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Extracellular Matrix and Fibroblast Communication Following Myocardial Infarction

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Abstract

The extracellular matrix (ECM) provides structural support by serving as a scaffold for cells, and as such the ECM maintains normal tissue homeostasis and mediates the repair response following injury. In response to myocardial infarction (MI), ECM expression is generally upregulated in the left ventricle (LV), which regulates LV remodeling by modulating scar formation. The ECM directly affects scar formation by regulating growth factor release and cell adhesion, and indirectly affects scar formation by regulating the inflammatory, angiogenic, and fibroblast responses. This review summarizes the current literature on ECM expression patterns and fibroblast mechanisms in the myocardium, focusing on the ECM response to MI. In addition, we discuss future research areas that are needed to better understand the molecular mechanisms of ECM action, both in general and as a means to optimize infarct healing.

Keywords

extracellular matrix; myocardial infarction; fibroblasts; cardiac myocytes; cell-ECM communication; proteomics

Introduction

The extracellular matrix (ECM) is an important component of multicellular organisms, serving to fill the extracellular space and support cell and tissue organization. ECM consists mainly of structural proteins and non-structural matricellular proteins, as well as proteinase enzymes and their inhibitors. Structural ECM includes collagens, fibronectin, and laminins. Matricellular proteins are composed of CCN family members, osteopontin, periostin, secreted protein acidic and rich in cysteine (SPARC), tenascins, and thrombospondins [1]. Proteinases and their inhibitors well studied in cardiovascular diseases include 25 matrix metalloproteinases (MMPs) and 4 tissue inhibitor of metalloproteinases [2–4]. Most ECM proteins are macromolecules that contain several functional domains that bind bioactive factors or receptors. Therefore, the ECM is an important transducer of mechanical, electrical, and chemical signaling during development, aging, physiological, and pathophysiological remodeling. The cell-ECM interaction regulates multiple cell functions, including survival, proliferation, migration, adhesion, differentiation, and gene expression [5]. In addition, matricryptins, which are ECM-derived fragments, may mediate post-injury tissue remodeling and repair by binding corresponding receptors to activate intracellular signaling pathways [1].

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Following myocardial infarction (MI), fibroblasts differentiate into myofibroblasts (Fig. 1), which results in the abundant synthesis and deposition of collagen, the major component of scar [6]. Due to the negligible regenerative capacity of the heart, a collagen-based scar is necessary to replace the extensive loss of cardiomyocytes [6]. In response to MI, matricellular proteins are also upregulated to regulate key molecular repair signals. Concomitantly, MMPs regulate post-MI remodeling by degrading ECM and processing a wide variety of substrates to influence the inflammatory, fibrotic, and angiogenic responses [7]. The dynamic balance of ECM turnover is critical for stable scar formation post-MI. Inadequate ECM accumulation, due to excessive degradation of ECM or defective formation of newly synthesized ECM, contributes to infarct wall thinning, dilation of LV chamber, and cardiac rupture post-MI [7]. Excessive ECM deposition, however, also has negative consequences, namely increased wall stiffness and impaired compliance [8], which can promote continual dilation of the LV. Several recent reviews have focused on the roles of MMPs and their inhibitors in post-MI ventricular remodeling [2,9,10]. In this review, we will discuss the roles of structural and matricellular ECM, as well as matricryptins to mediate cardiac intercellular communication, focusing on the post-MI setting.

Cardiac Fibroblasts and the Infarct Scar

In order to understand how the ECM regulates the post-MI response, it is necessary to first discuss the infarct scar. The infarct scar is a cellular, vascularized, and highly metabolically active tissue with contractile function [11]. Myofibroblasts, which express α-smooth muscle actin and microfilaments that guide contractile behavior, contribute to local angiotensin II generation that is distinct from the circulating renin angiotensin aldosterone system [12]. Cardiac myofibroblasts also respond to an array of pro-inflammatory cytokines (e.g. tumor necrosis factor-α, interleukin (IL)-1, IL-6, transforming growth factor-β), vasoactive peptides (e.g. endothelin-1, natriuretic peptides), and hormones (e.g. noradrenaline), all of which are increased in the post-MI LV [13,14].

The Blankesteijn laboratory has recently proposed the novel idea that a well-healed infarct will actually contain more myofibroblasts than the infarct undergoing adverse remodeling [15]. These myofibroblasts are responsible for the production and deposition of collagen, leading to the establishment of a dense ECM that maintains support and minimizes expansion of the infarct area [6,15]. Treatment strategies that increase myofibroblast numbers and blood vessel density in the infarcted area have a protective effect on outcomes, by improving both LV function and cardiac remodeling [16]. In addition to collagens, cardiac fibroblasts produce a wide spectrum of ECM proteins, including fibronectin, laminins, and matricellular proteins [6]. These ECM proteins are key mediators of intercommunication between the cardiac fibroblasts and other cell types, including cardiomyocytes and endothelial cells [1].

Structural ECM

Fibrillar ECM proteins contribute directly to LV structure and include collagens, fibronectin, and laminins. Below, we will briefly summarize their roles in the MI setting.

Collagens

Collagen is the most highly abundant ECM and is an integral part of the infarct scar that forms in response to MI [17]. Of the 28 subtypes of collagen, the types known to exist in the heart include types I, III, IV, V and VI, with collagen type I being the most abundant and representing over 70% of the total under normal conditions [18]. Collagen types I, III, IV, V and VI are all significantly upregulated in the infarct region, and types I and III are the major constituents of the scar [19,20]. Proper collagen deposition and cross-linking are

crucial for preventing progressive remodeling post-MI [21]. Most studies that measure collagen content, however, do so as a terminal measurement to help explain the observed change in LV function. How collagen regulates downstream signaling has not been evaluated. Recent studies have shown that collagen derived fragments mediate aspects of wound healing [22], but the role of collagen peptides in post-MI remodeling has not been explored.

Fibronectin

Fibronectin is an adhesive glycoprotein present in the extracellular space and is produced by fibroblasts, macrophages, and endothelial cells in response to injury. A previous proteomic analysis of post-MI LV by our lab identified fibronectin as an *in vivo* MMP-9 substrate, as MMP-9 null mice showed decreased generation of 180 and 120 kDa fibronectin fragments [23]. The extra domain A of fibronectin (EDA) acts as an endogenous ligand for toll like receptors-2 and -4, which are part of the innate immunity response [14,24]. EDA activates mast cells and induces pro-inflammatory gene expression by nuclear factor-κB activation [25]. In addition, EDA regulates cell adhesion and proliferation by binding VLA-4/CD49d, and induces myofibroblast phenotype by stimulating the TGF-β1 pathway [26,27]. EDA null mice show lower LV volumes and attenuated cardiac function compared with wild type (WT) mice that have similar infarct sizes [24]. In the remote region of 28 days post-MI hearts, EDA deletion led to less collagen accumulation, consistent with improved LV function; but the collagen content, cross-linking, and deposition are not altered in the infarct area, indicating that scar formation is not negatively affected [24]. The mechanisms of action included reduction in the inflammatory response, MMP-2 and MMP-9 activity, and myofibroblast transdifferentiation.

The extra domain B of fibronectin (EDB) has a 91 amino acid sequence that is identical in mouse, rat, rabbit, dog, and human, suggesting an important role for this highly conserved fragment. Although EDB is highly expressed during early embryogenesis, EDB null mice show no abnormal phenotype [28]. However, EDB null fibroblasts grow slowly *in vitro* and deposit less fibronectin than fibroblasts isolated from WT mice [28]. EDB is highly expressed in normal tissues during angiogenesis, but is undetectable in mature vessels, suggesting crucial roles in angiogenesis. The role of EDB in the MI setting, however, has not been explored.

Laminins

Laminins are heterotrimeric proteins composed of α, β, and γ chains that are essential components of basement membranes. Five α, four β, and three γ chains have been identified to date, and these isoforms associate to form at least 15 different laminin isoforms [29]. In response to MI, laminin is initially upregulated at day 3 in the granulation tissue of the infarct area, peaking at days 7 to 11 post-MI [30]. Laminin distribution post-MI is not limited to the pericellular basement membrane region but rather is diffusely present throughout the infarct region, which suggests a post-MI role that exceeds the normal maintenance of basement membranes [31]. This pattern of laminin expression tracked with collagen IV changes post-MI. Of note, this immunohistochemical study was performed using a pan laminin antibody, which means that the different laminin subtypes that contribute to the increase were not investigated. We have shown that the γ1 chain increases in WT mice at day 7 post-MI, and this increase is attenuated in the MMP-9 null mice [23]. In humans, laminin concentration measured by ELISA is significantly higher in the serum of acute MI patients than subjects with stable coronary artery disease (CAD) or subjects without CAD [32]. Further, laminin levels negatively correlated with LV function, suggesting that laminin may be a marker of adverse LV remodeling [33]. Future studies exploring the roles of different laminin subtypes will provide additional insight.

Matricellular Proteins

Matricellular proteins do not directly participate in the structural integrity of the tissue, but rather regulate cell-ECM interaction and assist ECM to deposit and cross-link correctly by interacting with cell surface receptors, growth factors, proteases, and structural ECM proteins [34]. In general, most matricellular proteins are expressed only at low levels in normal adult tissues but are highly induced after injury, indicating roles in tissue repair [1,35].

CCN

The CCN family members are a group of highly conserved secreted proteins that have been identified by differential expression screening, and exert distinct but overlapping roles in tissue remodeling [36]. CCN1 (cysteine-rich protein 61, Cyr61), which is mainly detected in cardiomyocytes and blood vessels under normal conditions, is strongly induced in cardiomyocytes in both infarct and remote regions in a mouse model [37]. In humans, CCN1 expression also increases in cardiomyocytes during end-stage ischemic cardiomyopathy, compared to non-failing human hearts [37]. The roles of CCN1 in MI induced cardiac remodeling have been linked with the regulation of myocyte apoptosis, as well as the inflammatory, fibrotic, and angiogenic responses [38–41].

CCN2, also named connective tissue growth factor (CTGF), is markedly induced post-MI and is robustly expressed by myofibroblasts and border zone cardiomyocytes [42]. TGF-β1, Ang II, and endothelin-1 are effective inducers of CTGF *in vivo*. TGF- β1 mediates CTGF upregulation, and this regulation is dependent on phosphorylation of Smad 3 and 4, but not Smad 2 [43]. In an ischemia-reperfusion model, cardiomyocyte specific overexpression of CTGF decreases infarct size, an effect that may be mediated by the regulation of the Akt/p70S6 kinase/GSK-3β salvage kinase pathway within the cardiomyocyte and induction of several genes with cardioprotective functions [44].

Post-MI, increased CCN4 (Wnt-inducible secreted proteins, WISP1) expression is seen in the border and remote zones, which peaks at 24 hours post-MI [45]. Although the *in vivo* role of CCN4 remains unknown, *in vitro* CCN4 promotes hypertrophy and attenuates apoptosis in cardiomyocytes, and stimulates proliferation in cardiac fibroblasts [45]. In contrast, CCN5 (WISP2) shows anti-hypertrophic effects, evidenced by reduced hypertrophic and fibrotic responses triggered by pressure overload in CCN5 overexpressing mice, and this effect is caused by attenuated TGF-β/Smad signaling [46].

Osteopontin

Osteopontin (OPN), also named Eta-1, is a phosphorylated, secreted glycoprotein originally identified as a bone matrix protein before subsequently being recognized as a cytokine [47]. OPN is secreted by immune cells and is abundantly expressed in macrophages in response to stress or insult. OPN can engage integrins α_V (β_1, β_3, or β_5) and (α_4, α_5, α_8, or α_9) β_1. OPN may also act as a ligand for CD44 variants, but probably only in conjunction with binding to the β_1 integrin [48].

OPN is induced in humans following MI, as well as in multiple animal MI models [49,50]. MI patients with acute ST elevation have higher OPN plasma levels than healthy controls, but the plasma OPN content did not correlate with LV wall motion score index. OPN, therefore, will not likely be a suitable plasma biomarker for MI outcomes [50]. In a mouse model of MI, OPN mRNA levels in the infarct region peaks at day 3 post-MI and starts to decrease at day 7, but continues to remain higher at day 28 than baseline levels [49]. In the remote area, OPN expression is biphasic, with peaks at days 3 and 28 post-MI [49], indicating a role of OPN in both early and late phases of cardiac repair. The CC chemokine

CCL2/monocyte chemoattractant protein-1 and Ang II mediate OPN upregulation in the infarcted heart [51,52]. Genetic loss of function experiments confirm a key role for OPN in post-MI cardiac repair [49]. OPN deletion exacerbates LV chamber dilatation and remodeling following MI, compared to WT counterparts. Both genotypes show similar infarct size, heart weight, survival rates, and cardiomyocyte apoptosis rates. Electron microscopy reveals higher collagen content in both infarct and remote regions of WT mice than OPN null, suggesting that OPN regulates post-MI LV remodeling by promoting collagen synthesis and accumulation. OPN deletion also leads to reduced TGF-β1 signaling and neovascularization, indicating that OPN mediates protective roles in the MI response [53]. OPN may facilitate ECM accumulation by modulating T cell subsets and TGF-β [54]. Moreover, OPN mediates Ang II-induced proliferation and TGF-β1-induced differentiation of cardiac fibroblasts, and protects cardiac fibroblasts from apoptosis [55–57], which may explain the reduced collagen accumulation in OPN null mice after MI.

Periostin

Periostin has an extracellular signal sequence, four repeat domains, an N-terminal cysteine-rich region, and a heparin-binding domain in the C-terminus. However, the function of these domains has not been demonstrated. Periostin is primarily expressed in collagen-rich connective tissues subjected to mechanical stress, such as heart valves, tendons, perichondrium, cornea, and periondontal ligament [58,59]. Consistent with this expression pattern, periostin is significantly upregulated in response to MI [60]. *In vitro*, TGF-β, bone morphogenetic protein-2, fibroblast growth factors (FGFs), platelet derived growth factor (PDGF)-BB and Ang II are all potent inducers of periostin expression [1].

Periostin binds directly to fibrillar ECM proteins, including collagen type I and type V, fibronectin, and tenascin-C, to modulate assembly of ECM fibrils. Periostin null mice show impaired collagen cross-linking and lower collagen fibril diameters in the skin [61]. Following MI, periostin expression increases at day 4 post-MI and retains at high levels for several weeks [60]. Periostin is highly expressed in the border zone and in cardiac fibroblasts. As such, periostin null mice are more susceptible to cardiac rupture in the first 10 days post-MI than their WT counterparts [60]. Consistent with this phenotype, the periostin null mice that survive MI have less interstitial fibrosis and attenuated LV function. Further, the specific overexpression of periostin in cardiac myocytes prevents mice from MI-induced ventricular rupture. *In vitro*, fibroblasts isolated from periostin null hearts show decreased adhesiveness and a dramatic change in gene expression [60], which may explain the higher rupture rates in the periostin deficient mice. Shimazaki and colleagues demonstrated that periostin deletion reduces fibroblast numbers and impairs collagen fibril formation, which is rescued by the gene transfer of a splice form of periostin [62]. Kuhn and colleagues have recently found that periostin induces reentry of differentiated cardiomyocytes into the cell cycle, by activating integrins and phosphatidylinositol-3-OH kinase signaling [63]. This serves to attenuate post-MI LV remodeling and dysfunction and extends the functions of periostin to include a role in myocardial regeneration.

SPARC

SPARC, also named osteonectin or BM-40, is a highly conserved, multifunctional glycoprotein with three domains. SPARC levels are very low in the normal heart [64,65]. Following MI, SPARC is substantially upregulated in the infarct region [66,67]. SPARC expression increases at day 3, peaks at days 7–14 post-MI, and is primarily secreted by myofibroblasts and macrophages [64,68]. Targeted inactivation of SPARC results in a four-fold increase in mortality, attributable to a higher incidence of cardiac rupture and heart failure. SPARC null mice show disorganized granulation tissue and immature collagenous ECM [68]. In contrast, SPARC overexpression in WT mice improves collagen maturation

and attenuates cardiac dysfunction after MI. *In vitro* recombinant SPARC increases Smad 2 phosphorylation, indicating that SPARC activates TGF-β pathway. In agreement with the *in vitro* data, infusion of TGF-β rescues SPARC null mice from post-MI cardiac rupture. These results indicate that the beneficial roles of SPARC on MI may be dependent on TGF-β signaling pathway activation, which is crucial for the formation of a stable scar.

In addition, SPARC mediates assembly of newly formed collagen and regulation of angiogenesis in infarct area may play an important role to facilitate generation of a supportive matrix [1]. Like other matricellular proteins, SPARC also regulates cell-ECM communication and triggers focal adhesion disassembly in endothelial cells by a follistatin-like region and Ca^{2+}-binding EF-hand [69]. The loss of focal adhesion and stress fibers in endothelial cells, fibroblasts, and smooth muscle cells transforms a strong cell-ECM adhesion to a modestly adhesive state, a phenomenon known as de-adhesion [69].

Tenascin-C

Tenascins are an oligomeric glycoprotein family with 4 members: tenascin-C, R, X, and W. Of these, only tenascin-C has been evaluated in the post-MI LV. Tenascin-C is rarely detected in normal adult hearts, except at the chordae tendineae of papillary muscles and base of valve leaflets [70]. Interestingly, tenascin-C is re-expressed during cardiac pathologies, including MI, myocarditis and dilated cardiomyopathy, suggesting a role in post-injury remodeling. *In vitro*, tenascin-C is induced by various kinds of growth factors, including PDGF, FGF-2 and TGF-β. Importantly, mechanical stress is an additional inducer of tenascin-C expression. Post-MI, tenascin-C is robustly upregulated and localizes in the border zone [71]. This increase in tenascin-C in the border zone may serve to limit infarct expansion into the non-infarcted remote region. Tenascin-C deficiency alleviates LV remodeling and cardiac dysfunction in the infarct heart compared with WT, despite comparable infarct sizes and survival rates [72]. These beneficial effects are associated with attenuated fibrosis in the non-infarct remote myocardium. Tenascin-C, *in vitro*, promotes cardiac fibroblast migration and transdifferentiation into myofibroblasts, as well as collagen gel contraction, without altering fibroblast proliferation [73]. Tenascin-C mediates de-adhesion of cell-ECM involving cardiomyocytes and leads to cardiomyocyte slippage, which thereby contributes to tissue reorganization [71]. In humans, serum levels of tenascin-C positively correlate with the incidence of adverse LV remodeling and worse outcomes in MI patients [74], indicating that serum tenascin-C level is a novel predictor of MI prognosis.

Thrombospondins

Thrombospondins (TSPs) are large secreted, multimodular, calcium-binding glycoproteins. On the basis of their oligomerization status and molecular architecture, TSPs are divided into 2 groups: group A (TSP-1 and -2) and group B (TSP-3, -4, and -5). TSP-1 and -2 exist as trimers, while TSP-3, -4 and -5 are pentameric macromolecules [75]. Each TSP displays a different expression pattern in adult tissues, suggesting context dependent roles.

TSP-1 is a potent inhibitor of angiogenesis that limits vessel density in normal tissues and curtails vessel growth in tumors. TSP-1 is also an activator of TGF-β. TSP-1 mRNA and protein are markedly upregulated post-MI. Interestingly, TSP-1 exhibits a strikingly robust ECM deposition pattern, showing expression surrounding the microvascular endothelium and in a subset of mononuclear cells at the border zone [76]. This localization pattern indicates that TSP-1 may serve as a barrier to protect the remote non-infarct myocardium from invasion of inflammation and ECM degradation, in an attempt to limit the extent of LV remodeling to the infarct region.

TSP-1 deletion aggravates MI induced LV remodeling by amplifying and prolonging the inflammatory response, as well as expanding inflammation into the remote region [76]. TSP-1 inhibits TGF-β activation, without markedly impacting the angiogenic response. TSP-1 induced endothelial apoptosis involves the upregulation of CD35, p38 mitogen-activated protein kinases, and caspase-3 pathway, which is crucial in mediating its angiostatic effects [77].

The roles of other TSPs have been extensively explored in models of cardiac hypertrophy and fibrosis induced by pressure overload or genetic modification, but have not been extensively evaluated post-MI. Among 48 genes overexpressed in the failing hearts, TSP-2 is selectively overexpressed only in animals that later progress to heart failure [78]. Ang II infusion into the TSP-2 null mouse induces a 70% cardiac rupture rate, significant mitochondrial swelling, interstitial edema, and myocyte damage compared to WT. This phenotype is associated with increased MMP-2 and MMP-9 activity, and impaired collagen fibril assembly [78]. Cardiac TSP-4 is upregulated in the presence of pressure overload and is involved in the transition from LV hypertrophy to hypertensive heart failure in spontaneously hypertensive rats [79]. In view of the distinct mechanisms between MI and hypertension induced LV hypertrophy and fibrosis, additional studies focusing on in MI setting are warranted.

Matricryptin Signaling

Matricryptins are biologically active fragments of the ECM. Matricryptins contain a cryptic domain that is not exposed in the mature, secreted form of ECM, but exposed after structural or conformational alterations of the parent ECM [80]. The appearance of cryptic sites may provide crucial signals to modulate cell migration, proliferation, differentiation, morphogenesis, survival, ECM assembly, angiogenesis, and tissue repair by binding to corresponding receptors [22].

Mechanisms that generate matricryptins include enzymatic degradation, protein multimerization, adsorption, cell-mediated mechanical forces, and denaturation [80]. A matricryptin can exist as several forms, depending on the presence of differential cleavage sites in the parent molecule and on which enzyme cleaves the parent molecule. MMPs are involved in the generation of matricryptins, and a lot of research has focused on matricryptins that serve as angiogenesis inhibitors. For example, the α_3 chain of collagen IV is cleaved by MMP-9 to generate tumstatin [81]. The NC1 domain of collagen XVIII is cleaved by MMP-7 and MMP-14, but not by MMP-2 or MMP-9, to generate endostatin [82,83]. Angiostatin is generated from plasminogen cleavage by multiple MMPs [84]. Reactive oxygen species have also been reported to expose cryptic sites [85].

Matricryptins exert multiple biological effects by regulating angiogenesis, inflammation, and fibrosis. Several matricryptins including endostatin, arrestin, canstatin, tumstatin and vastatin are endogenous inhibitors of angiogenesis [86,87]. These ECM fragments suppress the proliferation and migration of endothelial cells, and induce endothelial cell apoptosis. In contrast, some matricryptins generated from plasminogen, collagen, and hyaluronan exhibit pro-angiogenic roles by inducing endothelial cell proliferation, migration, and tube formation [88,89]. Collagen IV, for example, can be cleaved by MMPs to generate both anti- and pro-angiogenic fragments [90]. Matricryptins also mediate the inflammatory reaction by regulating chemotactic activity for inflammatory cells, amplifying phagocytic functions, stimulating immune responses, and altering inflammatory cell gene expression [91].

The fact that matricryptins regulate multiple aspects of angiogenesis and inflammation suggest that matricryptins play important roles in post-MI remodeling. Endostatin is a

carboxy-terminal proteolytic cleavage fragment of collagen XVIII upregulated post-MI [92]. Neutralization of endostatin exacerbates post-MI LV remodeling, dysfunction, and mortality, despite increasing vessel numbers [92]. The potential mechanisms are associated with increased expression and activity of MMP-2, MMP-9, and angiotensin-converting enzyme [92]. The increased collagen content with endostatin inhibition implicates endostatin in the direct or indirect regulation of myofibroblast proliferation and function.

Summary and Future Directions

This review discusses the roles of ECM proteins in the post-MI setting. As summarized in Fig. 2, there are several potential mechanisms by which ECM regulates post-MI remodeling. First, collagen is the major component of the infarct scar, and collagen content in terms of quantity and quality determines scar strength, which in turn directly correlates with infarct dilation. Fibroblasts, including all fibroblast subtypes, are the major source of ECM post-MI, and as such their roles regulate remodeling outcomes. There are large knowledge gaps, however, in terms of which collagen subtypes are present in the post-MI LV and what their individual roles are. Second, ECM offers structural and mechanical support but also coordinates cell-ECM interaction by transmitting signaling through engagement with cell surface receptors. Third, matricellular proteins and ECM-derived matricryptins can modulate cell-ECM adhesion, inflammation, growth factor pathways, fibroblast functions, and angiogenesis, all of which are indispensable to the formation and maintenance of a stable infarct scar.

Future research is needed to address several aspects of ECM roles in the post-MI LV. First, we need more information on the individual ECM constituents and their roles. At this time, we know about only a few ECM proteins, but there are likely a few hundred different ECM proteins in the post-MI LV. The individual roles as well as their functions as part of the entire remodeling response remain to be examined. Even collagen types I and III, the most widely studied ECM proteins in the post-MI LV, are largely only output measurements. Mechanistic studies that dissect out how these collagen types regulate remodeling are needed. Second, we need to examine the *in vitro* phenotypes of fibroblasts and inflammatory cells isolated from infarct hearts, which will provide clues to their *in vivo* roles in coordinating the ECM response. We use the term fibroblast as a general term to include all phenotypes of fibroblasts, from infiltrating fibrocytes to resident fibroblasts to myofibroblasts. Third, the roles and mechanisms for ECM peptides generated by proteolytic cleavage of full length ECM proteins need to be further explored, both *in vitro* and *in vivo*. Finally, while *in vitro* experiments isolate out individual component roles, we need to better understand how the individual components regulate remodeling in the context of the entire post-MI myocardium. This will allow us to design experiments that have the best translational potential.

In conclusion, post-MI remodeling remains a primary cause of congestive heart failure. Elucidating how the ECM regulates this transition will identify novel targets for intervention that may help to stimulate an optimal wound healing response.

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Statement of Clinical Relevance

Myocardial infarction (MI) is a leading cause in morbidity and mortality worldwide. Although one month survival rates have dramatically improved over the past 30 years, the number of patients that progress to congestive heart failure has increased, and the five year survival rates for heart failure remain approximately 50%. Additional therapeutic approaches that can delay, limit, or reverse adverse remodeling, therefore, are needed.

Following MI, a reparative scar predominantly containing collagen is formed to replace necrotic myocytes. The balance between extracellular matrix (ECM) synthesis and degradation is critical for stable scar repair. Excessive ECM deposition increases wall stiffness and diastolic dysfunction, while insufficient ECM accumulation and impaired collagen cross-linking contribute to progressive infarct wall thinning and dilation of the left ventricle chamber. In this review, we summarize the current understanding of the roles of different ECM molecules in the MI setting. A better understanding of how individual ECM molecules regulate the post-MI remodeling response is needed, to identify promising intervention targets to stimulate an optimal infarct healing response.

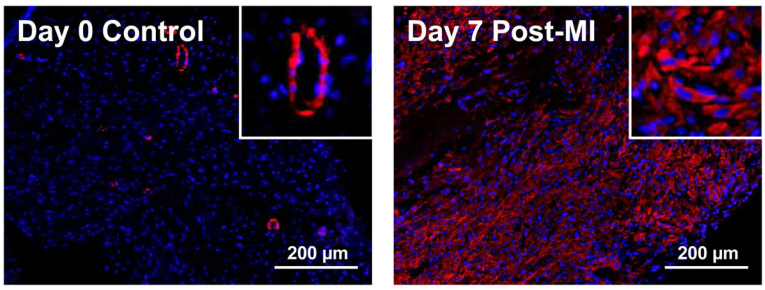

Fig. 1.

Myofibroblast numbers are markedly increased post-MI. The left panel shows smooth muscle cells localized in the vessel at baseline (day 0). The right panel shows that myofibroblasts are significantly upregulated in the non-vessel interstitium at day 7 post-MI. Nuclei are stained with DAPI (blue). Smooth muscle cells and myofibroblasts are stained with anti-α-smooth muscle actin antibody (red). This is our own unpublished result.

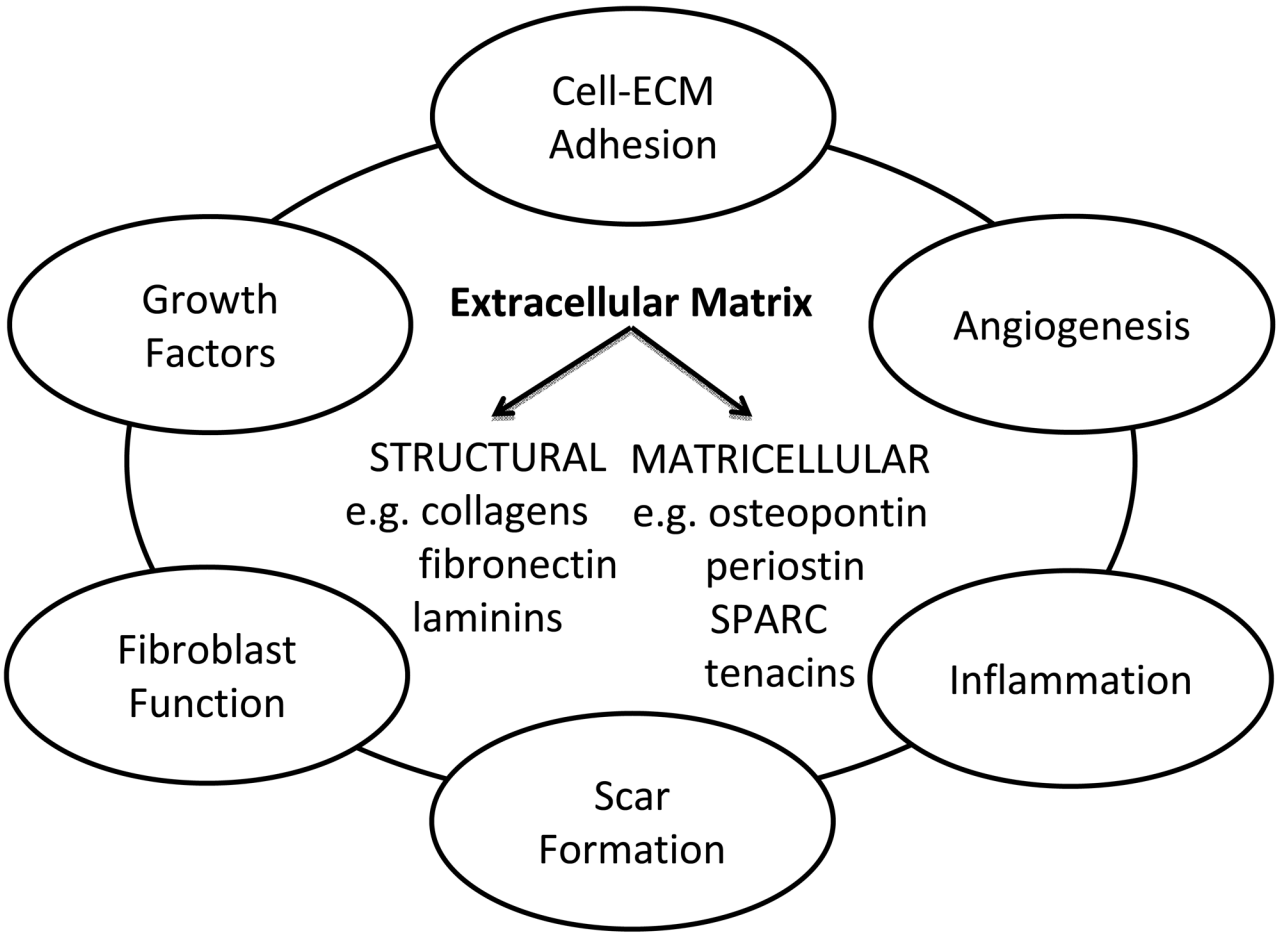

Fig. 2.
Schematic representation of the mechanisms of ECM action in the MI setting. ECM, consisting of structural and matricellular proteins, mediates post-MI remodeling and repair by regulating scar formation, inflammation, angiogenesis, cell-ECM adhesion, growth factor production and release, and fibroblast function.