Published in final edited form as:

Congest Heart Fail. 2013 July ; 19(4): E5–E8. doi:10.1111/chf.12023.

Left ventricular remodeling: one small step for the extracellular matrix will translate to a giant leap for the myocardium

Andriy Yabluchanskiy, Ph.D^{1,2,4}, Robert J. Chilton, DO, FACC^{1,3}, and Merry L. Lindsey, Ph.D^{1,2,4}

¹San Antonio Cardiovascular Proteomics Center

²Barshop Institute for Longevity and Aging Studies

³Division of Cardiology

⁴Division of Geriatrics, Gerontology and Palliative Medicine, Department of Medicine

Keywords

myocardial infarction; left ventricular remodeling; extracellular matrix; matrix metalloproteinases

Introduction

Myocardial infarction (MI) is initiated by an acute disruption of blood supply. Prolonged ischemia in the region downstream of the occlusion culminates with tissue necrosis. Inflammation follows the induction of necrosis and orchestrates the wound healing response. Key components of wound healing are the recruitment and engagement of leukocytes and the reorganization of the extracellular matrix (ECM). Due to the poor regenerative capacity of the heart, cardiomyocyte loss is compensated by the generation of a collagen-based ECM scar.

The early post-MI scar is mainly composed of collagen III, but as the collagen scar matures, the ratio of collagen types changes towards a predominance of collagen I. Long-term outcomes post-MI depend on the quality of scar formed, in terms of quantity, quality, and extent of cross-linking. The irreversible changes in the biomechanics and geometry of the left ventricle (LV) are collectively known as LV remodeling, and adverse LV remodeling stimulates the progression to congestive heart failure.

The most promising treatments for the MI patient involve detection pre-MI to avert ischemia, early diagnosis to limit myocyte loss during ischemia, or targeting mechanisms that occur during resolution of the inflammatory and fibrotic responses to prevent the progression to heart failure (Figure 1). As such, understanding how the ECM influences remodeling will identify novel targets for clinical intervention.

Reorganization of the ECM during post-MI remodeling

The adult mammalian heart is characterized by a myocardium that is highly organized with an overlapping layered structure, and the ECM scaffold surrounds and support the cells of the myocardium. ECM is mainly composed of fibrillar collagen that provides structural

Address for Correspondence: Merry L. Lindsey, Ph.D., Department of Medicine, Division of Geriatrics, Gerontology and Palliative Medicine, The University of Texas Health Science Center at San Antonio, 15355 Lambda Drive, MC 7755, San Antonio, TX 78245, phone: 210-562-6052, fax: 210-562-6110, lindseym@uthscsa.edu.

strength through its three-dimensional structure that interdigitates between cardiac muscle fibers. As such, the ECM plays a pivotal role in the transmission of contractile forces. Collagen I accounts for approximately 70–85% of total cardiac collagen in the LV and provides tensile strength, whereas collagen III accounts for about 10% of total cardiac collagen. The thin collagen III fibers maintain the elasticity of the ECM network.¹ In addition to collagen and other glycoproteins, glycosaminoglycans, basement membrane components, and proteoglycans are components of the ECM.² In addition to providing an environment for cells, ECM also serves as a reservoir for growth factors and proteases. Under normal conditions, ECM homeostasis is maintained by signaling interactions between cardiac cells and matrix proteins through cell surface receptors, e.g., integrins.

Prolonged ischemia that turns into irreversible ischemia ultimately leads to cell death, and this event requires ECM network reorganization. Key players in the degradation of ECM are the matrix metalloproteinases (MMPs). Neutrophils are a rich source of MMPs, and neutrophil infiltration occurs as early as 15 minutes after the initiation of reperfusion.³ MMPs cleave collagens and other ECM proteins at site specific locations to generate ECM fragments.⁴ Early post-MI, this degradation of ECM is accompanied by the continuous generation of a fibrin-based provisional matrix that provides structural support for the infarct region.

Necrotic cell debris and matrix fragments activate membrane-bound toll-like receptors, the complement system, high-mobility group box 1, and the receptor for advanced glycation end-products, all of which play important roles in the early steps of the wound healing response, by stimulating the generation of reactive oxygen species and initiating the nuclear factor κ B pathway to produce inflammatory cytokines.^{5,6} Cytokines attract inflammatory cells into the infarcted region, where these cells are activated to initiate scavenging and repair processes. Macrophages infiltrate beginning at day 3 post-MI, serving to engulf necrotic myocytes and apoptotic neutrophils, as well as promote anti-inflammatory processes. Activated macrophages also release growth factors to stimulate collagen synthesis and fibroblast activation, which stimulates formation of the ECM scar.⁷ Over time, the provisional fibrin-based matrix is degraded by proteolytic enzymes and replaced by a secondary fibroblast-derived matrix containing several ECM proteins, including fibronectin and hyaluronan. At this point, a number of matricellular proteins are released by both fibroblasts and macrophages to orchestrate the signaling pathways responsible for infarct repair.

Matricellular proteins, unlike fibrillar ECM components, are not involved in structural roles but rather modulate cell function by interacting with cell-surface receptors, proteases, hormones, and other bioeffector molecules, as well as with structural matrix proteins such as collagens.³ Among the most studied matricellular proteins are thrombospondin (TSP)-1, -2 and -4, secreted protein acidic and rich in cysteine, tenascin-C and -X, osteopontin, periostin, and members of the CCN family (including CCN1 and CCN2/connective tissue growth factor).³

The expression of matricellular proteins in the normal adult myocardium is low and generally is only observed during development or as a response to injury. In the infarct environment, matricellular protein expression rapidly increases. Matricellular proteins stimulate cell migration, proliferation, and adhesion, but also serve crucial roles in mediating the inflammatory response. For example, TSP-1, an important transforming growth factor beta activator with potent angiostatic and anti-inflammatory properties, is significantly increased in the border area between the infarct and remote areas and serves to limit infarct expansion.⁸

In the infarct environment, cardiac fibroblast cells are important sources of ECM, MMPs, and growth factors that stimulate angiogenesis.⁹ While the source of the cardiac myofibroblast is controversial, resident and infiltrating cells can undergo phenotypic change to differentiate into myofibroblasts.^{10,11} Myofibroblasts in particular produce robust amounts of ECM that provides structural support to the infarcted region. Fibroblasts also initiate the contraction of the provisional matrix deposited in the affected region. Alterations in the composition of ECM over time mediate multiple components of the inflammatory and fibrotic responses.

Targeting ECM proteins

Treatment strategies for the MI patient have dramatically improved over the past 40 years. The current optimal approach includes reperfusion of the ischemic myocardium within one hour of symptom onset. For approximately 20% of patients, however, reperfusion is either not successful or not possible, and this translates to approximately 250,000 patients each year with non-reperfused infarcts.¹² In addition, adverse LV remodeling progressing to heart failure occurs in approximately 5% of MI patients who have received optimum therapy, and this percentage approaches 40% for MI patients with co-morbidities such as advanced age or diabetes.¹³ Five year mortality rates for congestive heart failure remains at 50%, which underscores the need for additional therapies to impede the progression to heart failure.

Understanding ECM turnover during LV remodeling and targeting ECM proteins will likely provide fruitful targets to develop novel treatment strategies for post-MI patients. A list of ECM proteins known to be altered post-MI is provided in Table 1. To date, very limited progress has been achieved in targeting specific ECM components as a therapeutic option post-MI.

A search for direct MMP inhibition began in late 1970s.¹⁴ At that time, however, only a few MMPs had been identified, which made selectivity difficult to assess. The first several generations of MMP inhibitors also had very poor bioavailability and numerous side effects, which tempered enthusiasm for this therapeutic approach.^{15,16} Over the past two decades, a number of MMP inhibitors have been tested. Of all MMP inhibitors tested to date, only doxycycline (Periostat) has been FDA-approved.^{17–19}

Most of the therapies, such as ACE inhibition or beta-adrenergic receptor blockade have both direct and indirect effects on ECM.

ECM-derived peptide fragments provide one such novel therapeutic option in the treatment of post-MI patients (Table 2). ECM fragments affect cellular response and behavior in other models of wound healing, however little is known about their roles post-MI.^{20–23} The Lee lab, for example, has shown that ECM fragments stimulate angiogenesis and significantly improve cardiac function in a mouse model of MI.²⁴ Further exploration of the role of ECM fragments in stimulating cardiac inflammatory cells, fibroblasts, or other endogenous cell types will likely provide new strategies to optimize scar formation post-MI.

Several ECM-derived fragments from collagen IV have been used as scaffolds for the infarcted myocardium, to provide structural support. These ECM fragments were shown to interact with themselves and the infarct scar to form an enhanced scaffold matrix.²⁵ Future methods of injecting polymers into the infarcted hearts will likely also be a promising strategy. For example, intramyocardial injection of fibrin significantly improved cardiac function after MI, indicating the formation of a scaffold provides support for the infarct region.^{26,27} Whether the injection of ECM fragments also stimulate cell signaling has not been explored. Understanding what role exogenously administered ECM fragments have significant potential to improve current treatment schemes. Further insights into the

molecular and signaling pathways may bring new breakthroughs and capabilities to influence the early generation of stable scar.

Acknowledgments

We acknowledge support from NIH/NHLBI HHSN 268201000036C (N01-HV-00244) for the San Antonio Cardiovascular Proteomics Center and R01 HL075360, the Max and Minnie Tomerlin Voelcker Fund, and the Veteran's Administration (Merit) to MLL.

References

1. Bishop JE, Laurent GJ. Collagen turnover and its regulation in the normal and hypertrophying heart. *European heart journal*. May; 1995 16(Suppl C):38–44. [PubMed: 7556271]
2. Lindsey ML, Mann DL, Entman ML, Spinale FG. Extracellular matrix remodeling following myocardial injury. *Annals of medicine*. 2003; 35(5):316–326. [PubMed: 12952018]
3. Frangogiannis NG. Matricellular proteins in cardiac adaptation and disease. *Physiological reviews*. Apr; 2012 92(2):635–688. [PubMed: 22535894]
4. Villarreal FJ, Griffin M, Omens J, Dillmann W, Nguyen J, Covell J. Early short-term treatment with doxycycline modulates postinfarction left ventricular remodeling. *Circulation*. Sep 23; 2003 108(12):1487–1492. [PubMed: 12952845]
5. Mann DL. The emerging role of innate immunity in the heart and vascular system: for whom the cell tolls. *Circulation research*. Apr 29; 2011 108(9):1133–1145. [PubMed: 21527743]
6. Andrassy M, Volz HC, Igwe JC, et al. High-mobility group box-1 in ischemia-reperfusion injury of the heart. *Circulation*. Jun 24; 2008 117(25):3216–3226. [PubMed: 18574060]
7. Vanhoutte D, Schellings M, Pinto Y, Heymans S. Relevance of matrix metalloproteinases and their inhibitors after myocardial infarction: a temporal and spatial window. *Cardiovascular research*. Feb 15; 2006 69(3):604–613. [PubMed: 16360129]
8. Bornstein P. Matricellular proteins: an overview. *Journal of cell communication and signaling*. Dec; 2009 3(3–4):163–165. [PubMed: 19779848]
9. van Nieuwenhoven FA, Turner NA. The role of cardiac fibroblasts in the transition from inflammation to fibrosis following myocardial infarction. *Vascular pharmacology*. Aug 3.2012
10. Dobaczewski M, de Haan JJ, Frangogiannis NG. The Extracellular Matrix Modulates Fibroblast Phenotype and Function in the Infarcted Myocardium. *Journal of cardiovascular translational research*. Sep 7.2012
11. Ma Y, Halade GV, Lindsey ML. Extracellular Matrix and Fibroblast Communication Following Myocardial Infarction. *Journal of cardiovascular translational research*. Aug 28.2012
12. Gharacholou SM, Alexander KP, Chen AY, et al. Implications and reasons for the lack of use of reperfusion therapy in patients with ST-segment elevation myocardial infarction: findings from the CRUSADE initiative. *American heart journal*. May; 2010 159(5):757–763. [PubMed: 20435183]
13. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. Feb 1; 2011 123(4):e18–e209. [PubMed: 21160056]
14. Hodgson J. Remodeling MMPs. *Biotechnology (N Y)*. Jun; 1995 13(6):554–557. [PubMed: 9634794]
15. Bachmann LH, Stephens J, Richey CM, Hook EW 3rd. Measured versus self-reported compliance with doxycycline therapy for chlamydia-associated syndromes: high therapeutic success rates despite poor compliance. *Sexually transmitted diseases*. May; 1999 26(5):272–278. [PubMed: 10333280]
16. Renkiewicz R, Qiu L, Lesch C, et al. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. *Arthritis and rheumatism*. Jun; 2003 48(6):1742–1749. [PubMed: 12794843]
17. Skiles JW, Gonnella NC, Jeng AY. The design, structure, and therapeutic application of matrix metalloproteinase inhibitors. *Current medicinal chemistry*. Mar; 2001 8(4):425–474. [PubMed: 11172697]

18. Whittaker M, Floyd CD, Brown P, Gearing AJ. Design and therapeutic application of matrix metalloproteinase inhibitors. (Chem. Rev. 1999, 99, 2735–2776. Published on the web september 8, 1999). Chemical reviews. Jul 11; 2001 101(7):2205–2206. [PubMed: 11749369]
19. Peterson JT. Matrix metalloproteinase inhibitor development and the remodeling of drug discovery. Heart failure reviews. Jan; 2004 9(1):63–79. [PubMed: 14739769]
20. Barilla ML, Carsons SE. Fibronectin fragments and their role in inflammatory arthritis. Seminars in arthritis and rheumatism. Feb; 2000 29(4):252–265. [PubMed: 10707992]
21. Homandberg GA. Potential regulation of cartilage metabolism in osteoarthritis by fibronectin fragments. Frontiers in bioscience : a journal and virtual library. Oct 15.1999 4:D713–730. [PubMed: 10525477]
22. Poole AR, Nelson F, Dahlberg L, et al. Proteolysis of the collagen fibril in osteoarthritis. Biochemical Society symposium. 2003; (70):115–123. [PubMed: 14587287]
23. Weathington NM, van Houwelingen AH, Noerager BD, et al. A novel peptide CXCR ligand derived from extracellular matrix degradation during airway inflammation. Nature medicine. Mar; 2006 12(3):317–323.
24. Mihardja SS, Yu J, Lee RJ. Extracellular matrix-derived peptides and myocardial repair. Cell adhesion & migration. Mar-Apr;2011 5(2):111–113. [PubMed: 21048428]
25. Mihardja SS, Gao D, Sievers RE, et al. Targeted in vivo extracellular matrix formation promotes neovascularization in a rodent model of myocardial infarction. PloS one. 2010; 5(4):e10384. [PubMed: 20442783]
26. Yu J, Christman KL, Chin E, Sievers RE, Saeed M, Lee RJ. Restoration of left ventricular geometry and improvement of left ventricular function in a rodent model of chronic ischemic cardiomyopathy. The Journal of thoracic and cardiovascular surgery. Jan; 2009 137(1):180–187. [PubMed: 19154923]
27. Christman KL, Fok HH, Sievers RE, Fang Q, Lee RJ. Fibrin glue alone and skeletal myoblasts in a fibrin scaffold preserve cardiac function after myocardial infarction. Tissue engineering. Mar-Apr; 2004 10(3–4):403–409. [PubMed: 15165457]
28. Cleutjens JP, Verluyten MJ, Smiths JF, Daemen MJ. Collagen remodeling after myocardial infarction in the rat heart. Am J Pathol. 1995; 147(2):325–338. [PubMed: 7639329]
29. Lopez B, Gonzalez A, Hermida N, Valencia F, de Teresa E, Diez J. Role of lysyl oxidase in myocardial fibrosis: from basic science to clinical aspects. American journal of physiology. Heart and circulatory physiology. Jul; 2010 299(1):H1–9. [PubMed: 20472764]
30. Casscells W, Kimura H, Sanchez JA, Yu ZX, Ferrans VJ. Immunohistochemical study of fibronectin in experimental myocardial infarction. The American journal of pathology. Oct; 1990 137(4):801–810. [PubMed: 2221013]
31. McCurdy SM, Dai Q, Zhang J, et al. SPARC mediates early extracellular matrix remodeling following myocardial infarction. American journal of physiology. Heart and circulatory physiology. Aug; 2011 301(2):H497–505. [PubMed: 21602472]
32. Shimazaki M, Nakamura K, Kii I, et al. Periostin is essential for cardiac healing after acute myocardial infarction. The Journal of experimental medicine. Feb 18; 2008 205(2):295–303. [PubMed: 18208976]
33. Dobaczewski M, Bujak M, Zymek P, Ren G, Entman ML, Frangogiannis NG. Extracellular matrix remodeling in canine and mouse myocardial infarcts. Cell and tissue research. Jun; 2006 324(3):475–488. [PubMed: 16496177]
34. Tamaoki M, Imanaka-Yoshida K, Yokoyama K, et al. Tenascin-C regulates recruitment of myofibroblasts during tissue repair after myocardial injury. The American journal of pathology. Jul; 2005 167(1):71–80. [PubMed: 15972953]
35. Frangogiannis NG, Ren G, Dewald O, et al. Critical role of endogenous thrombospondin-1 in preventing expansion of healing myocardial infarcts. Circulation. Jun 7; 2005 111(22):2935–2942. [PubMed: 15927970]
36. Knowlton AA, Connelly CM, Romo GM, Mamuya W, Apstein CS, Brecher P. Rapid expression of fibronectin in the rabbit heart after myocardial infarction with and without reperfusion. The Journal of clinical investigation. Apr; 1992 89(4):1060–1068. [PubMed: 1556175]

37. Wiggers H, Klebe T, Heickendorff L, et al. Ischemia and reperfusion of the porcine myocardium: effect on collagen. *Journal of molecular and cellular cardiology*. Jan; 1997 29(1):289–299. [PubMed: 9040044]
38. Cannon RO 3rd, Butany JW, McManus BM, et al. Early degradation of collagen after acute myocardial infarction in the rat. *The American journal of cardiology*. Aug; 1983 52(3):390–395. [PubMed: 6869292]
39. Imanaka-Yoshida K, Hiroe M, Nishikawa T, et al. Tenascin-C modulates adhesion of cardiomyocytes to extracellular matrix during tissue remodeling after myocardial infarction. *Laboratory investigation; a journal of technical methods and pathology*. Jul; 2001 81(7):1015–1024.
40. Ip JE, Wu Y, Huang J, Zhang L, Pratt RE, Dzau VJ. Mesenchymal stem cells use integrin beta1 not CXCR4 chemokine receptor 4 for myocardial migration and engraftment. *Molecular biology of the cell*. Aug; 2007 18(8):2873–2882. [PubMed: 17507648]
41. Trueblood NA, Xie Z, Communal C, et al. Exaggerated left ventricular dilation and reduced collagen deposition after myocardial infarction in mice lacking osteopontin. *Circulation research*. May 25; 2001 88(10):1080–1087. [PubMed: 11375279]
42. Oka T, Xu J, Kaiser RA, et al. Genetic manipulation of periostin expression reveals a role in cardiac hypertrophy and ventricular remodeling. *Circulation research*. Aug 3; 2007 101(3):313–321. [PubMed: 17569887]
43. Komatsubara I, Murakami T, Kusachi S, et al. Spatially and temporally different expression of osteonectin and osteopontin in the infarct zone of experimentally induced myocardial infarction in rats. *Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology*. Jul-Aug;2003 12(4):186–194. [PubMed: 12826287]
44. Sezaki S, Hirohata S, Iwabu A, et al. Thrombospondin-1 is induced in rat myocardial infarction and its induction is accelerated by ischemia/reperfusion. *Exp Biol Med (Maywood)*. Oct; 2005 230(9):621–630. [PubMed: 16179730]
45. Lal A, Veinot JP, Ganten D, Leenen FH. Prevention of cardiac remodeling after myocardial infarction in transgenic rats deficient in brain angiotensinogen. *Journal of molecular and cellular cardiology*. Sep; 2005 39(3):521–529. [PubMed: 15950985]
46. Morishita N, Kusachi S, Yamasaki S, Kondo J, Tsuji T. Sequential changes in laminin and type IV collagen in the infarct zone--immunohistochemical study in rat myocardial infarction. *Japanese circulation journal*. Feb; 1996 60(2):108–114. [PubMed: 8683853]
47. Chan CY, Chen YS, Lee HH, et al. Erythropoietin protects post-ischemic hearts by preventing extracellular matrix degradation: role of Jak2-ERK pathway. *Life sciences*. Aug 9; 2007 81(9):717–723. [PubMed: 17707437]

Figure 1.

Table 1

ECM proteins known to change post-MI.^{28–47} SPARC- secreted protein acidic and rich in cysteine.

ECM protein
Collagen I
Collagen III
Fibronectin
Hyaluronan
Laminin
Osteopontin
Periostin
SPARC
Tenascin C
Thrombospondin-1

Table 2

Effects of ECM-derived fragments *in vitro* and *in vivo* in models of wound healing and myocardial infarction.^{18,19,22–27}

ECM	Peptide	Effects
Collagen IV	Hep I [TAGSCLRKFSTMY-OH]	Promotes endothelial cell adhesion, migration, and proliferation Interacts with α_2 , α_3 , and β_1 integrin subunits Interacts with full-length Col IV Increases capillary density in the infarcted region Reduces infarct size
	Hep III [GEFYFDLRLKGDKY-OH]	Promotes endothelial cell adhesion, migration, and proliferation Interacts with $\alpha_2\beta_1$ and $\alpha_3\beta_1$ integrins Increases capillary density in the infarcted region Reduces infarct size and improves LV function
Elastin	Val-Gly-Val-Ala-Pro-Gly	Stimulates chemotaxis of fibroblasts and monocytes
Fibronectin	RGD [GRGDSPASSPISC-OH]	Promotes endothelial cell adhesion, migration, and proliferation Interacts with $\alpha_v\beta_3$ integrin Increases capillary density in the infarcted region Reduces infarct size
	120-kDa cell-binding FN fragments	Decreases VLA-5 receptor expression Reduces monocyte migration
Laminin	LGTPG and YIGSR	Inhibits macrophage migration
	A119 [LSNIDYILIKAS]	Promotes cell attachment, neurite, outgrowth, and amyloid like fibril formation, and binds to syndecans
	A13 and C16	Highly angiogenic, binds to integrins $\alpha\beta_3$ and $\alpha_5\beta_1$, stimulates fibroblast migration and wound contraction