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Minireview

Extracellular matrix roles during cardiac repair

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ABSTRACT

The cardiac extracellular matrix (ECM) provides a platform for cells to maintain structure and function, which in turn maintains tissue function. In response to injury, the ECM undergoes remodeling that involves synthesis, incorporation, and degradation of matrix proteins, with the net outcome determined by the balance of these processes. The major goals of this review are a) to serve as an initial resource for students and investigators new to the cardiac ECM remodeling field, and b) to highlight a few of the key exciting avenues and methodologies that have recently been explored. While we focus on cardiac injury and responses of the left ventricle (LV), the mechanisms reviewed here have pathways in common with other wound healing models.

Contents

Introduction

The extracellular matrix (ECM) is the intricate network that fills the space between cells. Composed of proteins locally secreted and organized, the ECM includes fibrillar and non-fibrillar proteins that serve primary and accessory roles. In connective tissue (e.g. cartilage, bone, tendons, skin), ECM is more abundant than cells. In the heart under normal physiological conditions, cardiac myocytes occupy the highest volume of space and the ECM is less abundant than cells. The ECM is very diverse and adaptable both among different tissue types and in terms of composition and quality within the same tissue under different conditions. ECM proteins known to be expressed in myocardial tissue following injury are listed in Table 1. We have known for almost 40 years that ECM is not an inert scaffold, but rather serves critical signaling functions (Meier and Hay 1975). The ECM provides mechanical support to the heart that allows it to pump blood; ECM allows cell–cell signaling by providing a pathway for signals to traverse; and ECM regulates cell functions including proliferation, adhesion, and migration (Holmes et al. 2005).

Under normal physiological conditions, the ECM in the left ventricle (LV) is sufficient to maintain architecture and preserve tissue function. Following injury, such as myocardial infarction (MI), cardiac myocytes undergo cell necrosis and are replaced by an infarct scar that is primarily composed of ECM. We will use MI as a prototypic cardiac injury model in this review, because MI is a highly prevalent cardiac disease (1.5 million Americans each year are diagnosed with

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Table 1
Myocardial ECM proteins upregulated post-MI (Dobaczewski et al. 2006).

Collagen I, III, IV, V, and VI
Fibronectin
Fibullin
Hyaluronan
Laminins
Matrix Metalloproteinase
Osteopontin
Periostin
Secreted Protein Acidic and Rich in Cysteine
Tenascins
Thrombospondin-1and -2
Tissue Inhibitors of Metalloproteinase-1, -2, -3, and -4
Transforming Growth Factor β
Versican
Vitronectin

MI) (Kolansky 2009) and because the LV reaction to MI follows a classic wound healing response (Frantz et al. 2009). Below, we highlight 7 major concepts about cardiac ECM remodeling and discuss major directions that the field is taking to answer remaining issues.

Inflammation is a key component in the cardiac ECM response

MI, commonly referred to as a heart attack, occurs when an atherosclerotic artery in the coronary vasculature becomes totally occluded, which cuts off the oxygen supply to the downstream myocardium. When ischemia is of sufficient duration (>60 min), cardiac myocytes undergo necrosis leading to the upregulation of the complement cascade, stimulation of the toll-like receptor pathway, and increased reactive oxygen species (Frangogiannis and Entman 1997; Frangogiannis et al. 2002; Oyama et al. 2004; Riad et al. 2008; Rossen et al. 1988; Stutz et al. 2009). These three components induce NF-κB signaling to upregulate chemokines and cytokines, which in turn sequentially recruit platelets, neutrophils and mononuclear cells. This in turn leads to an inflammatory response involving the amplified upregulation of cytokines, chemokines, and growth factors (Table 2) (Deten et al. 2002; Irwin et al. 1999). Levels of these cytokines influence remodeling by coordinating the inflammatory response (Irwin et al. 1999; Ono et al. 1998).

Neutrophils are the first leukocyte responders, and neutrophil influx in the absence of reperfusion peaks at 24 h post-MI. Beginning around day 3 post-MI, macrophages infiltrate to engulf necrotic myocytes and apoptotic neutrophils (Lambert et al. 2008). Inflammatory cells release remodeling enzymes that degrade the ECM to help to remove necrotic cells but also leave the myocardium structurally weak. Macrophages also activate fibroblasts, in part by releasing transforming growth factor β_1 (TGFβ_1) (Sun et al. 2000). TGFβ_1 potently suppresses the inflammatory response and stimulates ECM synthesis in cardiac fibroblasts by activating the conversion of fibroblasts to myofibroblasts (Wynn 2008). Angiogenesis is also stimulated by activating endothelial cells to promote vascularization of the granulation tissue (Banerjee et al. 2009; Bowers et al. 2010; Dobaczewski and Frangogiannis 2009; Frangogiannis 2008; Hori and Nishida 2009). If all goes well, the healing infarct will mature, fibroblasts will undergo apoptosis and be removed, and the inflammatory response will resolve. The LV response to MI shares many common features with other wound healing models. For example, inflammation, fibrotic, and angiogenic responses are common to MI, skin, and lung responses to injury (Hogg and Timens 2009; Palatinus et al. 2010; Wilson and Wynn 2009).

When the coronary artery is re-opened (reperfusion), the main effects to the inflammatory response are that inflammatory cell infiltration is accelerated and amplified and all types of leukocytes enter the tissue at the same time (Frangogiannis 2008; Herskowitz et

Table 2
Cytokines, chemokines, and growth factors that increase Post-MI (Apostolakis et al. 2010; Bujak and Frangogiannis 2009; Fischer and Hilfiker-Kleiner 2007; Frangogiannis 2008; Henning et al. 2008).

Factor	Roles
Cardiotrophin-1	Stimulates LV hypertrophy and protects cardiomyocytes from apoptosis; stimulates cardiac fibroblast proliferation
Ciliary neutrophic factor	IL-6 family member; anti-inflammatory
Epithelial cell-derived neutrophil-activating peptide-78 (CXCL5)	Neutrophil chemoattractants; angiogenic
Fractalkine (CX3CL1)	Neutrophil and monocyte chemoattractant; stimulates vascular oxygen free radicals
Granulocyte colony-stimulating factor	Prevents cardiomyocyte and endothelial cell apoptosis
Growth related oncogene α/β/γ (CXCL1/2/3)	Neutrophil chemoattractants; angiogenic
Interferron γ	Stimulates TNFα production and leukocyte migration; increases oxygen free radical production; activates MMPs
Interleukin-1α/β	Upstream modulators of pro-inflammatory mediators; stimulates MMPs in cardiac fibroblasts
Interleukin-6	Upstream modulator of inflammation and fibrosis
Interleukin-8 (CXCL8)	Neutrophil activator; induces smooth muscle cell proliferation and migration; angiogenic
Interleukin-10	Stimulates anti-inflammatory pathways; inhibits NF- B; decreases macrophage activation
Interleukin-11	Stimulates atrial fibrillation and hypertrophy
Interleukin-12	Induces TNFα and IFNγ
Interleukin-17	Pro-inflammatory; induces fibroblasts, endothelial cells and macrophage to produce cytokines and chemokines
Interleukin-18	Induces IFNγ; pro-inflammatory
Interferon g inducible protein-10 (CXCL10)	Angiostatic
IFN-inducible T cell α (CXCL11)	Leukocyte recruitment, angiostatic
Leukemia inhibitory factor	Stimulates myocyte hypertrophy and survival; stimulates cardiac fibroblast proliferation, reduces collagen and MMP production, decreased conversion to myofibroblasts; *in vivo*, limits infarct size and induces neovascularization, and decrease fibrosis
Lipopolysaccharide-induced CXC (CXCL-5)	Leukocyte recruitment
Lymphotactin (XCL1)	Lymphocyte recruitment
Monocyte chemotactic protein-1/-3/-5 (CCL2/7/12)	Monocyte chemoattractants; induces smooth muscle cell proliferation; angiogenic
Monokine induced by interferon γ (CXCL9)	Angiostatic
Macrophage inflammatory protein-1α/β (CCL3/4)	Neutrophil activator; induces pro-inflammatory cytokines; monocyte chemoattractant
Neutrophil-activating peptide-2 (CXCL7)	Neutrophil chemoattractants; angiogenic
Oncostatin M	Protects myocytes and stimulated increased production of TIMP-1 and plasminogen activator inhibitor 1; stimulates endothelial cell MCP-1 expression, proliferation, and migration; induces cardiac fibroblast release of CXCL-1 and -5, cell survival, proliferation, and increased ECM synthesis
Platelet factor-4 (CXCL-4)	Angiostatic; MMP-9 substrate
Regulated on activation, normal T expressed and secreted (CCL5)	Monocyte chemoattractant
Stromal derived factor-1 (CXCL-12)	Chemoattractant for CD34+ progenitor and primitive hematopoietic cells
Transforming growth factor β 1,2,3	Regulates the transition from inflammation to fibrosis
Tumor necrosis factor α	Effects all cell types in the post-MI LV; suppresses myocyte contractility and induces apoptosis; neutrophil chemoattractant; is pro-inflammatory; increases MMPs and decreases collagen synthesis in cardiac fibroblasts
Vascular endothelial growth factor	Stimulates angiogenesis

al. 1995). For example, leukocytes have been measured in the cardiac lymph drainage as early as 15 min post-reperfusion (Lindsey et al. 2001). In the canine MI model of reperfusion, neutrophil influx is 80% increased compared to permanent occlusion (Chatelain et al. 1987). In comparing permanent occlusion to reperfusion, the Entman laboratory showed that for mice, when infarct sizes were similar (30% at 24 h), permanent occlusion resulted in more infarct expansion (Michael et al. 1999). Mortality rate in the reperfused group was 30% lower than total occlusion at 28 days post-MI, and left ventricular ejection and filling velocities return to control levels after 2 weeks and are sustained with reperfusion (Michael et al. 1999; Vandervelde et al. 2006). Reperfusion, therefore, yields a functionally improved LV compared to the non-reperfused LV.

Fibroblast activation is a prerequisite for cardiac repair

During the MI response, cardiac fibroblasts are recruited from resident cells and from a pool of circulating fibrocytes and are stimulated to undergo phenotypic modulation to become myofibroblasts (Fig. 1) (Brown et al. 2005; Camelliti et al. 2005; Espira and Michael 2009; Porter and Turner 2009; Porter et al. 2004; Turner et al. 2004, 2007, 2009). In between the fibroblast and myofibroblast stage, there is an intermediary cell known as the protomyofibroblast (Desmouliere et al. 2005). While not much is presently known about the conversion from a fibroblast to protomyofibroblast, the conversion to a myofibroblast has been directly attributed to the production of TGFβ_1 and the local presence of the cellular fibronectin splice variant ED-A (Serini et al. 1998; Serini and Gabbiani 1999).

Myofibroblasts are a critical component of the repair process following myocardial injury (Espira and Michael 2009). Indeed, these cells ensure adequate scar formation required to maintain the structural integrity of the LV. In addition, the presence of myofibroblasts in the site of injury reduces infarct expansion due to increased contractile properties of myofibroblasts (Hinz et al. 2001a,b, 2007). Similar to the inflammatory response, the fibroblast response post-MI is similar to what is seen in the skin during wound healing. The Gourdie lab has written a comprehensive review on how we can translate lessons from the skin, particularly related to fibroblast function, to the post-MI setting (Palatinus et al. 2010).

During the repair phase, factors that both diminish or enhance fibroblast activation are associated with increased incidences of post-MI rupture, indicating that scar formation follows a U-shaped curve response. For example, periostin gene deletion is associated with increased rupture rates and decreased fibroblast activation markers in post-MI mice (Shimazaki et al. 2008). At the same time, the Blankesteijn lab has shown that mouse strains with high rupture rates (129SV and C57/BL6) also have the highest myofibroblast numbers at day 14 compared with more rupture resistant strains (FVB, Swiss, and Balb/c) (van den Borne et al. 2009). Further, anti-TGFβ_1 treatment before or after MI in mice paradoxically increases both mortality and LV remodeling (Frantz et al. 2008; Ikeuchi et al. 2004). This effect was accompanied by decreased levels of early collagen deposition and decreased matrix metalloproteinase-9 (MMP-9) levels. The above discussion on rupture has focused on the mouse model of permanent coronary artery occlusion, because rupture is not a common complication in other animal models of MI and rupture is not a frequent occurrence in the presence of reperfusion. While fibroblast activation, therefore, has both negative and positive effects on remodeling, therapeutic strategies that temper fibroblast activation to influence negative aspects need to also take into account effects on the positive aspects of fibroblast activation.

Another factor to be considered is the myofibroblast origin. In recent years, there has been greater appreciation for the 3 different potential origins for the myofibroblasts in the remodeling process. These sources are: a) the resident interstitial fibroblast that undergoes transformation (Dewald et al. 2004; Virag and Murry 2003; Yano et al. 2005); b) the circulating precursor cells of bone marrow origin or fibrocytes that undergo differentiation (Haudek et al. 2006; Keeley et al. 2009; van Amerongen et al. 2008); and c) the endothelial–mesenchymal transition (EndMT) originated cells (Zeisberg et al. 2007). Of these three sources, recruitment of the resident interstitial fibroblast is thought to be the major source, although no studies have counted cells

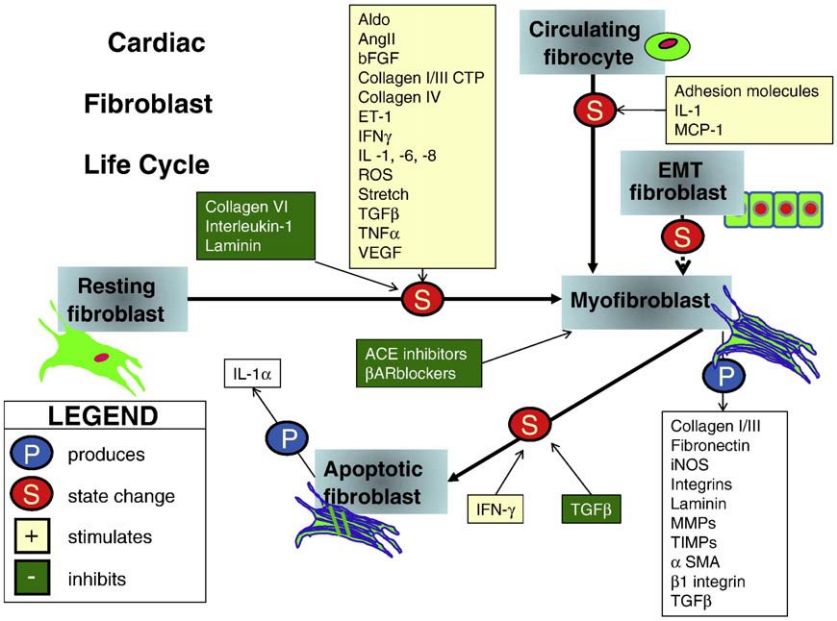

Fig. 1. During the MI response, cardiac fibroblasts are recruited from resting resident cells and from a pool of circulating fibrocytes and are stimulated to undergo phenotypic modulation to become myofibroblasts. Increased proliferation and increased ECM synthesis are prime characteristics of the cardiac fibroblasts within the infarct zone. If infarct wound healing occurs optimally, the fibroblast undergoes apoptosis to decrease numbers. Persistent fibroblast activation occurs during adverse remodeling that will progress to heart failure. Abbreviations: ACE — angiotensin converting enzyme; Aldo — aldosterone; Ang II — angiotensin II; βAR — β-adrenergic receptor; bFGF — basic fibroblast growth factor; CTP — C-terminal peptide; ET-1 — endothelin-1; IFNγ — Interferon γ; IL — interleukin; iNOS — inducible nitric oxide synthase; MCP-1 — monocyte chemotactic protein-1; MMP — matrix metalloproteinase; ROS — reactive oxygen species; αSMA — α smooth muscle actin; TGFβ — transforming growth factor β; TIMP — tissue inhibitor of metalloproteinase; TNFα — tumor necrosis factor α; VEGF — vascular endothelial growth factor.

from the different sources in the post-MI setting. Whether myofibroblasts of different origin have similar or distinct roles in scar formation is still unclear and may be injury or tissue specific (Hertig et al. 2010; Keeley et al. 2009). Resident fibroblasts can become α smooth muscle actin (αSMA) positive cells and produce increased ECM proteins upon activation by various cytokines and growth factors as numerously demonstrated in models of wound healing in skin and *in vitro* cardiac fibroblast studies (Weber 1997). One interesting concept to consider is that when normal resident fibroblasts are isolated and stimulated *in vitro*, in an attempt to gain mechanistic insight into fibroblast roles, are we missing potential differences because we are not evaluating fibroblasts from the other two origins?

In heart injury models, fibrocytes have been found expressing collagen and αSMA (Haudek et al. 2006; van Amerongen et al. 2008). In contrast, Yano et al. (2005) propose that proliferating myofibroblasts are derived solely from resident fibroblasts. This discrepancy raises important questions: what factors stimulate the migration of bone marrow-derived cells into the injured tissue and what factors influence subsequent fibrocyte-derived fibroblast function? The presence of T lymphocytes may be an important element for the recruitment and differentiation of fibrocytes (van Amerongen et al. 2008; Yano et al. 2005). Caution needs to be taken on mechanisms of activation and function of the fibrocytes, however, as it has been shown that fibrocytes in the kidney do not produce collagen during renal fibrosis (Roufosse et al. 2006). In lung fibrosis, on the other hand, collagen I α1 is used as a fibrocyte marker. The exact role for fibrocytes in the LV response to MI remains to be fully elucidated to clarify these paradoxical results.

Another potential origin for myofibroblasts is cells undergoing EndMT, although this source may be relevant predominantly during embryogenesis (Goumans et al. 2008). In a model of aortic banding, EndMT is promoted by TGFβ and prevented by bone morphogenetic protein-7, as demonstrated by the presence of cells expressing markers of endothelial and mesenchymal cells but also αSMA (Zeisberg et al. 2007).

After repair, myofibroblasts need to regress by an apoptotic mechanism in association with the completion of necrotic tissue replacement with fibrotic scar (Takemura et al. 1998). Myofibroblasts have been observed in human hearts as late as 17 years after the MI, and fibroblasts numbers at the chronic stage reflect a state of sustained activation (Frantz et al. 2009; Porter and Turner 2009). Persistent fibroblast activation is deleterious and promotes adverse remodeling that can transition to congestive heart failure.

Collagen is a critical component of the infarct scar

Cardiac ECM is composed of fibrous proteins, such as collagen and elastin that serve as steel reinforcements for the myocardium. ECM is composed of two types of glycosaminoglycans (GAGs), glycoproteins and proteoglycans, which serve as the space filling concrete. The exact ECM composition of the heart varies with age and physiological status.

Combined, collagens are an abundant family and have been calculated to account for up to 33% of the total protein in a tissue. Collagen is a glycoprotein, with 10% of its weight being composed of carbohydrate. While collagen is a family of more than 25 distinct proteins, collagen I is the major fibrillar collagen in the heart (Carver et al. 1993). For collagen I, three α chains generate a rope-like collagen that has a stiff, helical structure. Collagen synthesis is under the regulation of multiple transcription factors (Ghosh and Varga 2007; Kypriotou et al. 2007). For example, the collagen I α2 gene is regulated in cardiac fibroblasts by the transcription factor scleraxis (Espira et al. 2009; Espira and Michael 2009). Collagen I is processed in the endoplasmic reticulum and golgi apparatus, where it is glycosylated, hydroxylated on selected proline and lysine residues, and the 3 α chains are covalently linked by disulfide bonds. The 3 chains twist together to form a left-handed triple helix. A unique feature of collagen is the repeating basic unit Gly-X–Y, where X is frequently proline and Y is frequently hydroxyproline. Glycine and proline residues are important for the triple-stranded helix conformation. Glycine is the smallest amino acid and allows the α chains to pack together tightly, while the proline ring structure stabilizes the left-handed helical conformation in each α chain. Because of the unique repeating unit, collagen levels are often measured by determining hydroxyproline levels (Bishop and Laurent 1995; Krane 2008). While this method offers quantitative information on total collagen levels, it does not provide qualitative information regarding subtype contributions or information on full length versus degraded forms as would be obtained by immunoblotting with specific collagen antibodies.

Secreted as pro-chains containing N and C-terminal globular domains that keep collagen soluble, collagen is processed extracellularly to form collagen fibers. Hsp47 serves as a molecular chaperone during processing and secretion of pro-collagen and is a marker of collagen synthesis that increases in the post-MI setting (Sauk et al. 2005; Takeda et al. 2000). Collagen fibers are then assembled into fibrils, followed by covalent crosslinking within and between lysine residues to crosslink fibrils. Matricellular proteins help collagen fibrils incorporate into the ECM, and ascorbic acid (vitamin C) is a required co-factor for prolyl hydroxylase, the enzyme that post-translationally modifies proline to hydroxyproline. Therefore, a lack of vitamin C in the diet can cause scurvy due abnormal collagen formation.

In the normal heart, collagen I is the major collagen type, and collagens I and III account for 90% of the total collagen (Carver et al. 1993). Post-MI, collagen covers 30% of the infarct area at day 7 and 60% of the area at day 21 (Lindsey et al. 2003). It is important to note, however, that in addition to collagen I, more than 24 other collagen types have been reported (Espira and Michael 2009). Post-MI, increases in collagens I, III, IV, V, and VI have been described. While cardiac fibroblasts are the predominant source of collagens, macrophages are also a source of collagen VI, highlighting a diverse function for this inflammatory cell (Schnoor et al. 2008). The Meszaros laboratory wrote an excellent review on the non-fibrillar collagens, particularly collagens IV, V, and VI, and their roles post-MI (Shamhart and Meszaros 2010). However, there is not a lot of literature on other collagen types beyond these five, particularly in cardiovascular research. We know that collagen XVIII is anti-angiogenic when processed by MMPs to form endostatin (Wenzel et al. 2006), but this area is ripe for investigation.

Collagen is not the only relevant ECM component

While collagen is the most studied ECM protein in the post-MI LV, it is not the only relevant ECM component that regulates MI wound healing. The fact that cardiac ECM is composed of varied proteins explains the structural and functional adaptability but also provides additional important regulators of scar formation (Espira and Michael 2009). In particular, laminin, fibronectin, thrombospondin, and tenascin are glycoproteins that have critical roles in post-MI remodeling. One interesting idea that has recently emerged is that ECM in the post-MI setting may recapitulate the timing and sequence (but not quantities) of ECM formation and deposition seen during development. If this is true, then time course data on ECM protein sequence may provide clues into how scar formation is coordinated.

Laminin is the first ECM glycoprotein seen in the developing embryo and may be a key coordinator of subsequent ECM formation (Espira and Michael 2009). Composed of 3 peptide chains (α, β, and γ) cross-linked by disulfide bonds, laminin is found in the basement membrane but is not exclusively a basement membrane protein. Involved in cell-matrix interactions, laminin functions by anchoring cells to ECM and has binding sites for collagen IV, heparin, heparan sulfate, entactin, and laminin receptors (Suzuki et al. 2005). Laminin helps maintain tissue organization, crosslinks other ECM, and serves

as a very fine molecular sieve. In a rat post-MI model, laminin protein is seen by immunohistochemistry beginning at day 3 post-MI (Morishita et al. 1996). Laminin levels gradually increase to peak at about days 7–11 and return towards baseline thereafter. This pattern follows precisely the expression of collagen IV in the infarct. Laminin is processed by several matrix metalloproteinases, including MMP-9. Laminin peptides have been shown to be chemotactic for neutrophils (Adair-Kirk and Senior 2008; Mydel et al. 2008) and to further induce MMP levels (Adair-Kirk et al. 2003). Laminin, accordingly, coordinates multiple levels of the post-MI response.

Fibronectin is composed of type I, II, and III repeats that vary from monomer to monomer due to differential splicing of fibronectin mRNA, and more than 20 different monomer variants have been identified to date (White et al. 2008). Formed from 2 subunits of approximately 250 kD each, fibronectin subunits are disulfide-bonded at the C-terminal regions. The cell-binding domain contains the arginine–glycine–aspartic acid (RGD) sequence essential for cell interactions between integrins and the RGD site. Fibronectin also has heparin and collagen binding sites and is soluble in blood but insoluble in the ECM. Fibronectin crosslinks and stabilizes other ECM components, and regulates cell shape and cell movement. For example, macrophages are guided into the cardiac wound area by fibronectin, and soluble fibronectin crosslinks platelets and facilitates blood clotting (Frangogiannis 2006; Trial et al. 2004). Fibronectin is involved in mechanotransduction and cell-matrix relationships, and has been shown to increase dramatically in the post-MI setting (Ulrich et al. 1997). We have recently shown using a proteomics approach that fibronectin is an *in vivo* substrate of MMP-7 and MMP-9 in the LV infarct (Chiao et al. 2010; Zamilpa et al. 2010). Fibronectin fragments stimulate monocyte migration (Trial et al. 1999) and increase MMP production (Schedin et al. 2000), setting up a positive feedback loop in the remodeling myocardium. At the same time, macrophages stimulated with the 120 kD fibronectin fragment prevent apoptosis in injured cardiac myocytes, indicating that the same ECM fragment generated in the post-MI setting can have both positive and negative functions (Trial et al. 2004).

Matricellular proteins do not directly contribute to ECM structure, but rather serve as accessory proteins to regulate cell–ECM interactions and help ECM to deposit properly. Matricellular proteins include the secreted protein acidic and rich in cysteine (SPARC), hevin, thrombospondins 1 and 2, tenascins C and X, periostin, all members of the CCN family, and osteopontin (McCurdy et al. 2010). The CCN family was named after the first 3 members identified: cysteine-rich protein 61, connective tissue growth factor, and the nephroblastoma overexpressed gene. SPARC binds collagens I, III, IV, and V and regulates the assembly of the ECM containing these proteins. SPARC levels are high during cardiac development and are re-expressed following MI, consistent with a role in scar formation (McCurdy et al. 2010; Schellings et al. 2009; Wu et al. 2006). The absence of SPARC results in an ECM that is disarrayed in terms of structure and composition (Bradshaw et al. 2003). In a pressure-overload model, the Bradshaw team has shown that SPARC deletion results in a blunted fibrotic response, resulting in decreased levels of insoluble collagen and increased levels of soluble collagen that decreased LV stiffness (Bradshaw et al. 2009).

Thrombospondin-1 (TSP-1) is a matricellular protein with angiostatic properties (Frangogiannis 2008). TSP-1 can activate TGFβ by disrupting non-covalent interactions between TGFβ and the latency associated peptide. Following MI, TSP-1 is markedly upregulated at the border zone, and the Frangogiannis laboratory has speculated that TSP-1 may serve as a barrier to prevent or limit infarct expansion and to protect the remote region from macrophage infiltration and myofibroblast activation (Frangogiannis 2008). As evidence for this theory, TSP-1 null mice show sustained increases in several chemokines (monocyte chemotactic protein-1, macrophage inflammatory protein-1α, and CXCL-10) and several cytokines (interleukin-1β, interleukin-6, and TGFβ) during ischemia/reperfusion, which suggests that TSP-1 may help to curtail the inflammatory response (Chatila et al. 2007; Frangogiannis et al. 2005). Consistent with this, TSP-1 null mice show increased macrophage and myofibroblast densities.

Tenascins are ECM glycoproteins with high bioactivity (Brellier et al. 2009). Tenascins support tissue structure and regulate cell fates. Among the members of the tenascin family protein, tenascin-C (TN-C) is expressed early post-MI at the interface between infarcts and intact myocardium (Willems et al. 1996). TN-C modulates cardiomyocyte adhesion to the newly synthesized ECM and regulates myofibroblast recruitment (Imanaka-Yoshida et al. 2001; Tamaoki et al. 2005). While adhesion proteins, such as TN-C, are necessary at the early stage of repair, prolonged expression is detrimental. A high serum level of TN-C in patients associates with a greater incidence of excessive remodeling and poor prognosis (Fujimoto et al. 2009). This association data were confirmed in a cause and effect mouse MI model, as TN-C deficient mice presented reduced interstitial fibrosis post-MI (Nishioka et al. 2010).

Biglycan is a small leucine-rich proteoglycan that has been shown to increase post-MI in rats, mice, and humans (Doi et al. 2000; Tiede et al. 2010; Westermann et al. 2008). Biglycan levels increase at day 2 and peak at day 14 in the rat (Doi et al. 2000). Biglycan binds collagen fibrils and modulates fibril diameter and lateral fusion with other fibrils, which increases collagen network stability (Yamamoto et al. 1998). Biglycan association with collagen also renders collagen less susceptible to proteolytic digestion. Biglycan inhibits TGFβ activity, while TGFβ stimulates biglycan production in cardiac fibroblasts. Biglycan stimulates macrophage activation through interactions with toll-like receptors 2 and 4 (Schaefer et al. 2005). Biglycan deficient mice show increased post-MI rupture, consistent with its crucial role in collagen deposition.

Decorin is a small dermatan sulfate proteoglcyan that has been shown in the rat to increase at day 7 post-MI and peak on day 14, with fibroblasts being the primary cell source (Doi et al. 2000). MMP-2, -3, and -7 can degrade decorin *in vitro* (Imai et al. 1997), and decorin matricryptins have been shown to inhibit angiogenesis (Sulochana et al. 2005). Decorin null mice show abnormal scar tissue formation post-MI (Weis et al. 2005).

Perlecan is another proteoglycan; specifically it is a heparan sulfate proteoglycan found in basement membranes. Perlecan synthesis increases in mouse cardiac fibroblasts post-MI (Nakahama et al. 2000). Perlecan null mice are embryonic lethal due to cardiac defects, which precludes examining effects of perlecan using this deletion strategy in the post-MI setting (Sasse et al. 2008).

Hyaluronic acid is the simplest glycosaminoglycan, composed of regular repeating sequences of nonsulfated disaccharide units. The only glycosaminoglycan that does not contain sulfated sugars, hyaluronic acid attracts water to swell the ECM, which may be an important mechanism to facilitate cell migration during tissue injury. Hyaluronan accumulates in the post-MI LV, peaking at day 3 post-MI in the rat (Waldenstrom et al. 1991). Hyaluronan also increases during inflammatory conditions such as sarcoidosis, idiopathic pulmonary fibrosis, and bleomycin-induced lung injury models. The hyaluronan receptor, CD44, regulates both the inflammatory and fibrotic responses to MI (Huebener et al. 2008). Together, these studies indicate that hyaluronan may serve to increase tissue edema and increase presentation of ligands for inflammatory cell receptors (Gerdin and Hallgren 1997; Waldenstrom et al. 1991).

Collagen I does not always equal collagen I

During the remodeling process, collagen I is cleaved by matrix metalloproteinases (e.g., MMP-1, -8, -9, -13, and -14) and other

proteases to generate 75 and 25 kD collagen fragments (Krane 1982; Krane et al. 1996; Wu et al. 1990). Additional proteinases can then break collagen into further peptide fragments. In the 1990s, several teams including the Davis laboratory, showed that collagen fragments are biologically active. Termed matricryptins or matrikines, these fragments have been shown to regulate angiogenic, inflammatory, and fibrotic responses (Davis 2010). Other ECM components, including fibronectin, thrombospondin-1, laminin, tenascin-C, decorin, and elastin have also been shown to generate matricryptins (Tran et al. 2004; Tran et al. 2005). Therefore, measuring collagen at the gene level or only by total hydroxyproline levels will not provide information on matricryptin generation as would be obtained by immunoblotting or proteomic techniques. Considering the ECM quality, in addition to quantity, will provide a necessary additional level of information for the LV remodeling field.

ECM turnover following myocardial infarction is a balance between synthesis and degradation

ECM degradation is regulated by a multitude of proteases (Table 3). Of these, the serine proteases and matrix metalloproteinases (MMPs) are the best studied (Liaw and Crawford 1999; Singh et al. 2004). MMP-1, for example, was first identified in 1962 by Gross and Lapiere, who described the breakdown of collagen in the metamorphosing tadpole tail (Gross and Lapiere 1962). MMPs process at least one ECM component *in vitro*, require calcium and zinc for full activity, and are inhibited in tissue by the tissue inhibitors of metalloproteinases (TIMPs) and in circulation by α_2 macroglobulin and other non-specific proteinase inhibitors. Because calcium is required for full MMP activity, calcium chelators (e.g., EDTA) are used *in vitro* to demonstrate MMP-specific activity (Tyagi et al. 1993). Another *in vitro* inhibitor of MMP activity is 1,10 phenanthroline, which inhibits by chelating calcium and zinc (Dean et al. 1985).

MMPs are synthesized as secreted or membrane bound forms. The secreted MMPs are released as a pro-enzyme, with activation occurring when approximately 10 kD is cleaved from the N-terminus. MMP-11 is an exception, as it is activated intracelluarly by furin and secreted as an active enzyme (Santavicca et al. 1996). MMP activation occurs via the cysteine switch mechanism (Van Wart and Birkedal-Hansen 1990). During this process, the propeptide domain in the latent enzyme provides a cysteine that interacts with the Zn^{2+} in the active site and prevents enzyme activity. Propeptide cleavage dissociates the bond and exposes the active site. While the pro-domain contains a conserved sequence (PRCGVPDV) that is common to all 25 MMPs, the flanking sequence surrounding this domain is unique and MMP-specific (Park et al. 1991). MMP activators include trypsin, plasmin, cathepsins, kallikrein, other MMPs, SH reactive agents, denaturants, and organomercurials (such as 4-aminophenylmercuric acetate). Interestingly, sodium dodecyl sulfate can activate MMPs by inducing a conformational change without cleaving the pro-domain, which explains why zymograms detect both latent and active MMPs (Makowski and Ramsby 1996). The MT-MMPs are exceptions to the activation process described above. MT-MMPs are cell surface receptors that retain their propeptide domain, which is required for TIMP binding and subsequent MMP activation (Cao et al. 1998). MT1-MMP is a tightly regulated MMP-2 activator, whose mechanism has been worked out in great detail (Butler et al. 1998; Itoh et al. 1998; Kinoshita et al. 1998; Pei and Weiss 1996).

In addition to (or as a result of) cleaving ECM components, MMP roles include regulation of cell migration and invasion; protein processing to activate or degrade the protein; cell shedding of proteins; cell turnover; and activation of MMPs or MMP activators. The net effect of the MMP on cell function is determined by substrate availability. For example, MMPs can promote or inhibit cell growth, can regulate cell survival or cell death, and can influence angiogenesis in a positive or negative manner—all depending on which substrate is processed by the MMP (Sternlicht and Werb 2001). Recent investigations by the Schulz laboratory have shown that MMP-2 activation can occur intracellularly, resulting in cleavage of intracellular substrates such as contractile proteins such as troponin I and myosin light chain in cardiac myocytes (Ali and Schulz 2009; Kandasamy and Schulz 2009; Viappiani et al. 2009). MMP-2 activation can be modulated by the presence of peroxynitrite and glutathione, which modifies

Table 3
Proteases that regulate ECM turnover.

Protease	Type	Examples
Serine	Neutral	Elastase, cathepsin G, thrombin, plasmin, tryptase, proteinase 3
Cysteine	Acidic	Cathepsin S, cathepsin L, cathepsin B
Aspartic	Acidic	Cathepsin D
Matrix metalloproteinase	Neutral	MMP-1 to -3; -7 to -28

Table 4
ECM and non-ECM substrates processed by MMP-9 (Cauwe et al. 2007; Chintala et al. 2002; Egeblad and Werb 2002; Gearing et al. 1995; Gu et al. 2005; Lindsey 2006; Marom et al. 2007; McCawley and Matrisian 2001a,b; Morodomi et al. 1992; Sasaki et al. 1997; Takafuji et al. 2007; Vaisar et al. 2009).

α1 Proteinase inhibitor
α2 Macroglobulin
A disintegrin and metalloproteinase with thrombospondin motifs-4
CD 16, 18, 25, 27, 30, 31, 40 L, 44, 54, 120, 163, 206
C-kit ligand
Collagen I, II, III, IV, V, VII, X, XI, XIV, XVIII
Complement C1q
Chemokine CXC Ligand-1, -4, -5, -6, -7, -8, -10, -12, -17
Desmocollin-3
Desmoglein-1, -3
β Dystroglycan
Elastin
Endothelin-1
Entactin
Fibrin
Fibrinogen
Fibroblast growth factor receptor 1
Fibronectin
Galectin-3
Heparin-binding EGF-like growth factor
Heparan sulfate proteoglycans
Insulin-like growth factor binding protein-3
Interleukin-1β (pro and active)
Interleukin receptors-2α, -6α
Integrins-β_2
Laminin
Latent TGFβ binding protein
Macrophage colony-stimulating factor
MMP-2, -13
NG2 proteoglycan
Nidogen
Occludin
Osteopontin
Plasminogen
Proteoglycans
Proteoglycans link protein
Stromal cell-derived factor-1
Secreted protein acidic and rich in cysteine
Substance P
Syndecan-1, -3, -4
Tissue Factor Pathway Inhibitor
Thyrotropin receptor
Tumor necrosis factor α (pro)
Tumor necrosis factor receptors
Urokinase plasminogen activator receptor-1

the cysteine residue in the autoinhibitory domain (Viappiani et al. 2009). During cardiac injury, oxidative stress levels increase, providing a source for the increased peroxynitrite and glutathione levels. The Schulz group has shown that glycogen synthase kinase-3β can be processed at the N-terminus by MMP-2, resulting in the release of the inhibitory phosphorylated serine-9 to generate a truncated kinase that has increased activity (Kandasamy and Schulz 2009). MMP-7 has also been shown to have intracellular substrates, including connexin 43 that is cleaved at the intracellular C-terminal domain post-MI (Lindsey et al. 2006). The revelations that MMPs have non-ECM substrates and that MMPs can process intracellular substrates were two critical junctures in our quest to grasp the complexity of MMP biology. In the MI setting, for example, there are a wide array of cytokines and chemokines processed by MMP-9 (Table 4).

ECM remodeling in the post-MI setting is time and space dependent

At all stages post-MI, from the myocyte release of complement to initiate the inflammatory response to the fibrotic and angiogenic responses to transition to congestive heart failure, ECM remodeling is a continuum of progressive changes. Therefore, space and time considerations need to be kept in mind when evaluating data snapshots. For example, MMP-9 increases early post-MI and again during the transition to heart failure, but studies evaluating the in between phases may miss the importance of this particular MMP.

Another concept is the importance of looking at both the remote and infarct regions when examining post-MI tissue, as increases in either or both regions will provide functional clues. While an increase in MMP plasma levels is clinically more relevant than sampling tissue, this approach will not tell you where the increase is localized. Infarct tissue is highly active, such that mRNA levels are higher in the infarct compared to remote region, and the remote region is higher than control levels. Therefore, consideration should be given to both remote and infarct responses.

Where do we go from here?

Key areas that remain to be explored are shown in Table 5. The dynamics of ECM assembly, including the roles of matricellular accessory proteins, such as SPARC, thrombospondins, and tenascins, need to be better understood (McCurdy et al. 2010; Poobalarahi et al. 2006; Puolakkainen et al. 2005; Tamaoki et al. 2005). Downstream effects of matricryptin production likely play key roles, but little is known regarding which peptides may be clinically relevant for diagnostics or therapeutic intervention. Effects of co-morbidities, such as aging, diabetes, or the presence of systemic inflammation, are known to exacerbate the LV response to MI. However, studies are still needed to delineate the mechanisms involved. Two methodologies that will help provide answers to these remaining questions include systems biology and proteomic approaches. Systems biology approaches that include complex computational methods using mathematical modeling are needed for us to better understand the LV response to MI on a global tissue level. Proteomic approaches will also inform us as to the pattern of global changes seen.

Table 5
Key areas to be explored.

1. Dynamics of ECM assembly
2. Downstream effects of ECM turnover
3. Effects of co-morbidities
4. Systems biology approaches for multi-dimensional kinetic analysis
5. Comparative studies across species and tissue types
6. Driver vs passenger effects to assign cause and effect roles

Comparative studies will also provide useful information. Comparisons across species will inform us on processes that are conserved across species and therefore, likely candidates for therapeutic interventions in humans (Dewald et al. 2004). Comparisons across tissues (skin vs lung vs kidney vs heart) and how these tissues differentially (or similarly) respond to injury will provide information that has relevance to LV remodeling. Few studies incorporate multiple animal models in the experimental design or evaluate multiple tissue responses, in part due to time and cost issues.

In summary, we provide here an overview of cardiac ECM types present in post-MI LV and discuss how individual components contribute to cell and tissue level responses. Finally, we discussed key areas of research that may elucidate additional mechanisms and identify additional therapeutic options for the post-MI patient.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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