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Extracellular matrix turnover and signaling during cardiac remodeling following MI: causes and consequences

Rogelio Zamilpa, Ph.D.¹ and Merry L. Lindsey, Ph.D.¹

¹ Division of Cardiology, Department of Medicine, The University of Texas Health Science Center at San Antonio

Abstract

The concept that extracellular matrix (ECM) turnover occurs during cardiac remodeling is a well-accepted paradigm. To date, a multitude of studies document that remodeling is accompanied by increases in the synthesis and deposition of ECM components as well as increases in extracellular proteases, especially matrix metalloproteinases (MMPs), which break down ECM components. Further, soluble ECM fragments generated from enzymatic action serve to stimulate cell behavior and have been proposed as candidate plasma biomarkers of cardiac remodeling. This review briefly summarizes our current knowledge base on cardiac ECM turnover following myocardial infarction (MI), but more importantly extends discussion by defining avenues that remain to be explored to drive the ECM remodeling field forward. Specifically, this review will discuss cause and effect roles for the ECM changes observed following MI and the potential role of the ECM changes that may serve as trigger points to regulate remodeling. While the pattern of remodeling following MI is qualitatively similar but quantitatively different from various types of injury, the basic theme in remodeling is repeated. Therefore, while we use the MI model as the prototype injury model, the themes discussed here are also relevant to cardiac remodeling due to other types of injury.

Introduction

A myocardial infarction (MI) occurs when a previously atherosclerotic coronary artery becomes totally occluded, resulting in ischemia of the downstream myocardium. Metabolic distress of sufficient duration to result in cardiomyocyte necrosis is termed infarction. Following MI, the left ventricle (LV) undergoes a continuum of molecular, cellular, and extracellular responses that manifest clinically as changes in LV size, shape, and function.[2] Coined by Jan and Marc Pfeffer,[3] the term LV remodeling encompasses LV wall thinning, LV dilation, and infarct expansion; inflammation and necrotic myocyte resorption; fibroblast accumulation and scar formation; and endothelial cell activation and neovascularization.[4] LV remodeling is influenced by variations in inflammatory response (neutrophil and macrophage influx), hemodynamic load, molecular changes (neurohormonal activation and cytokine production), and extracellular responses (fibrosis and activation extracellular proteases including matrix metalloproteinases (MMPs) and serine proteases).[5] In addition, pre-existing conditions such as diabetes or periodontal disease and the use of drugs such as angiotensin converting enzyme inhibitors and β adrenergic receptor inhibitors can influence

Address for Correspondence: Merry L. Lindsey, Ph.D., Cardiology Division, Department of Medicine, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Mail Code 7872, San Antonio, TX 78229-3900, (phone) 210-567-4673, [1] 210-567-6960, email: lindseym@uthscsa.edu.

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remodeling outcomes. Remodeling occurs in response to MI, but is also a common end point for the LV responses to pressure overload, volume overload, cardiomyopathy, infection, or cardiotoxic agents (see the other reviews in this issue for more detailed discussions). Basically, changes in the ECM represent a dynamic interaction between the various cell types and the acellular components. In this review, we will focus on ECM turnover in response to MI.

ECM gene and protein synthesis increases post-MI

ECM is tissue specific, in that it varies in quality and quantity among different tissues. In the heart the ECM includes collagens (types I, III, IV, V, and VI); glycoproteins (fibronectin, laminins, periostin, fibromodulin, and vitronectin); proteoglycans (versican, lumican, and biglycan); glycosaminoglycans (hyaluronic acid and dermatan sulfate); and matricellular proteins (secreted protein acidic and rich in cysteine, thrombospondins, tenascins).[6] In addition, extracellular proteases include serine proteases and MMPs that are present either bound to the ECM, in various cell types, or circulating in blood. Several ECM proteins have been proposed as candidate markers of post-MI adverse LV remodeling (Table 1), and mechanistic roles have been elucidated using null mice.[7] In the baseline state, the cell source for most of the ECM proteins is primarily the cardiac fibroblast; post-MI, cell sources include the myofibroblast, neutrophils, mast cells, lymphocytes, and the macrophage. For example, post-MI the macrophage contributes increased levels of MMPs and osteopontin.[8] In addition, Schnoor and colleagues have recently demonstrated that macrophages contain mRNAs for a large number of collagens (particularly collagen VI) and fibronectin.[9] Fibroblasts in the post-MI LV are primarily myofibroblasts that have differentiated from resident fibroblasts or from infiltrating fibrocytes. Whether the source (resident or infiltrating) yields myofibroblasts with different characteristics has not been examined. Studies that isolate cardiac fibroblasts and stimulate *in vitro* assume that resident fibroblasts comprise the major source. The rapid changes to the ECM following MI are thought to be critical alterations that contribute to the propagation of structural and functional decline. As shown in Figure 1, the net balance between ECM construction and destruction determines the net structural and functional outcome and both sides of the scale stimulate the other.

Protease levels increase post-MI

Multiple MMPs and tissue inhibitors of metalloproteinases (TIMPs) have been shown to be altered post-MI in both human and animal studies. MMPs -1, -2, -3, -7, -8, -9, -12, -13, -14 and TIMPs -1 and -2 levels increase, while TIMP-3 and TIMP-4 levels decrease post-MI. [10–12] It is important to note that of the 25 MMPs identified to date, only the MMPs listed above have been evaluated post-MI. These studies are warranted, particularly for the other membrane type MMPs.

Of the MMPs that have been examined, MMP-9 has surfaced as a leading candidate for having direct effects on cardiac remodeling: a) MMP-9 levels increase early post-MI,[13] b) MMP inhibition improves post-MI outcomes by decreasing MMP-9 levels,[14,15] and c) MMP-9 gene deletion reduces remodeling and stimulates post-MI angiogenesis.[16] Plasma MMP-9 levels predict cardiovascular mortality, as coronary artery disease patients with the highest MMP-9 levels at baseline showed the greatest cardiovascular mortality rates at the 4 year follow-up.[17] Horne and colleagues examined over 5000 patients for associations between MI and polymorphisms in 4 MMPs (MMP-1, -2, -3, and -9) and 3 TIMPs (TIMP-1, -2, and -3).[18] In this study, only composite MMP-9 genotypes, not any of the other MMP/TIMP polymorphisms, associated with MI. In another study of 404 post-MI patients, plasma MMP-9 ($p=0.005$) and TIMP-1 ($p=0.036$), but not NTproBNP, correlated with the change in LV EDV, indicating that MMP-9 may be a useful clinical biomarker of LV remodeling and adverse prognosis.[19] Following MI, the neutrophil is a rich source of MMP-9 and serine proteases

including serine elastase, a potent MMP-9 activator.[13] The macrophage is also an abundant MMP-9 source.[20]

Another family of proteases include the a disintegrin and metalloproteinase (ADAM), a disintegrin and metalloproteinase with thrombospondins motifs (ADAMTS), and ADAM-TS-like (ADAMTSL) members. [21,22] While the tumor necrosis factor α converting enzyme (TACE; ADAM-17) is the best known of these members, new roles for this family are currently under investigation. To date, however, fewer than a dozen papers are listed when ADAM and myocardial infarction are used as keywords in PubMed, indicating that this topic remains largely unexplored. Gilliam Murphy has written an excellent review of ADAM roles in cancer. [23] Based on this review, we can speculate that ADAMs -9, -12, -15, -17, and -19 may have important roles in the post-MI setting.

Soluble ECM fragments are generated post-MI

Matricryptins (also known as matrikines) are peptides generated from ECM proteins, including collagens (I, IV, XVIII, and XV), connective tissue glycoproteins (fibronectin, thrombospondin-1, laminin, and SPARC), elastin and potentially other ECM components. [24–27] Of these, collagen and fibronectin fragments have been the most studied in cardiac remodeling. In the late 1990's, Diez and colleagues developed serum assays to measure the C-terminal propeptide of collagen I (PICP), the N-terminal propeptide of collagen III (PIINP), and the C-terminal telopeptide of collagen I (ICTP). [28] Several groups have since measured serum markers of collagen I and III turnover post-MI. McGavigan and colleagues measured PICP and CITP, markers of collagen I synthesis and degradation, respectively, in 51 patients with acute MI.[29] When dichotomized to wall motion index, patients with abnormal wall motion index showed higher baseline levels of CITP and decreased levels of PICP, indicating a net increase in collagen I breakdown. Francisco Villarreal and colleagues assessed the time course of collagen I degradation post-MI in pigs.[30] ICTP levels peaked at 6 h post-MI and remained significantly elevated at day 2 post-MI. The increase in collagen I degradation was ameliorated by pre-treatment with doxycycline, implicating MMP activity. In patients with MI and percutaneous coronary intervention, day 4 PICP levels above 110 ug/l and PIINP levels above 4 ug/l associated with increased LV dilation at 6 months follow up, indicating that increased collagen synthesis at day 4, above a threshold limit, was a predictor of adverse remodeling.[31] While these studies show that collagen peptides are generated post-MI, little has been done to examine the effect of these peptides on downstream cell signaling.

To date, most studies examining matricryptins effects have evaluated angiogenic/anti-angiogenic and tumor promoting/inhibiting properties.[24,32–35] In particular, how MMP-9 regulates ECM turnover by generating matricryptins post-MI remains unclear, and the effects of ECM peptides on inflammatory cell, endothelial, and fibroblast cell function needs further investigation.

MMP-9 degrades denatured collagen I and III, and these collagen peptides influence MMP production and stimulate collagen synthesis.[36,37] Of note, MMP-9 processes collagen into more fragments than MMP-2 does, suggesting different downstream signaling when collagen is processed by different MMPs.[38] MMP-9 processes fibronectin to multiple peptides, including 70 and 45 kD peptides. Fibronectin and laminin peptides stimulate macrophage migration and MMP-9 secretion.[39,40] TNF α -stimulated macrophages release fibronectin peptides, suggesting a role for macrophage-derived MMP-9 in fibronectin processing.[40] The laminin γ 1 peptide KAFDITYVRLKF promotes migration and MMP-9 secretion in mouse melanoma cells, but effects on cardiac cells have not been examined.[41] When all overlapping peptides of the γ 1 chain of laminin were systematically examined for cell adhesiveness, only 12 peptides had activity. SPARC is a matricellular protein that binds collagen and is

upregulated by transforming growth factor β . For a detailed review of SPARC roles in extracellular matrix remodeling, please see Amy Bradshaw's review in this issue. Produced by endothelial cells, fibroblasts, and macrophages, only M2 macrophages take up SPARC via the stabilin-1 receptor.[42] In blood monocytes, SPARC stimulates MMP-9, and SPARC peptides generated by MMP-9 induced MMP production.[43] MMP-9 also increases TGF β activity.[39] Therefore, a positive feedback loop among MMP-9, SPARC, and TGF β makes it difficult to isolate out individual roles.

Assigning cause and effect functions to ECM changes that occur post-MI

There is strong evidence that excess ECM turnover associates with LV functional capacity and outcome. In the Research into Etanercept Cytokine Antagonism in Ventricular Dysfunction (RECOVER) trial, baseline levels of the amino-terminal propeptide of collagen III (PIIINP), MMP-1, TIMP-1, high sensitivity C reactive protein, interleukin-10, and interleukin-18 were measured in 1009 patients at baseline.[44] In an adjusted multivariate model that included all 6 markers, only PIIINP and MMP-1 independently predicted 6 min walk test results, and only PIIINP associated with death and CHF hospitalization numbers. In addition, the fact that ECM genetic mutations can result in cardiomyopathy lends support to the concept that altered ECM can initiate LV dysfunction.[45] Using null and transgenic mice for several ECM and MMP genes has also allowed us to isolate out individual and overlapping functions, although many gene deletion and transgenic models remain to be examined (Table 2).[10,16,46–52] Interestingly, different interventions (e.g., deletion of MMP-9 or osteopontin) that similarly reduce collagen accumulation post-MI reduce or increase LV remodeling, indicating that measuring total collagen levels may not predict outcomes. This topic is also discussed in Marielle Scherrer-Crosbie's review in this issue. ECM turnover lies between cardiomyocyte loss and LV functional decline, but the complete mechanistic pathway remains to be elucidated. Potentially, as more matrikines are identified, these peptides may serve as critical biomarkers and help to distinguish signaling pathways involved in adaptive versus maladaptive remodeling.

Determining which ECM changes are trigger points for remodeling

Several issues need to be resolved before we can know how different ECM components change during remodeling to effect post-MI outcomes. For one, a complete catalogue of ECM changes that occur in the infarct, remote, and border zones over time need to be made. Since the relationship between the cellular and acellular components is dynamic, spatiotemporal considerations are especially important. The post-MI response is a continuum, and the same therapeutic perturbation given at different times will likely have different consequences. For example, measuring total collagen levels by picrosirius red staining at one time point and in one region will not provide as much information as individually measuring collagen I, III, IV, V, and VI over time and location.

It is important to note that morphometric techniques for measuring ECM components are frequently less accurate than biochemical analyses. With improved genomic and proteomic techniques, assigning key roles to individual ECM components is only now beginning. Specific protein and RNA arrays are now available that give a broader profile of the dynamic interaction among the various components. For example, measuring total levels of ECM proteins or integrins that connect cells to the ECM do not tell us the quality of these proteins, in terms of whether full-length or soluble forms are present. MMPs release ECM to cell connections by direct processing of the ECM and by shedding integrins from the cell surface, which also prevents the development of mechanical tension. As we begin to amass this information, more sophisticated statistical approaches such as cluster analysis and principle component analysis

and mathematical modeling using differential equations can be used to systematically evaluate ECM roles in cardiac remodeling.

Another issue that we need to deal with is individual biology versus population biology. In human, animal, and cell studies there is individuality in responses, meaning that the average applies for the majority but not necessarily the entirety of the group. This is often seen clinically, in the variation between drug responders and non-responders. We also see this with our post-MI mice, where a group of mice with identical strain and age and with equal infarct sizes will show a wide range of LV dilation (Figure 2, unpublished data). Paying attention to and understanding unequal responses will provide insight into how disparities occur, which will be important for developing optimal therapeutic strategies.

Pathoplasticity refers to the way in which a disease process is molded by the context in which it occurs, and this concept is relevant to the post-MI LV. For example, strain, gender, and age-related differences in mice responses are well documented. C57/BL6J male mice are highly prone to rupture post-MI and will develop heart failure symptoms,[46] while FVB mice are resistant to developing heart failure[53] and aging mice show poorer survival rates post-MI.[54] Using computational simulation approaches that are soundly based on real experimental data, we can develop flexible applications of therapeutic models that will meet the needs of diverse individuals and allow us to identify the high need for therapy patient group at an earlier intervention time.

MMP inhibition as a practical therapeutic option

In the Prevention of Myocardial Infarction Early Remodelling (PREMIER) trial, 253 patients with ST segment elevation MI and ejection fractions <40% were randomized to placebo or oral administration of the MMP inhibitor PG-116800.[55] At 90 days follow-up, there were no significant effects on LV remodeling indices or clinical outcomes. Since the failure of this and several other MMP inhibitor trials, we must ask ourselves if it is wise to continue thinking about MMP inhibition as a clinically viable therapeutic option.

One issue with MMP inhibition is that to date the inhibitors used have very broad specificity and selectivity profiles.[56] The fact that most inhibitors were developed when MMPs 1–3 and TIMP-1 were the only known players and the fact that MMPs share high sequence homology in the active site region means that developing drugs that target only one MMP will be challenging. In addition, pro-MMPs have function that is activation-independent. For example, pro-MMP-9 has catalytic activity when it is bound to substrate,[57] and pro-MMP-9 can stimulate cell migration that does not depend on MMP activation or ECM substrate cleavage.[58] The hemopexin domain of MMP-9 can bind several membrane receptors, including lipoprotein receptor-related proteins (LRP-1 and -2), CD44, reversion-inducing-cysteine-rich protein with kazal motifs (RECK), and the DNA repair protein KU. Dendritic cells secrete MMP-9, which can bind $\alpha_M\beta_2$ integrin and to CD44 to modulate CCL5 and activate the jun N-terminal kinase (JNK) signaling pathway. Pro-MMP-9 effects on cell migration, therefore, may reflect intracellular signaling.[58] Thus, coming up with a strategy that targets MMP-9 will be challenging. Interestingly, Yamamoto and his group have shown that several angiotensin converting enzyme (ACE) inhibitors, including imidapril and lisinopril, can bind to the active site of MMP-9.[59] Whether ACE inhibitors can bind to pro-MMP-9 or other MMPs has not been investigated. Nonetheless, designing ACE inhibitors with improved MMP-9 inhibition may be a useful strategy.

What about ECM peptides as therapeutic options?

One way to bypass the non-selective nature of MMP inhibitors is to focus on the downstream substrates processed by MMPs. Because MMPs process substrates that are both detrimental

and beneficial to the MI response, selective MMP inhibition may not be clinically desirable. Instead of focusing on inhibiting MMP-2 or MMP-3 or MMP-9, perhaps a more practical strategy will be to focus on the substrates processed by MMPs. For example, MMP-9 processes fibronectin to release a peptide that contains the RGD sequence, and RGD has been extensively evaluated in cell culture and in vivo experiments. Randall Lee's group recently showed that rats injected with RGD modified alginate at 5 weeks following ischemia/reperfusion had improved function compared to uninjected hearts, and this benefit was due to stimulation of the angiogenic response. [60] These data suggest that over-expressing RGD may serve a net beneficial function. Given the many ECM and non-ECM substrates available for MMP processing, this line of questioning remains fruitful.

Conclusion

In summary, the ECM is a dynamic component involved in every stage of remodeling in the infarcted myocardium. While many studies have documented the qualitative and quantitative changes in individual components, few have approached the problem of remodeling by dealing with the complexity of the interactions between the cellular and acellular components. From these studies, it is anticipated that new insights into the potential regulatory nature of the ECM will provide new therapeutic insights.

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Figure 1.

Post-MI, the net ECM response is determined by the balance between ECM construction and destruction. If ECM accumulation predominates, then fibrosis can predispose the LV to congestive heart failure and arrhythmias. If ECM degradation predominates, then wall thinning can lead to LV aneurysm and rupture. Both pathways interact and feed on each other.

Figure 2.

Infarct size predicts the average, but not the individual, LV remodeling response. For 65 C57/BL6J mice examined at day 7 post-MI, infarct size positively associated with the change in end diastolic dimension. However, for mice within a similar infarct size range (40–50% infarct size is highlighted by the dashed box), the response was not predictable.

Table 1

Candidate Plasma ECM Biomarkers of Cardiac Remodeling

Collagen I telopeptides (CITP)
Collagen III telopeptide (CIITP)
Connective Tissue Growth Factor
Fibronectin
Granzyme B
Matrix Metalloproteinase-9
Tenascin C
Thrombospondin-1
Tissue Inhibitor of Metalloproteinase-1
Transforming Growth Factor β

Table 2

Summary of ECM and MMP Null and Transgenic Mice Post-MI Studies

Factor	Post-MI Effects
Collagenase Resistant Collagen Transgenic [46]	No effect seen on early post-MI remodeling
Osteopontin Null [47]	Increased LV dilation and reduced collagen deposition in remote and infarct regions
Secreted Protein Acidic and Rich in Cysteine Null [48]	Increased cardiac rupture and LV dysfunction
Thrombospondin-1 Null reviewed in [49]	Sustained upregulation of chemokines and cytokines; increased macrophage and myofibroblast density; more extensive remodeling
MMP-2 Null [50]	Decreased early rupture rate and improved late survival and decreased LV dilation
MMP-7 Null [10]	Decreased connexin 43 processing, decreased arrhythmias, and improved survival
MMP-9 Null [16]	Decreased remodeling and collagen deposition, decreased macrophage infiltration, increased angiogenesis
TIMP-1 Null [51]	Increased LV end diastolic volume and pressure; more pronounced hypertrophic response
TIMP-3 Null [52]	Increased mortality, LV dilation, apoptosis, blood vessel numbers; decreased collagen

Table 3

Questions that remain to be answered

1	Do any of the other 25 MMPs that have not been examined change in a significant way post-MI? Very little information is available for MMPs identified after MMP-14, and these MMPs (particularly the other membrane type MMPs) may influence remodeling.
2	What roles do matricryptins play in post-MI remodeling? To date, most matricryptin functions that have been elucidated pertain to angiogenesis, but matricryptin regulation of fibrosis and inflammation is likely.
3	What is the complete catalogue of ECM changes that occur post-MI? Is collagen I degradation the only one that matters? Multiple ECM proteins are degraded and synthesized in the post-MI setting, but little consideration has been given to many of these proteins.
4	What is the complete catalogue of MMP substrates in the post-MI LV? While numerous ECM and non-ECM (cytokines, growth factors, and membrane proteins) MMP substrates are known, we still need to know whether the most important (vs most abundant) have been identified.
5	Do ADAM family members contribute to cardiac remodeling? Studies for the ADAM protease family in the post-MI setting lag behind the MMP field by at least five years.