototypical matricellular proteins have a limited structural role, but are overexpressed in injured and remodeling tissues, and bind to structural matrix proteins and cell surface receptors (like integrins or syndecans), transducing cytokine and growth factor signals, or modulating the activity of proteases and other bioactive mediators (71). The family includes SPARC (Secreted protein, acidic and rich in cysteine), thrombospondins (TSP)-1, −2, and −4, tenascin-C and -X, periostin, osteopontin, and the members of the CCN (**C**ystein rich protein 61/ **C**onnective tissue growth factor)/ **N**ephroblastoma overexpressed gene) family (81). The term is also used to describe other secreted proteins that may exhibit some matricellular functions within the broad range of their effects (including the galectins, fibulins, and small leucine rich proteoglycans such as osteoglycin). Considering the growing evidence suggesting that even prototypical matricellular proteins may act as intracellular mediators or exert cytokinelike functions, the term may be more useful to describe specific functions that govern the interactions between the ECM and cellular elements, rather than to define a group of proteins. In the infarcted heart, neurohumoral signals, cytokines and growth factors induce the expression and secretion of a wide range of matricellular proteins in fibroblasts, macrophages, cardiomyocytes and vascular cells (Central Illustration) (13,82,83). Our current understanding of the role of matricellular proteins in the infarcted heart is derived from studies using genetically targeted mice (71,84). Although each member appears to exert unique actions *in vivo* (Table 2), several unifying patterns have emerged on the functional properties of matricellular macromolecules. First, matricellular proteins act on many cell types, modulating fibroblast, macrophage and vascular cell phenotypes, and regulating survival, hypertrophy and dysfunction of border zone cardiomyocytes (85-87). However, the relative significance of these cell-specific actions of matricellular proteins is unclear. Second, matricellular proteins may also contribute to the cellular plasticity of interstitial cells observed in healing infarcts (88-91), both through direct actions and via modulation of growth factor-mediated pathways. Third, several members of the family exhibit a highly selective localization in the infarct border zone (92), possibly reflecting macrophage-derived secretion in this leukocyte-rich environment, or the unique interactions between surviving cardiomyocytes, macrophages and fibroblasts in this area. The localized induction of matricellular proteins in the infarct border zone highlights their role in spatial regulation of cellular responses. Large amounts of growth factors and cytokines are secreted in the infarct border zone and could diffuse into neighboring viable areas, promoting fibrogenic or inflammatory responses. The selective induction and deposition of matricellular proteins may serve to localize inflammation and fibroblast activation within the area of injury, restraining the fibrotic response and protecting from adverse remodeling. Fourth, members of the matricellular family are transiently upregulated in the healing infarct. Although the mechanisms responsible for removal of matricellular proteins from the healing area remain poorly understood, the signals involved in their clearance may protect the infarcted heart from expansion of the fibrotic response following injury.

Deposition of fibrillar collagens in the infarcted heart

De novo fibrillar collagen synthesis (i.e. collagens I and III) confers mechanical strength to the healing scar, thus protecting the infarcted myocardium from rupture and attenuating dilative remodeling. In addition to their structural role, fibrillar collagens may also transduce signals to interstitial immune and vascular cells. Infarct myofibroblasts are capable of secreting large amounts of collagens in response to neurohumoral stimuli, or growth factors (such as TGF-β), and are the major collagen-synthesizing cells in the healing infarct (93). Although the functional heterogeneity of fibroblasts is increasingly appreciated (94,95), whether exaggerated matrix synthesis marks a distinct subset of myofibroblasts remains unknown.

In experimental models of MI, type III procollagen exhibits early induction, followed by the marked upregulation of procollagen I synthesis (93,96). Whether the time course of collagen isoform synthesis reflects isoform-specific effects of various fibrogenic stimuli is unknown. The relative expression of collagen I and collagen III has been suggested to regulate cardiac compliance. Collagen I forms thick and stiff fibers; in contrast, the fine reticular collagen III fibers are more compliant and may improve elasticity of the infarcted ventricle.

The synthesis of procollagens by infarct myofibroblasts is followed by secretion of soluble procollagen protein in the infarct zone (Figure 2). Subsequent processing of procollagen chains and assembly of fibrils is of critical significance for formation of an organized scar. Cleavage of the C-terminal propetide attached to procollagen involves the C proteinase bone morphogenetic protein (BMP)1 (97), which is induced in the infarcted heart (98,99). Secreted frizzle-related protein 2 (Sfrp2) is also upregulated in infarct fibroblasts and likely enhances the BMP1-procollagen interaction, promoting collagen processing (99). In addition, collagen processing may require further interactions with matricellular proteins, such as SPARC (100).

The role of non-fibrillar collagens

Myocardial infarction is also associated with the induction of non-fibrillar collagens; a subfamily of collagens that do not form large fibrillar bundles, but which can associate with type I or III collagen fibrils to regulate anchoring, networking and organization of the ECM (101). Some non-fibrillar collagens may exert signaling functions through binding to cell surface receptors. Other members of the family may be proteolytically cleaved, generating bioactive fragments that regulate the fibroblast or vascular cell phenotype. Collagen VI, the best studied non-fibrillar collagen in MI, has been suggested to exert protective effects, reducing the size of the infarct and attenuating adverse remodeling (102). Specific actions of collagen VI on cardiomyocyte survival and activation of reparative myofibroblasts have been proposed to explain the protective effects (103,104).

The ECM in scar maturation

Maturation of the healing infarct is associated with cross-linking of the collagenous ECM and reduction of the cellular content of the scar. The molecular signals suppressing fibrogenic activation in the mature scar remain enigmatic. As the scar matures, there is a progressive reduction of the density of activated myofibroblasts in the infarct zone (105).

Some descriptive studies have documented apoptosis of infarct fibroblasts, suggesting that cell-specific activation of an apoptotic program may be involved (106,107). Depletion of growth factors and clearance of matricellular proteins required for fibroblast survival may be sufficient to trigger fibroblast death or quiescence in the mature infarct (108,109). Whether active secretion of specific pro-apoptotic or de-activating signals that target infarct fibroblasts also plays a role in negative regulation of the fibrogenic response remains unknown. Recent lineage tracing approaches have suggested that fibroblasts persist in the mature infarct, but that they transition to a distinct phenotype that produces tendon genes and which may be specialized to support the scar (110). However, the mechanisms responsible for cell-specific activation of a pro-apoptotic program in the late phase of infarct healing have not been investigated, and the acquisition of a quiescent phenotype may precede apoptosis of infarct myofibroblasts. Vascular cells may also respond to the mature ECM environment by undergoing changes that profoundly affect the morphology and function of the infarct microvasculature. As the scar matures, infarct microvessels acquire a coat of mural cells through activation of platelet-derived growth factor receptor (PDGFR)-β signaling (105,111); while uncoated vessels regress. The composition of the ECM modulates interactions between pericytes and endothelial cells (112,113); however, the role of such actions in the maturation of infarct microvessels has not been investigated.

Chronic ECM expansion in the non-infarcted remodeling myocardium may play a role in heart failure progression

In the presence of a large MI, massive loss of contractile tissue results in increased ventricular filling pressures, and typically also with progressive fibrotic changes in viable myocardial segments (114). The deposition of interstitial collagen in the non-infarct zone is attributed to the pathophysiological effects of pressure and volume loads, and may be dependent on neurohumoral pathway activation (115). Moreover, in viable segments, increased wall stress may locally activate mechanosensitive cascades in macrophages and fibroblasts, triggering myocardial interstitial fibrosis (MIF; see Part 3 of this review series) and expansion of the cardiac interstitial matrix network (116,117).

The ECM in chronic ischemic cardiomyopathy

Alterations in the ECM network have been extensively documented in patients with ischemic cardiomyopathy, even in the absence of frank MI. Patients with chronic ischemic cardiomyopathy typically exhibit MIF (118), and have increased myocardial collagen levels (119) associated with accentuated MMP expression (120,121) and increased deposition of matricellular proteins such as tenascin-C (122). Considering the high prevalence of comorbidities (including hypertension, diabetes and metabolic dysfunction) that may profoundly affect ECM deposition and remodeling, the relative impact of chronic ischemia in the matrix remodeling patterns noted in ischemic cardiomyopathy patients is unclear.

Pathophysiologically-oriented studies examining the effects of brief intermittent ischemic insults, or low flow ischemia on the myocardial ECM are limited. Some animal evidence suggests that ischemia may cause significant alterations in the ECM network, even in the absence of infarction. In a pig model, reduction of coronary flow to 50% of baseline for 90

min was sufficient to activate MMP9, but had no effects on the structure of cardiac ECM (123). Whether longer intervals of chronic ischemia stimulate MMP-mediated matrix degradation remains unknown. In a mouse model, daily brief repetitive myocardial ischemia and reperfusion for 7 days was associated with interstitial collagen deposition and increased expression of the matricellular protein tenascin-C, in the absence of a completed infarction (124). The activation of oxidative stress pathways by brief repetitive ischemic insults was implicated in the observed fibrotic changes. This suggests that repetitive ischemic events of low duration or intensity may be sufficient to trigger remodeling of the cardiac ECM in the absence of cardiomyocyte necrosis (125). A small clinical study supports this notion, demonstrating that in human patients undergoing aorto-coronary bypass surgery, MMP2 and MMP9 are activated in the myocardium following reperfusion after cardioplegia (126).

Therapeutic opportunities: Targeting the ECM in ischemic heart disease

Matrix-based strategies to preserve the structure, geometry and function of the remodeling heart after MI

Because of its importance in preserving cardiac structural integrity and function (127), and its role in the regulation of cellular responses in cardiac injury, repair, and remodeling (71), the cardiac ECM may provide unique opportunities for therapeutic interventions. Following acute MI, cardiac rupture is an uncommon but dramatic complication, typically associated with accentuated matrix degradation (128), perturbed deposition of new structural matrix (129), or disorganized architecture of the scar (65). The application of patches containing ECM proteins may be sufficient to restore the structural integrity of the ventricle in acute left ventricular free wall rupture (130).

The effects of biomaterial scaffolds have been extensively studied in experimental MI models. Implantation of cellular or acellular ECM bioscaffolds, and administration of injectable materials, have been reported to exert beneficial actions on the infarcted heart (131-135), not only by improving the mechanical properties of the healing scar, but also by modulating inflammatory and reparative signals, by stimulating pro-survival pathways and promoting angiogenesis (136). Composite cell-matrix scaffolds can also be effective cell delivery platforms to enhance the reparative actions of cell therapy (137). Recently, transendocardial injection of VentriGel, a cardiac ECM hydrogel derived from decellularized porcine myocardium, was tested in 15 patients with chronic remodeling and moderate left ventricular dysfunction following MI (138). Although the study supported the safety and feasibility of the approach, it was not designed to evaluate efficacy, and large randomized clinical trials testing the efficacy of ECM hydrogels have not been performed. More importantly, despite extensive experimental work, there is currently no consensus regarding the optimal composition and method of administration of biomaterials following MI. Systematic study of the effects of various strategies in large animal models of MI is needed prior to attempts for therapeutic translation.

In chronic ischemic heart disease, there is little doubt that ECM deposition needs to be tightly regulated: excessive accumulation of cross-linked collagens may increase stiffness, promoting diastolic dysfunction, whereas overactive protease-driven matrix degradation pathways may promote dilative remodeling, causing systolic dysfunction. Established

therapeutic approaches, such as angiotensin converting enzyme (ACE) inhibition, angiotensin type 1 (AT1) receptor blockade, β-adrenergic receptor antagonism, and mechanical unloading, all act to modulate the deposition and metabolism of ECM proteins (139) and may exert their protective actions (at least in part) by targeting the ECM network. However, the implementation of direct approaches to target matrix remodeling has been hampered by the broad effects of proteases in the infarcted myocardium, while attempts to inhibit MMPs in patients with MI have produced mixed results. Thus, early non-selective MMP inhibition with doxycycline attenuated dilative remodeling in patients surviving MI complicated by left ventricular systolic dysfunction (140). In contrast, administration of a selective oral MMP inhibitor in patients with MI and reduced ejection fraction showed no significant protection from adverse remodeling (141). The wide range of actions of MMPs that may affect not only ECM remodeling, but also the molecular signals involved in inflammation and repair, complicates interpretation of these findings. As also suggested in the context of MIF in the non-ischemic heart (see Part 3 of this JACC series), it is likely that successful approaches targeting the ECM may require the development and validation of biomarkers or imaging methods to identify patient subpopulations with specific patterns of ECM alterations (142). Thus, individuals with overactive matrix synthetic responses following infarction may require different approaches compared to patients with predominantly protease-driven matrix degradation.

Targeting the matricellular proteins

The critical role of the ECM in repair and remodeling of the infarcted heart suggests that therapeutic approaches modulating the biochemical composition and mechanical properties of the matrix may hold promise for patients with MI. Strategies based on matricellular proteins seem particularly attractive, as they could allow localized modulation of growth factor and cytokine signaling in the infarct area. However, despite evidence suggesting the critical actions of matricellular proteins in the infarcted heart, therapeutic translation is hampered by the complexity of their biological actions. The effects of the matricellular proteins are exerted through many cell types and may be context-dependent, depending on the local cytokine environment and the ECM composition. Moreover, matricellular proteins have multiple functional domains with different actions. Thus, successful therapeutic implementation of therapies based on matricellular proteins will likely require the identification of the functional domains responsible for their protective or detrimental actions *in vivo* (71,143). Considering the known limitations of *in vivo* models, this is a daunting task.

Matrix interventions for cardiac regeneration

ECM modulation may also hold the key to a visionary research goal: cardiac regeneration. This notion is based on several findings. First, in cardiomyocyte progenitors and neonatal cardiomyocytes, a compliant, elastin-containing ECM promotes cell cycle entry (144,145). Second, in zebrafish, fibronectin deposition has been suggested to play a critical role in myocardial regeneration (146), and in amphibians, a matrix network containing fibronectin, hyaluronan, and the matricellular protein tenascin-C has been suggested to activate a regenerative program (147). Third, in experimental cell therapy studies in mammalian models of cardiac injury, the application of matrix-based patches containing progenitor cells

showed enhanced effectiveness (148,149). Whether such effects may be due to direct actions of specific matrix proteins on cardiac progenitors, or reflect matrix-dependent activation of other cell types (like immune or vascular cells) remains unknown. Fourth, mammalian models of infarction have suggested regenerative actions of certain matricellular macromolecules that may promote the proliferation of differentiated cardiomyocytes. For example, agrin, a large extracellular heparan sulfate proteoglycan, promotes cardiomyocyte cell cycle re-entry in both neonatal and adult mice (150). In addition, the matricellular protein periostin triggers cell cycle re-entry in differentiated adult cardiomyocytes through integrin-dependent mechanisms, which results in improved cardiac function when administered as an epicardial gelfoam patch following infarction (151). Nevertheless, these promising early findings should be viewed with caution. Considering that the specialized ECM proteins suggested to be critical in regeneration of fish, amphibian and neonatal mouse hearts are also induced following adult mammalian cardiac injury in the absence of regeneration, it is unlikely that simple ECM-modulatory strategies will be sufficient to remuscularize adult mammalian hearts. Myocardial regeneration may require not only a "regenerative" matrix profile, but also enhanced phenotypic plasticity of progenitor cell populations, and a favorable local cytokine and growth factor microenvironment.

Summary and conclusions

Both acute MI and chronic myocardial ischemia are associated with profound changes in the ECM network. Furthermore, these ECM changes not only alter the cardiac interstitial milieu and its functional properties, but a growing body of evidence suggests that the ECM itself plays a key role in modulating both beneficial and adverse pathways, including inflammation and post-MI remodeling, but also cardiac repair. In this context, and also the broader context of the entire cardiovascular system as reviewed in this JACC series, the therapeutic targeting of the ECM and its many players is a compelling clinical avenue of research that is certain to see intense future interest.

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Abbreviations

BMP	bone morphogenetic protein
CITP	carboxy-terminal telopeptide of collagen type I
DAMP	damage-associated molecular patterns
ECM	extracellular matrix
IL	interleukin
MI	myocardial infarction

MIF	myocardial interstitial fibrosis
MMP	matrix metalloprotease
PGP	proline-glycine-proline
SPARC	secreted protein, acidic and rich in cysteine
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor

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Highlights

- Myocardial ischemia and infarction are associated with dynamic changes in the composition of the ECM network.
- In addition to their structural role, ECM proteins modulate cellular phenotype and function.
- Specialized matrix proteins transduce signals that regulate inflammation, fibrosis and angiogenesis.
- Targeting the ECM may attenuate remodeling and enhance repair and regeneration following infarction.

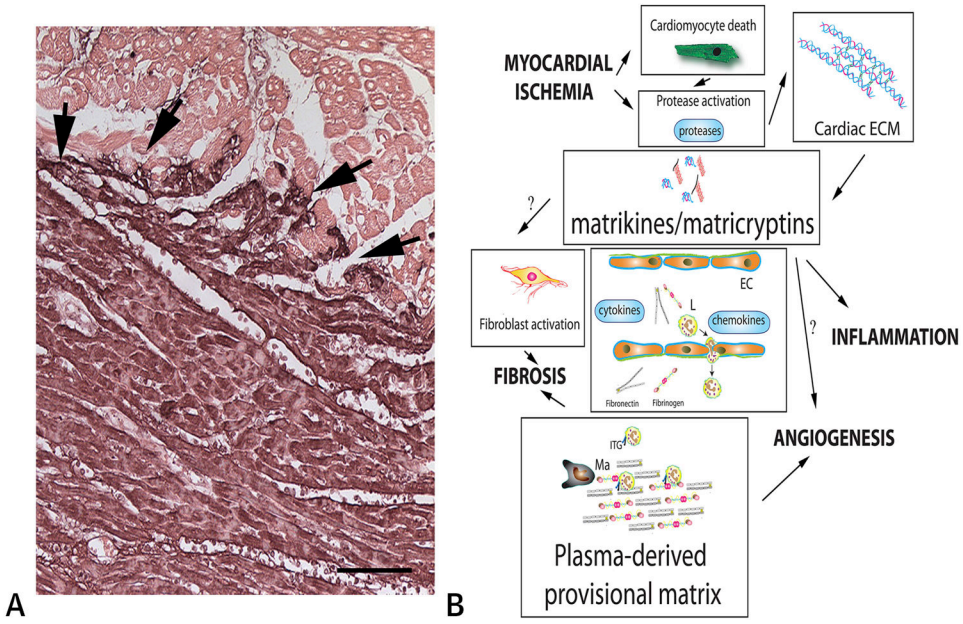


Figure 1. Generation of matrix fragments and formation of a plasma-derived provisional matrix during the inflammatory phase of cardiac repair.

A. Immunohistochemistry for fibrinogen/fibrin (black) shows deposition of plasma-derived proteins (including fibrin and fibronectin) that enrich the cardiac ECM during the early stages of infarct healing (arrows). Counterstained with eosin. Scalebar=120μm. Data from our own work in a canine model of reperfused MI (13). **B.** Schematic cartoon illustrating the dramatic changes in the interstitial ECM network during the inflammatory phase of infarct healing. Rapid activation and induction of proteases, such as MMPs and cathepsins, in the infarcted myocardium generates ECM fragments (matrikines and matricryptins) that modulate the phenotype of fibroblasts, macrophages (Ma) and endothelial cells (EC). MMPs have a wide range of substrates and process cytokines and chemokines, regulating their pro-inflammatory actions. Recruitment and migration of leukocytes (L), fibroblasts and vascular cells in the infarcted heart requires interactions between cell surface integrins (ITG) and provisional matrix proteins (such as fibrin and fibronectin). Thus, the provisional matrix plays an important role in regulation of inflammatory, fibrogenic and angiogenic responses.

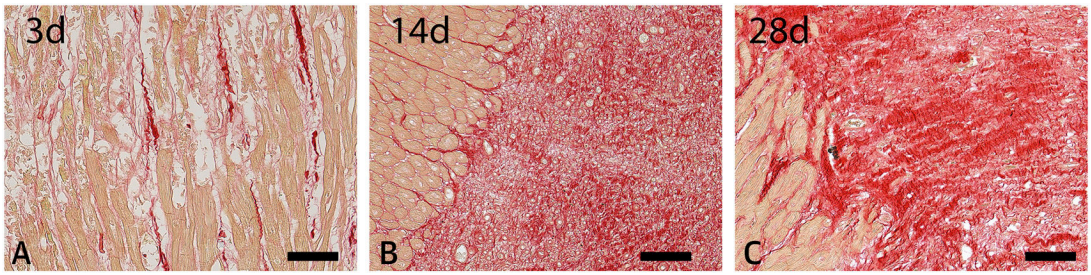
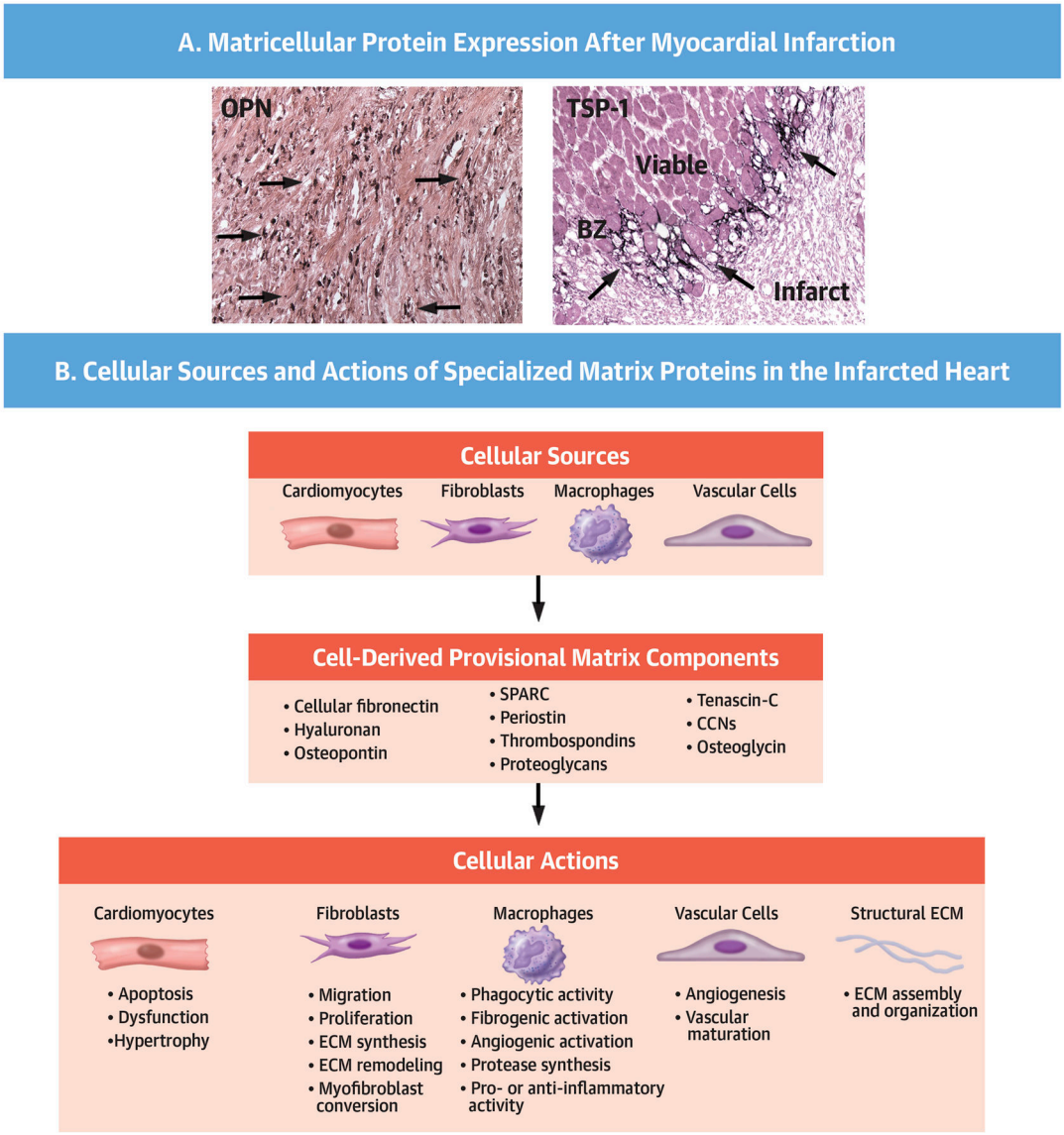


Figure 2. The time course of collagen deposition in the healing infarct.

Staining of canine infarct border zones with picrosirius red to identify collagen fibers at 3, 14 and 28 days after reperfused MI (1h of coronary occlusion followed by reperfusion). Collagen is identified by the red staining, with cardiomyocytes in light brown. Note the early disruption of the collagen network, accompanied by limited de novo synthesis at 3 days (A). After 14 days, extensive collagen deposition is noted in the healing infarct (B). The mature scar (28 days - C) exhibits a dense matrix network, typically associated with collagen cross-linking. Data from our own work in a canine model of reperfused MI (13). Scalebar=100μm.



Central Illustration. Matricellular proteins regulate inflammatory, reparative, angiogenic and fibrogenic cellular responses during the proliferative phase of infarct healing.

A. Immunohistochemical staining using a peroxidase-based strategy (black) shows expression of the matricellular proteins osteopontin (OPN–top panel) and thrombospondin (TSP)-1 (lower panel) in the infarcted myocardium. Counterstained with eosin. Scalebar=100μm. Data are from our own work in a canine model of reperfused MI (13,152). Each matricellular protein shows a unique pattern of localization, likely reflecting distinct cellular sources and mechanisms of regulation. OPN is predominantly expressed by macrophages (top-arrows), whereas TSP-1 is deposited in the infarct border zone (bottom-arrows). **B.** Schematic cartoon illustrating the complex matrix environment in the proliferative phase of infarct healing. Cell-derived fibronectin, hyaluronan, and a wide range of matricellular proteins (OPN, TSP-1, TNC/tenascin-C, periostin, SPARC, osteoglycin and members of the CCN family) and proteoglycans enrich the infarct ECM and regulate

assembly of the collagen-based structural matrix, while modulating a variety of cellular responses in cardiomyocytes, fibroblasts, macrophages and vascular cells.

Table 1.

Generation of ECM protein fragments in the infarcted heart.

ECM protein	Animal models	Human patients	Proposed role
Fibrillar collagens (collagen I, collagen III)	In the pig MI model, release of type I collagen fragments in the serum has been documented after 30 minutes of coronary occlusion (3). Experiments in the isolated perfused heart showed that global ischemia generates collagen I and collagen III fragments (153). Cathepsin K-specific collagen I fragments were found in infarcted mouse hearts (8). The collagen I α1 C-1158/59 fragment was identified in infarcted mouse hearts, generated through effects of MMP-2 and MMP-9 (24)	In patients with MI, an early increase in collagen degradation markers is noted (154) Plasma levels of carboxy-terminal telopeptide of type I collagen (CITP) reflect collagen I degradation, are higher in MI patients with systolic dysfunction (155) and correlate with the extent of acute injury (156). Plasma CITP levels 24h or 72h after acute MI are associated with late mortality (157) and adverse remodeling (158). A reduction in the ratio of biomarkers reflecting synthesis vs. degradation of collagen was also associated with worse post-MI remodeling (159).	Although collagen fragments have been suggested to exert pro-inflammatory actions, their role in initiation and progression of the post-MI inflammatory response has not been documented.Late generation of the collagen I α1 C-1158/59 matricryptin may promote repair by activating fibroblasts and vascular cells (4).
Elastin	N/A	Elastin fragments were identified in the serum of patients with MI (160).	Overexpression of elastin fragments (typically absent from myocardial infarcts) attenuated adverse remodeling in a rat MI model (161).
Collagen IV	Canstatin, a 24kDa polypeptide cleaved from the α2 chain of type IV collagen is found in infarcted rat hearts (30).	N/A	Canstatin may promote activation of infarct myofibroblasts (30). Tumstatin, a cleaved fragment of collagen type IV α3 chain, may generate a matricryptin that modulates fibroblast activation, angiogenesis, and cardiomyocyte survival (28,162).
Collagen XVIII	Endostatin, a 20kDa fragment of collagen XVIII, is upregulated in a rat MI model (163).	Serum endostatin levels were increased in patients with MI (164).	Endostatin inhibition in a rat MI model was reported to worsen outcomes (163). Endostatin may stimulate fibroblast proliferation (25), while exerting potent angiostatic actions (26).
Fibronectin	Fibronectin fragments were identified in the post-ischemic cardiac lymph (reflecting the cardiac extracellular environment) in a canine model of reperfused MI.	N/A	Fibronectin fragments reduced monocyte very late antigen-5 expression, attenuating the migratory capacity of monocytes in response to chemokines (15).

Table 2.

Expression and role of matricellular proteins in myocardial infarction.

Matricellular protein	Expression following MI	Function	Possible mechanisms of action
Thrombospondin (TSP)-1	Transient upregulation and deposition in the infarct border zone during the proliferative phase of healing in mouse, rat and canine models of MI (71,165). In human patients with end-stage heart failure, TSP-1 expression may be reduced, suggesting that injury-associated TSP-1 induction is transient (166).	Protects the infarcted heart from adverse remodeling, limiting expansion of inflammation and extension of fibrosis (71).	May activate TGF-β (167,168). May inhibit MMPs (169,170). May exert angiostatic actions (171). May modulate nitric oxide signaling and inflammation (172). May regulate ECM assembly and cross-linking (173). The relative contribution of these actions in TSP-1-mediated modulation of the reparative and remodeling responses following MI has not been studied.
TSP-4	Markedly upregulated in experimental models of MI (174).	Although TSP-4 has been suggested to exert protective actions in pressure-overloaded hearts (175,176), its role in MI has not been systematically studied.	Unknown.
Tenascin C	Transient upregulation in infarcted area, border zone, and remote remodeling myocardium has been documented in animal models of MI (177,178) and in human patients with ischemic heart disease.	May contribute to myocardial regeneration in fish and amphibians (147,179). Promotes fibrosis and accelerates adverse post-MI remodeling in adult mammals (85,180)	May exert pro-inflammatory actions, in part through activation of Toll-like receptor signaling (181). May promote fibrogenic actions and may drive peristence of fibrotic lesions (182). May promote recruitment of myofibroblasts (85). May modulate angiogénesis(183). May regulate macrophage recruitment (184) and polarization (87).
SPARC	Abundant, but transient upregulation in infarcted myocardium, predominantly localized in macrophages and myofibroblasts (185,186).	Protects from cardiac rupture. May promote systolic dysfunction during the early post-ischemic phase (185,186).	May play a role in procollagen processing and collagen fibril assembly (185,187). May accentuate growth factor signaling, promoting fibroblast activation (185). May exert inotropic actions on cardiomyocytes (188). May restrain angiogenesis (189), and inhibit angiogénic actions of VEGF in endothelial cells (190).
Osteopontin	Markedly and transiently upregulated following MI, primarily localized in galectin-3^{hi}/CD206+ macrophages (42,191,192).	Protects from adverse remodeling (35).	May promote proliferation and integrin-dependent activation of cardiac fibroblasts (193). May transduce survival signals (194), and activate a matrix-synthetic program in fibroblasts (195). May promote cardiomyocyte hypertrophy (196), and regulate metabolic pathways involved in diastolic dysfunction (197). May promote angiogenic responses (198). May activate macrophages to express galectin-3, promoting a fibrogenic phenotype (198).
Periostin	Marked, but transient upregulation in activated myofibroblasts in the infarct, border zone and remodeling area (199,200).	Protects from cardiac rupture, while promoting late fibrosis in remodeling segments (199,200). Has been suggested to promote a regenerative response in neonatal mouse myocardial injury (201) and may even activate a regenerative program in adult mice (151).	May promote migration and activate a matrix-synthetic program in cardiac fibroblasts (199,200). May regulate collagen fibrillogenesis (202). Has been suggested to promote cell cycle entry in cardiomyocyte progenitors and in cardiomyocytes (151). However, genetic manipulations of periostin in mouse models failed to confirm the significance of these actions (203).
CCN2	Marked, but transient upregulation in infarcted hearts (204-206).	Cardiomyocyte-specific CCN2 overexpression studies suggested that CCN2 reduces infarct size following ischemia/reperfusion and attenuates adverse remodeling in non-reperfused infarction (204,205). In contrast, antagonism of endogenous CCN2 using a neutralizing antibody had no effects on infarct size (207).	May activate pro-survival pathways in cardiomyocytes.May attenuate inflammation and promote fibrogenic activation (207). Studies using genetic approaches in models of cardiac remodeling did not support the proposed critical role of CCN2 as a downstream effector of TGF-β (208). CCN2 and CCN5 have been suggested to exert opposing actions in remodeling and fibrosis of the pressure-overloaded heart (206); however, interactions between CCN family members in MI have not been investigated.

Matricellular protein	Expression following MI	Function	Possible mechanisms of action
		CCN2 inhibition experiments in a model of non-reperfused MI suggested that CCN2 may accentuate adverse remodeling, promoting hypertrophy and fibrosis (207).	

Abbreviations: CCN, **C**YR61 (cysteine-rich angiogenic protein 61)/**C**TGF(connective tissue growth factor)/**N**OV(nephroblastoma overexpressed); SPARC, Secreted protein, acidic and rich in cysteine.