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Published in:
Matrix Biology

Link to article, DOI:
[10.1016/j.matbio.2017.12.001](https://doi.org/10.1016/j.matbio.2017.12.001)

Publication date:
2019

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):
Nielsen, S. H., Mouton, A. J., DeLeon-Pennell, K. Y., Genovese, F., Karsdal, M. A., & Lindsey, M. L. (2019). Understanding cardiac extracellular matrix remodeling to develop biomarkers of myocardial infarction outcomes. *Matrix Biology*, 75-76, 43-57. <https://doi.org/10.1016/j.matbio.2017.12.001>

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**Understanding Cardiac Extracellular Matrix Remodeling to Develop
Biomarkers of Myocardial Infarction Outcomes**

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Keywords: extracellular matrix, myocardial infarction, biomarkers, collagen, matrix
metalloproteinases

Word count: 11,306

Abstract

Cardiovascular Disease (CVD) is the most common cause of death in industrialized countries, and myocardial infarction (MI) is a major CVD with significant morbidity and mortality. Following MI, the left ventricle (LV) undergoes a wound healing response to ischemia that results in extracellular matrix (ECM) scar formation to replace necrotic myocytes. While ECM accumulation following MI is termed cardiac fibrosis, this is a generic term that does not differentiate between ECM accumulation that occurs in the infarct region to form a scar that is structurally necessary to preserve left ventricle (LV) wall integrity and ECM accumulation that increases LV wall stiffness to exacerbate dilation and stimulate the progression to heart failure. This review focuses on post-MI LV ECM remodeling, targeting the discussion on ECM biomarkers that could be useful for predicting MI outcomes.

Introduction

Cardiovascular disease (CVD) is the most common cause of death in industrialized countries [1], and myocardial infarction (MI) contributes significantly to CVD mortality [2]. The prevalence of CVD is estimated to increase by 10% over the next 20 years, and by 2030 cause 23.6 million deaths each year worldwide [3]. In addition, public health costs for MI are estimated to increase three-fold over the next 2 decades [4].

Following MI, the left ventricle (LV) undergoes a series of molecular, cellular, and extracellular matrix (ECM) changes that progress over time to alter LV geometry and impair LV physiology [5]. The ECM is a dynamic and complex structure, which serves to preserve LV physiology under homeostasis and regulate the development of the infarct scar in response to MI. The balance between ECM synthesis and degradation defines net ECM accumulation (synthesis minus degradation), with ECM degradation prominent in the early MI response and ECM synthesis prominent in the later post-MI period [6,7]. Evaluating ECM flux over the MI time continuum may provide early diagnostic or prognostic indicators of LV remodeling and allow clinicians to stratify patients based on risk or treatment strategy. Biomarkers are currently used for the timely diagnosis of MI; however, their use to date has shown limited use in heart failure due to lack of specificity and selectivity [8]. For example, while infarct size and the extent of post-MI LV dilation tracks with adverse remodeling and progression to heart failure, there is a lot of individual variation in response that may be due to differences in intensity of the inflammatory response[9]. The development of ECM remodeling biomarkers that detect structural changes during MI would provide information for the time period that occurs after MI and before heart failure development. This review will focus on ECM remodeling in the post-MI LV and concentrates the discussion on ECM changes that could serve as biomarkers to predict MI outcomes.

Cell structural and physiological changes induced by MI

MI is defined as the occurrence of cardiomyocyte cell death due to prolonged ischemia that most frequently occurs due to coronary artery occlusion. MI generates an intense wound repair process, which includes one type of LV remodeling characterized by robust inflammation and scar

formation [10]. Disruption of the ECM network due to degradation by matrix metalloproteinases (MMPs) interrupts the structural integrity and induces physiological impairment characterized by reductions in both systolic (due to myocyte loss) and diastolic (due to ECM) function [11]. LV remodeling encapsulates effects in the infarct region, which are structurally important for limiting infarct expansion induced LV dilation, and effects in the remote region, which increase LV wall stiffness [6,12]. A better understanding of the molecular and cellular LV remodeling events is important for maximizing long-term MI survival by limiting progression to heart failure. **Figure 1** depicts the molecular and cellular time continuum of the different MI response phases: inflammation, wound healing, and collagen deposition.

The fate of the myocardium following MI depends on the balance of several competing events, including pro- vs. anti-inflammatory processes and ECM degradation vs. synthesis pathways. Excessive ECM accumulation can increase myocardial stiffness [13–17] and impair electrical activity [18]. Understanding which factors contribute to this balance will provide mechanistic insight into how the progression to heart failure is stimulated and identify new targets to examine.

Myocyte cell physiology is immediately impaired after the onset of ischemia, and by 30 minutes of ischemia, cardiomyocytes undergo irreversible cell death that stimulates an acute inflammatory response by upregulating the complement pathway [19–21]. Neutrophils and macrophages infiltrate into the infarct region and release inflammatory mediators, including matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase (TIMP), to stimulate ECM degradation and necrotic cell removal [22]. While macrophage influx occurs first, neutrophil influx rapidly exceeds that of the macrophage and by post-MI day 1, the neutrophil is the predominant leukocyte component in the infarct region [23]. Neutrophil numbers peak at day 1 post-MI and return to baseline by days 5-7 post-MI [24]. Macrophage numbers (Mac-3+ cells) peak at day 3 post-MI and begin to decline after day 7 [25]. ECM is cleaved by proteases to release necrotic myocytes; and these ECM peptide fragments generated by proteolytic processing stimulate fibroblasts into an activated form (**Figure 2**). Cardiac fibroblasts are the major ECM producers in the LV, and cardiac fibroblast numbers and polarization begin to increase by day 3 post-MI [26].

The collagen-rich reparative scar begins to form around day 5 post-MI to replace the extensive loss of cardiomyocytes in the infarcted area [27].

Cardiac relevant ECM proteins induced by MI

The myocardial ECM is comprised of hundreds of components that include collagens, fibronectin, glycoproteins, glycosaminoglycans (GAGs), proteoglycans, and MMPs/TIMPs (**Table 1**). Some of these proteins can have matricellular properties, hence having a regulatory role rather than a structural one [7,28,29]. The cardiac ECM can be conceptually divided into proteins that reside in the interstitial matrix (e.g., collagen I, collagen III, and fibronectin) and proteins that reside in the basement membrane (collagen types IV, V, VII, X, and XIV and laminin) [30–32]. The basement membrane is the highly organized sheet-like ECM layer found on the surface of the cell sarcolemma and plays a key role in sarcomere formation via interactions with integrins [33].

Fibrillar collagens

Historically, the cardiac ECM has been reported to be mainly composed of collagen; in the mammalian heart, approximately 85% of fibrillar collagen is type I, whereas type III comprises about 11% of total collagen [30,31,34]. In addition to comprising the bulk of the interstitial matrix, collagens (such as collagen XIII) may also play important structural roles in intercalated discs that form between cardiac myocytes [35]. Collagens are secreted as procollagens into the extracellular space, with the carboxy- and end-terminal peptides being proteolytically cleaved to form a mature collagen fibril [36]. Mature collagen is rendered insoluble and resistant to degradation via cross-linking by the enzymes lysyl oxidase [36]. Myocardial collagen content shows a biphasic nature following MI, with collagen degradation dominating early and synthesis dominating later as collagen is organized into scar tissue. Early post-MI, during the inflammatory phase, collagen is degraded by MMPs released by infiltrating neutrophils and monocytes, allowing these inflammatory cells to effectively phagocytose necrotic cells and creating a favorable environment for angiogenesis [37]. Proteolytically cleaved ECM fragments (matricryptins or matrikines) have important post-MI biological roles, including effects on cell proliferation, migration, differentiation, and inflammation [6]. Following the inflammatory phase, collagen deposition becomes favored

over degradation. In rats with MI, collagen III gene expression is induced 2 days post-MI and continues to increase by 21 days post-MI, whereas collagen I gene expression is increased 4 days post-MI, peaks at 7 days post-MI, and remains at that level by 21 days post-MI [38]. The increase in collagen content remains throughout the life of the infarct scar and plays a crucial role in the maintenance or deterioration of cardiac physiology and the progression to heart failure (HF).

Expression of collagen cross-linking enzymes is also elevated during the maturation phase to enhance overall LV stiffness. Lysyl oxidase is ~5-fold elevated at day 3 post-MI, remains elevated by day 7, and then decreases [39]. Mice lacking matrix metalloproteinase-9 (MMP-9) are protected from MI-induced LV dilation, in part due to increased lysyl oxidase expression and collagen cross-linking [40]. In a rat model of cardiac volume overload-induced heart failure, inhibition of lysyl oxidase with beta-aminopropionitrile also offers cardioprotection [41,42]. Advanced glycation end-product (AGE) are another source of collagen cross-linking that have been associated with poorer outcome post-MI [43]. Unlike cross-links produced by LOX, AGEs are formed spontaneously. In mice, methylglyoxal-AGEs are produced in the post-MI LV, suggesting a role for accumulation of collagen and functional loss of the heart [43]. These results indicate that the effect of LV stiffness on dilation is U-shaped rather than linear, with too much or too little having detrimental effects.

Basement Membrane Proteins

The basement membrane is a dense network of ECM proteins that surrounds cardiomyocytes, and includes laminins, collagen type IV, and a number of proteoglycans [44,45]. Laminin $\alpha 1$ is involved in basement membrane assembly and architecture, and plays an important role in cell migration through interactions with integrins $\alpha 3\beta 1$ and $\alpha 6\beta 1$ [46]. Fragmentation of the cardiac laminin network occurs after 1 hour of occlusion and continues for up to 7 days following reperfusion [47]. Studies have shown that basement membrane thickness is significantly increased around intramyocardial capillaries in patients with acute MI, which may contribute to impairment of oxygen diffusion and hypoxic stress [48]. Autoantibodies against collagen type IV are increased in post-MI patients, which may be causative or contributory to impaired basement membrane structural integrity and consequently endothelial cell dysfunction [49]. Laminin-derived peptides

stimulate wound healing by facilitating angiogenesis [50]. Peptides derived from the degradation of collagen IV and perlecan play critical roles in angiogenesis, vascular structural integrity, and cell-cell interactions following myocardial ischemic injury [51].

Elastin

Elastin provides elasticity to tissues such as blood vessels and skin, and its expression is relatively low in the adult heart [33]. Elastin expression decreases in the post-MI scar, leading to decreased elasticity and resiliency to recoil, and contributing to stiffening of the scar tissue [52–55]. Implantation of COS-7 cells overexpressing elastin into the infarcted myocardium 6 days post-MI partially attenuated the decreases in fractional shortening (58% decrease in control rats versus 29% decrease in treated rats) and decreased infarct expansion by nearly 2-fold at 8-weeks post-MI, suggesting that elastin may be a therapeutic target for improving infarct strength and elasticity [42]. Like collagen, elastin can be cross-linked by lysyl oxidase, altering its tensile strength [33].

Fibronectin

Fibronectin is a glycoprotein that provides a scaffold for the infiltration of connective tissue and inflammatory cells [56]. Fibronectin is expressed in the developing heart and is a minor component of the adult uninjured LV [57]. Fibronectin is induced in the adult heart in response to MI, produced mainly by fibroblasts and endothelial cells. The alternatively spliced extra domain A (EDA) of fibronectin acts as a pro-inflammatory agent [58]. Fibronectin increases more than 10-fold in the infarcted area at day 2 post-MI and is believed to contribute to an increase in mechanical strength of the infarcted wall.

Proteoglycans

Proteoglycans are proteins covalently bound to long polysaccharide chains called glycosaminoglycans, including chondroitin/dermatan sulfate, keratan sulfate, and heparan sulfate [43,44]. Proteoglycans have been implicated in regulating the extent and organization of the collagen matrix [59]. Hyaluronan is a unique glycosaminoglycan in that it is not bound to a core protein, nor is it sulfated. Hyaluronan is increased post-MI in the LV infarct, and the generation of hyaluronan fragments promote inflammation, such that clearance of hyaluronan fragments is

necessary for resolution of post-MI inflammation [60,61]. Administration of IL-10, an anti-inflammatory cytokine, may improve functional outcomes post-MI by downregulating hyaluronidase-3 and thus preventing hyaluronan fragmentation and improving inflammation resolution [62].

Decorin binds and regulates assembly of collagen I and III fibrils and binds the pro-fibrotic transforming growth factor-beta (TGF- β) to inhibit its activity [48]. *In vitro*, collagen fibrils form more slowly and are of smaller diameter in the presence of decorin than those formed spontaneously, linking decorin with maintaining spatial order of collagen fibrils [63–65]. In rats, decorin increases by over 30% at week 5 post-MI and doubles by week 13 [63]. Mice lacking decorin show disorganized collagen fibril formation (lower packing density and increased heterogeneity in fibril size), more dilation (25% increase in LV circumference 2 weeks post-MI), and impaired physiology (ejection fraction reduced ~2-fold at 8 weeks post-MI) [66].

Versican, the major hyaluronan-binding proteoglycan expressed in the LV, mediates inflammatory cell-cell and cell-matrix interactions in the infarcted heart and is primarily expressed by infiltrating monocytes [67]. Versican is induced 6 hours following MI and peaks at 2 days, then declines gradually. Versican is also necessary for normal cardiac and vascular development [68].

Matricellular Proteins

Matricellular proteins such as osteopontin, galectin-3, periostin, secreted protein acidic and rich in cysteine (SPARC), thrombospondin, and tenascins are secreted by myocardial resident and infiltrating cells and play non-structural roles in the cardiac ECM [69]. Matricellular proteins mediate processes such as cell adhesion, migration, growth, and differentiation.

Osteopontin is present at very low levels under basal conditions [70]. After MI, osteopontin expression markedly increases by 40-fold in the infarct region [70,71]. Osteopontin expression coincides with the development of pressure overload-induced heart failure, and may play a contributory role through its stimulatory effects on inducible nitric oxide synthase expression [71]. However, osteopontin may be cardioprotective post-MI, as osteopontin null mice show 1.6-fold

increased normalized LV volume without concomitant increases in infarct collagen content 14 days following MI, suggesting that osteopontin is essential for collagen deposition and healing post-MI [72]. Osteopontin is cleaved at multiple sites by MMPs, including MMP-9, which may decrease its cardioprotective actions [72].

Galectin-3, a lectin expressed by inflammatory cells, particularly macrophages, plays critical roles in stimulating both inflammation and fibrosis, mainly by activating TGF- β , IL-1, and IL-2 signaling [44]. In mice, increased galectin-3 expression can be detected as early as 30 minutes post-MI, and is increased 3-fold by 24 hours [73]. At 7 days post-MI, mice lacking galectin-3 have more dilation (~10% increase in end-diastolic diameter), and decreased LV physiology (25% decreased ejection fraction and fractional shortening) [74].

Periostin, a collagen chaperone, is essentially undetectable in the adult myocardium except in valvular tissue, and is highly expressed in the infarct region 3 days post-MI mainly in cardiac fibroblasts [75]. Periostin appears to play dichotomous roles post-MI, being critical for normal healing and scar repair in the short term, but also contributing to cardiac fibrosis and LV stiffening in the long term. Mice lacking periostin have over 2-fold increased rupture rates 7 days post-MI and display 2-fold lower collagen content and 3-fold decreased cross-linked collagen [61]. In a porcine model, delivery of a periostin-derived peptide 2 days post-MI improves ejection fraction by about 25% at 3 months, but also leads to increases in myocardial fibrosis (6-fold increases in collagen content) in the remote region at one and 12 weeks post-treatment, limiting its clinical application as a viable therapeutic strategy [76]. ECM peptides have been well-studied in wound healing therapeutics, and there are a number of reasons for using a peptide rather than a whole molecule [77,78]. Peptides are easier to deliver, and cleaved protein fragments often have different functions than the whole molecule.

SPARC is a matricellular protein expressed by cardiac fibroblasts and endothelial cells that serves as an essential chaperone for procollagen processing and assembly of collagen fibrils [81]. SPARC expression is increased ~2-fold at 3 days post-MI, and mice lacking SPARC show less LV dilation (25% lower end-diastolic volume) and 33% increased ejection fraction following MI [81].

Cartilage oligomeric matrix protein (COMP) is a matricellular calcium-binding protein belonging to the thrombospondin family, which participates in cellular responses to growth factors and cytokines [79]. High levels of COMP have shown to be associated with lower risk of incident MI, suggesting a beneficial role in individuals without incident cardiovascular disease [80]. In this study, intact COMP was measured by a commercially available ELISA. As COMP is known to be degraded by ADAMTS7 [81] an assay measuring ADAMTS7-generated cleavage fragments of COMP may reveal a relationship between ADAMTS7 and COMP that has not yet been explored in the MI setting.

MMP roles in MI

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases responsible for ECM degradation and proteolytic activation of ECM proteins, inflammatory mediators, matricellular proteins, and other MMPs within the **infarct** region (**Table 2**) [82,83] Increased MMP activity in the vasculature can also lead to collagen degradation in fibro-atheromas, potentially resulting in plaque rupture and subsequent MI [82]. MMPs, therefore, are involved in all stages from atherosclerosis development to MI, post-MI wound healing, and progression to HF. MMP activity is dependent on the concentration of active enzyme and on the presence of a family of naturally occurring tissue inhibitors of metalloproteinases (TIMPs) [84]. Following MI, MMPs facilitate ECM degradation and recruit inflammatory cells to remove the necrotic cardiomyocytes. Initially the upregulation of pro-inflammatory cytokines results in robust MMP activation. After long-term stimulation of pro-inflammatory cytokines, TIMP level increase leading to decreased MMP/TIMP ratio and increases in fibrillar collagen deposition [85].

Of the 25 MMPs described to date, human MMP-1 has the highest affinity for fibrillar collagen and preferentially degrades collagen type I and collagen type III. Increases in MMP-1 synthesis have been reported in the infarcted myocardium in pigs and humans [86]. Inactivation of MMP-1 synthesis in the infarcted myocardium results in collagen accumulation, which in turn leads to a stiff and non-compliant LV and gradual cardiac dysfunction [87]. The interaction between MMP-1 and TIMP-1 is of critical relevance in the maintenance of the post-MI integrity of the cardiac collagen

network. The MMP-1:TIMP-1 ratio has been inversely correlated with ejection fraction in patients with either systolic or diastolic heart failure [88]. Using an MMP to TIMP ratio is artificial, however, because there are more than one MMP and more than one TIMP present in the post-MI myocardium.

MMP-2 and -9 are the most widely studied MMPs, because they have historically been the easiest to measure using gel zymograms [89,90]. In a rat MI model, MMP-2 and -9 expression increases within 24 hours post-MI. At day 14, MMP-2 expression peaks and returns to baseline after 10 weeks, whereas MMP-9 expression continues to be elevated until 16 weeks post-MI [91,92]. There are species differences in MMP and TIMP expression, as MMP-9 is returning to baseline values by day 7 post-MI in the mouse. Excessive MMP activity post-MI leads to ECM degradation, which increases LV compliance and promotes cardiac rupture [55]. As such, MMP-2 deletion improves survival rates after MI by limiting cardiac rupture [93]. Infiltrating macrophages are a major source of MMP-9 [94], and MMP-9 deletion attenuates LV dilation post-MI [95,96]. This is mainly due to MMP-9 regulation of inflammation through its proteolytic activity of both ECM and cytokine substrates. MMP-9 mediates the post-MI degradation of CD36 to decrease macrophage phagocytosis of apoptotic neutrophils; MMP-9 deletion increased phagocytosis and neutrophil apoptosis to improve post-MI LV dilation [97]. MMP-9 promotes a pro-inflammatory macrophage phenotype, as MMP-9 deletion increases pro-reparative M2 markers in macrophages following MI [94]. Although a number of *in vitro* MMP-9 substrates have been identified, including collagens (type I, IV, V, VII, X and XIV), fibronectin, elastin, IL-8, Cxcl4, and IL-1 β , the **mechanisms** whereby MMP-9 modulates LV remodeling post-MI have not been completely elucidated [98,99].

MMP-3 is a stromelysin sub-type, along with MMP-10 and MMP-11, and is actively involved in pro-MMP proteolysis [100]. Unlike MMP-9, the active form of MMP-3 is down-regulated by day 3 in the infarct region [101]. Elevated levels of MMP-3 associate with increased MI risk, most likely due to MMP-3 acting as an upstream regulatory step in the activation of many MMPs [102]. MMP-7 is responsible for degrading a number of ECM and matricellular proteins, as well as non-ECM proteins such as connexin-43, contributing to the development of MI-related arrhythmias [21].

MMP-7 protein levels are up-regulated 3-fold in both remote and infarct regions at 7 days post-MI [103]. Similar to MMP-9, MMP-7 deletion has been shown to be protective post-MI albeit through different mechanisms [104].

MMP-8 and -13 are two of the major collagenases in the heart [105]. In rats, MMP-8 levels increase after 2 weeks and remain high until 16 weeks post-MI [91]. In cryoinfarcted mice, MMP-8 levels are increased 3 days post-MI, but return to normal by 2 weeks, suggesting potentially different roles for this MMP in rats and mice [105]. MMP-13 shows an identical post-MI pattern of expression to MMP-8, thus mediating collagen degradation early post-MI [105]. In patients, elevated levels of plasma MMP-8 early post-MI is correlated with poor prognosis whereas higher levels more than 20 months after MI is associated with relative preservation of LV systolic function, indicating a biphasic profile [106]. MMP-12 (macrophage metalloelastase) increases 3-fold in the LV infarct region at day 1 post-MI and remains upregulated until day 7. MMP-12 inhibition exacerbates cardiac dysfunction by prolonging neutrophil mediated inflammation [61]. Contrastingly, MMP-28 decreases post-MI as the source moves from the highly abundant myocyte to macrophage. MMP-28 deletion aggravated MI-induced LV dysfunction and rupture as a result of defective inflammatory response and scar formation by suppressing M2 macrophage activation[5].

TIMP-1 (29 kDa), a glycoprotein member of the TIMP family, co-localizes with MMP-1 in normal myocardium and is expressed by cardiac fibroblasts and myocytes [107–110]. TIMP-1 expression increases early, peaks at day 1 and remains elevated through day 21 post-MI [91,111,112]. Circulating TIMP-1 levels closely associate with markers of HF severity, systemic inflammation, and LV remodeling [113]. In addition, high levels of TIMP-1 are associated with diastolic dysfunction [114]. TIMP-1 null mice have a greater degree of LV dilation post-MI [114,115]. TIMP-2 levels increase by 2 weeks post-MI, correlating with deposition of ECM by infiltrating myofibroblasts, and return to baseline after 8 weeks during the late remodeling phase [91]. In contrast, TIMP-3 and -4 are significantly reduced post-MI [91,112]. TIMP-3 has cardioprotective functions, as TIMP-3 deletion leads to spontaneous dilated cardiomyopathy, and

delivery of recombinant TIMP-3 post-MI improves LV ejection fraction, decreases LV dilation, and attenuates infarct expansion [116].

Biomarkers of MI: current state of the field

The use of biomarkers for early diagnosis of acute MI has been extremely valuable over the past 40 years [117]. The most widely established diagnostic biomarker of MI is cardiac troponin (cTn). The available assays target the C, I, or T subunits of troponin, which control the calcium mediated interaction of actin and myosin, leading to contraction and relaxation of the striated muscle [118]. Troponin I (cTnI) and troponin T (cTnT) are measured when they are released from cardiac myocytes upon myocardial damage. This biomarker is highly specific to cardiac tissue, since cTnI and cTnT have additional residues at the N- terminal end compared to the skeletal isoform of troponin [119]. Assays for troponins do present some disadvantages, including: high variability across commercial source; there could be misleading cTn levels in patients who receive reperfusion therapy; and there is no correlation between cTn and histopathology [10]. Nevertheless, cTn has since the year 2000 been the preferred biomarker for MI diagnosis [10].

C-reactive protein (CRP), myoglobin, and creatinine kinase (CK-MB) have been proposed as alternatives to cTn. CRP is a nonspecific acute-phase reactant protein produced in the liver used as marker of acute inflammation. Its use in MI is limited, since levels vary according to ethnicity, gender, genetics, and body weight. CRP is also non-specific for MI over other inflammatory conditions and has actually been described as a good indicator for non-cardiac pathologies [120,121]. CK-MB is an enzyme primarily located in the cardiac muscle. The MB isoenzyme is released upon myocardial injury [122]. During acute MI, the level of CK-MB doubles in the first 6 hours, and peaks within 12-24 hours [123,124]. CK-MB is a good indicator of infarct size and predicts risk of re-infarction. This marker elevates later than cTn and has in several cases been shown to be less sensitive and specific than cTn. Myoglobin is a small protein localized in the cytoplasm of cardiac and skeletal muscle cells. Due to its small size, myoglobin is rapidly released into the circulation upon injury and is generally one of the earliest to appear in the circulation.

Elevated levels can be observed 0.2-2 hours after acute MI, which is considered rapid; due to its presence in skeletal muscle, however, this marker lacks tissue specificity [125,126].

General perspectives on ideal biomarker(s) of MI remodeling: opportunities for identifying targets

The ideal biomarker of MI response should be as non-invasive as possible and should monitor disease progression and predict long-term prognosis following MI. The biomarker assay should be easy to perform, reproducible, accurate, fast, and inexpensive. While cardiac-specificity is important to ensure no cross reactivity to other biological processes, it is not essential if MI is the only inflammatory pathology present [118,127]. Such non-invasive biomarkers may provide patients and their physicians with a better and timely assessment of diagnosis as well as surveillance of progression and response to treatment. The ECM proteome, which is strongly regulated during MI, may be a large source of potential new targets.

Neo-epitope biomarkers of ECM peptides: an opportunity for post-MI monitoring

A finely regulated balance between ECM degradation and synthesis is required for maintenance of tissue homeostasis. In pathological conditions, such as cardiac fibrosis, this balance is disrupted. An excessive production and accumulation of ECM proteins combined with dysregulated turnover contributes to post-MI cardiac remodeling and its progression to HF. The neo-epitope technology takes into consideration the action of proteases such as MMPs, which are active post-MI and work on ECM proteins at specific sites, to identify specific markers [128]. Immunoassays detecting neo-epitope peptides generated after protease cleavage and released into circulation would provide information on the dynamic turnover of the ECM and distinguish between responses that favor ECM degradation over formation (Figure 3). Targeting either protease-mediated fragmentation products (indicative of protein degradation) or the pro-peptide that is cleaved off the molecule during its maturation (indicative of protein formation) will provide information on ECM turnover. ECM degradation fragments not only reflect active connective tissue remodeling, the fragments can also acquire bioactive properties and be key mechanistic players in LV remodeling [78].

Soluble ST2, which is a receptor for cardiac fibroblast-derived interleukin-33, is elevated in the circulation of patients with heart failure with preserved ejection fraction and is strongly associated with myocardial fibrosis [36]. Both cardiac fibroblasts and cardiac myocytes are sources of IL-33 [36].

Neo-epitope biomarkers have already proven useful as serological and urinary markers of ECM remodeling in several organ injury models, including liver, lung [129–133], and kidney [134–136] and could potentially be applied to myocardial fibrosis following MI. Elevated circulating carboxy-terminal telopeptide of collagen type I (CITP), a biomarker of collagen degradation, is elevated 2 days post-MI, peaks at 3 days, and remains at peak levels for 14 days [27]. Elevated CITP is associated with poor long-term clinical outcomes including mortality, cardiac arrest, heart failure, and recurrent MI for up to 1 year post-MI [27]. Other circulating peptides released during collagen synthesis, such as **aminoterminal propeptide of type I procollagen (PINP) and type III procollagen (PIIINP), TIMP-1, and type I collagen telopeptide (ICTP), have prognostic value following acute MI in human patients, and in combination with brain natriuretic peptide (BNP) levels may help predict development of a primary composite event following MI [137].** Poor outcome events such as death, development of HF, and recurrent MI significantly increase in patients presenting with elevated serum collagen matricryptins (matrikines) [27–31].

Matricellular proteins such as SPARC, thrombospondin, osteopontin, and galectin-3 are also elevated in the circulation following myocardial injury [36]. Galectin-3 is up-regulated in animal models of HF and can be detected before the development of clinical HF [143–145]. **Serum levels of galectin-3 increase in patients following acute MI, and progressive increases in circulating galectin-3 correlate with declining ejection fraction 24 weeks post-MI in patients [146].**

Furthermore, patients with higher baseline levels of galectin-3 have a higher prevalence of MI [147]. Circulating MMP-9 is a potential prognostic biomarker for risk of cardiovascular disease and mortality, and reflects LV dilation and dysfunction following MI [148]. In addition to collagen degradation, circulating MMP-9 levels can also reflect inflammation status [148].

The use of mass spectrometry based proteomics has gained increasing interest, due to its ability to determine changes in the ECM of the heart and other tissues [6,149]. Proteomics can be used to identify new biomarker targets in a variety of sample types and is used in biomarker assays [150,151]. Several excellent recent reviews have highlighted how proteomics has contributed to our understanding of ECM remodeling [28,152–157]. A major current limitation of ECM biomarkers for MI wound healing responses is that other organs may also contribute to the pool of neo-epitope peptides released in serum, since the same ECM proteins are present in more than one organ. Whether there is a signature biomarker panel that reflects MI response remains to be determined.

Final considerations

The development of non-invasive ECM specific biomarkers could predict imbalanced tissue turnover, and thereby post-MI outcomes. Such biomarkers could facilitate clinical studies to both identify patients at risk of progressing to HF after MI and monitoring response to treatment strategies.

Acknowledgements

We would like to thank past and present members of the Lindsey lab for their contributions to this knowledge. We acknowledge grant support from The Danish Research Foundation and the National Institute of Health HL075360, HL129823, HL051971, GM104357, GM114833, and GM115428, and from the Biomedical Laboratory Research and Development Service of the Veterans Affairs Office of Research and Development Award 5I01BX000505 and IK2BX003922. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Danish Research Foundation, the National Institutes of Health, or the Veterans Administration.

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Figure legends

Figure 1. Cellular and molecular events during the three phases 1) Inflammation, 2) Wound Healing and 3) Collagen deposition post-MI.

Figure 2. Illustration of the changes occurring in the ECM remodeling during development of MI.

Figure 3. Neo-epitope markers detecting ECM remodeling. A) Formation of detectable neo-epitopes generated by cleavage of ECM proteins by specific proteases. B) In the absence of proteolytic cleavage, the ECM protein is not recognized by the antibody.

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Tables

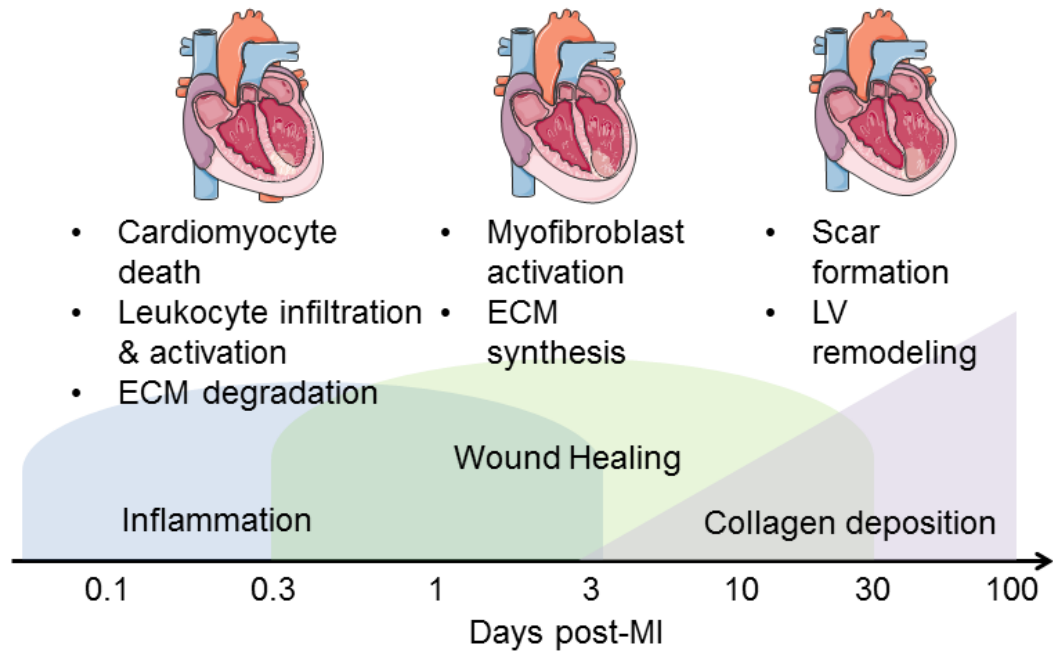
Table 1. Major myocardial extracellular matrix proteins and their functions

Protein	Function	Localization	Change during MI	Reference
Collagen I	Tensile strength and structural support	Interstitial matrix	↑	[30,31]
Collagen III	Tissue elasticity	Interstitial matrix	↑	[30,31,34]
Collagen IV	Maintain basement membrane architecture	Basement membrane	↑	[49]
Collagen VI	Organization of fibrillar collagens/Anchoring to basement membrane	Interstitial matrix/basement membrane	↑	[158]
Elastin	Tissue elasticity and recoil capability	Interstitial matrix	↑	[52]
Fibronectin	Infiltration of connective tissue and inflammatory cells	Interstitial matrix	↑	[56]
Galectin-3	Apposition of ECM proteins and increased collagen turnover.	Interstitial matrix	↑	[65]
Laminin	Maintain basement membrane architecture, cell migration, and angiogenesis	Basement membrane	↑	[46]
Osteopontin	Mediate adhesion, migration, growth, and differentiation	Interstitial matrix	↑	[159,160]
Periostin	Collagen fibrillogenesis and overall organization of ECM	Interstitial matrix	↑	[161]
Decorin	Bind to collagen type I and III, and affect formation of collagen fibrils	Interstitial matrix	↑	[63]
Versican	Mediate inflammatory cell-cell and cell-matrix interactions	Interstitial matrix	↑	[67]

Table 2. MMPs and TIMPs involved in MI remodeling

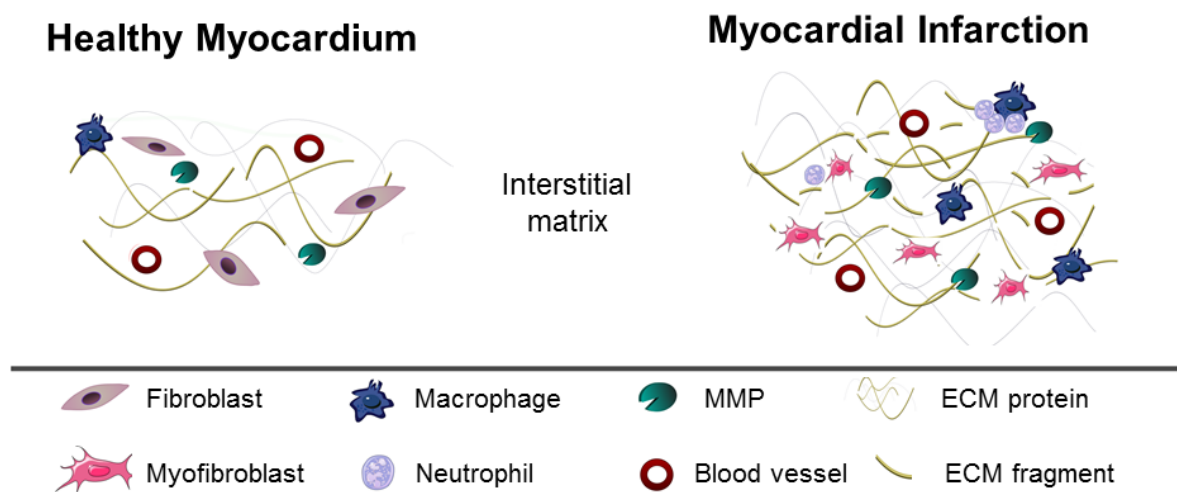
MMP/TIMP	Expression post-MI	Biological roles	Reference
MMP-1	↑	Degrade collagen type I and III MMP-1:TIMP-1 ratio is correlated with ejection fraction	[86]
MMP-2	↑	Increased LV rupture and delay post-MI remodeling	[91–93]
MMP-3	↑	Increased risk of long-term MI and independent predictor of LV systolic dysfunction	[162]
MMP-7	↑	Deletion attenuates LV dilation post-MI	[21]
MMP-8	↑	Early increase of MMP-8 is correlated with poor prognosis and promote infarct rupture in humans by degradation of collagens	[163]
MMP-9	↑	MMP-9 deletion attenuated LV dilation post-MI	[95,96]
MMP-12	↑	MMP-12 inhibition exacerbates cardiac dysfunction	[61]
MMP-28	↑	MMP-28 deletion aggravated MI-induced LV dysfunction Increased LV rupture	[5]
TIMP-1	↑	Associate with markers of HF severity, systemic inflammation and LV remodeling MMP-1:TIMP-1 ratio is correlated with ejection fraction	[107,109]
TIMP-2	↑	Correlate with ECM deposition	[91]
TIMP-3	↓	Cardioprotective and reduced post-MI	[114,116]
TIMP-4	↓	Deletion attenuates increased LV rupture and mortality	[114]

Figure 1



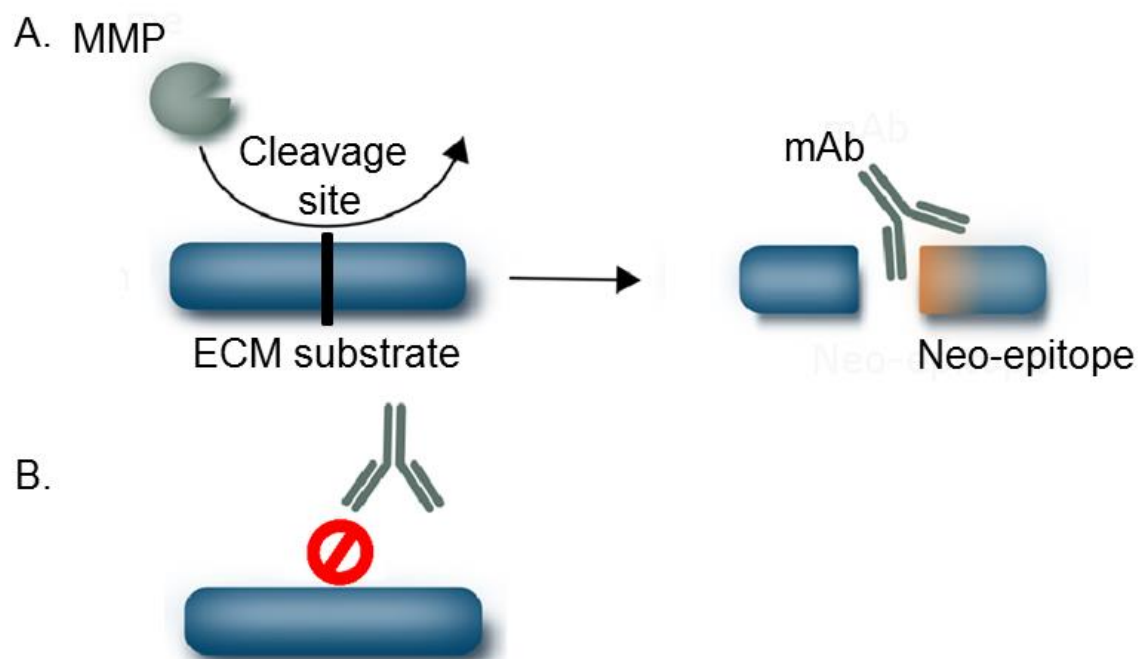
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Figure 2



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Figure 3



Highlights

- This review focuses on post-MI LV ECM remodeling, targeting the discussion on ECM biomarkers that could be useful for predicting MI outcomes.

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