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Changes in the Myocardial Interstitium and Contribution to the Progression of Heart Failure

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SYNOPSIS

The myocardial interstitium is highly organized and orchestrated whereby small disruptions in composition, spatial relationships, or content lead to altered myocardial systolic and/or diastolic performance. These changes in extracellular matrix structure and function are important in the progression to heart failure in pressure overload hypertrophy (POH), dilated cardiomyopathy (DCM), and ischemic heart disease. The myocardial interstitium is not a passive entity, but rather a complex and dynamic microenvironment which represents an important structural and signaling system within the myocardium.

Keywords

interstitium; extracellular matrix; heart failure; pressure overload hypertrophy; dilated cardiomyopathy; myocardial infarction

INTRODUCTION

With a prolonged cardiovascular stress or pathophysiological stimuli, a cascade of structural events occurs defined as myocardial remodeling, which occurs as a continuum of changes in the structure and function of the myocardium. It has been shown that adverse left ventricular (LV) myocardial events affects cellular signaling and extracellular signaling processes. Changes occurring in the cellular constituents of the myocardium that accompany remodeling are discussed in a previous chapter; therefore, the significant alterations in the structure and composition of the myocardial interstitium will be the focus of this chapter. Historically, the myocardial interstitium was considered a static entity with a passive and nonresponsive structure comprised of a fibrillar collagen network; however, it has now been demonstrated that it is a dynamic structure which plays a fundamental role in myocardial

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adaptation to a pathological stress facilitating the remodeling process. Therefore, the purpose of this chapter is threefold. First, present an up-to-date overview of myocardial extracellular matrix structure and function. Second, briefly demonstrate how the myocardial interstitium is altered in important disease states which can progress to chronic heart failure: POH in context of hypertension and aortic stenosis, ischemic heart disease in the context myocardial infarction (MI), and DCM. Third, identify potential diagnostic and therapeutic strategies relevant to myocardial matrix remodeling in the context of these cardiac disease states.

MYOCARDIAL INTERSTITIUM STRUCTURE AND FUNCTION

Traditionally, the myocardial interstitium was thought to be comprised mainly of fibrillar collagen; however, it is now known that there is a wide array of molecules besides collagen which compose greater than 95% of the extracellular matrix.^{1–2} Specifically, it contains noncollagen matrix proteins, proteoglycans, glycosaminoglycans, and a large reservoir bioactive signaling molecules.^{3–16} The interstitium is highly organized and orchestrated whereby small disruptions in composition, spatial relationships, or content lead to altered myocardial systolic and/or diastolic performance. For example, the fibrillar collagens ensure structural integrity of adjoining myocytes, provide the means by which myocyte shortening is translated into overall left ventricular pump function, and are essential for maintaining alignment of myofibrils within the myocyte through a collagen-integrin-cytoskeletal-myofibril relation.^{17–23} Using a papillary muscle preparation, Baicu et al. demonstrated that proteolytic digestion of the myocardial interstitium reduces the extent and velocity of cardiomyocyte shortening. In contrast, isolated cardiomyocyte shortening was preserved.²⁴ These findings are summarized in Figure 1 and underscore the importance of the interstitium to transduce myocyte shortening into overall myocardial ejection. This section will review the different molecules that comprise and contribute to the structure and function of the myocardial extracellular matrix. While this chapter is not meant to be an exhaustive overview, it will provide the prototypical examples to illustrate the diversity of constituents which exist within the myocardial interstitium.

Structural Matrix Proteins

Structural Matrix Proteins are both collagen and non-collagen proteins which comprise the organization of the myocardial interstitium. The non-collagen matrix proteins comprise the basement membrane, which forms anchoring points for the fibrillar collagen matrix and contact points for other proteoglycans within the extracellular matrix.

Fibrillar Collagen—Initially, the fibrillar collagen matrix, comprised mainly of collagen I and III, was considered to be a relatively static complex, but it is now well understood that these structural proteins can undergo rapid degradation and turnover.^{1, 17–23, 25} Early in its modification, collagen fibril formation entails post-translational changes where the aminoterminal and carboxyterminal of the pro-collagen fibril is cleaved by proteolytic reactions. These collagen-derived peptides (procollagen type III aminoterminal propeptide or PIIP and procollagen type I carboxyterminal propeptide or PIP, respectively) can be detected in the plasma and used as biomarkers of matrix synthesis, which will be discussed in a later section. The result of these modifications causes a necessary conformational change for collagen fibril cross-linking and triple helix formation.²⁶ While the newly formed, uncross-linked collagen fibrils are vulnerable to degradation, the triple helical collagen fiber is resistant to non-specific proteolysis and further degradation requires specific enzymatic cleavage, as will be discussed in a subsequent paragraph. The importance of collagen cross-linking with respect to overall left ventricular geometry and function has been demonstrated in several animal models and clinical studies.^{17, 27–30} For instance,

inhibition of lysyl hydroxylase a critical enzyme in collagen cross-linking by β -aminopropionitrile results in a collagen disease of humans known as Lathyrism.³¹ Treatment with β -aminopropionitrile in a porcine model causes a decrease in collagen cross-linking and collagen content resulting in a decrease in myocardial stiffness.²⁹ In patients with severe left ventricular dilation (DCM), reduced collagen cross-linking of fibrils have been reported; thus, not only is total collagen content relevant, but the degree of collagen cross-linking holds functional and clinical importance in the context of heart failure.^{17, 29–30}

Integrins—The integrins are a family of transmembrane proteins which aide in multiple functions affecting myocardial structure and function.^{20–21, 25} The binding interface with proteins comprising the basement membrane consists of integrins, which directly influences myocyte growth and geometry through ligand binding. More specifically, integrins affect cell migration and survival during both normal cardiac development and myocardial remodeling. While there is a long list of integrin ligands, it most commonly acts as a receptor for collagen I and III, laminin, fibronectin, and thrombospondin in the basement membrane.^{2, 32} While it has been determined that genetic polymorphisms affect the concentration of integrins within the basement membrane in platelets, this relationship remains to be studied in the myocardial interstitium where it may play an important role in the setting of cardiac disease.³²

Laminin and Fibronectin—Laminin and Fibronectin are heavily glycosylated glycoproteins in the basement membrane of cardiac myocytes that associates with many myocardial interstitium factors, including fibrillar collagen and cell membrane receptors. For example, the change in content and distribution of these glycoproteins will affect hydration within the extracellular space and subsequent myocardial compliance.^{33–36} These highly charged molecules within the myocardial interstitium result in the formation of a hydrated gel which serves as a reservoir for signaling molecules and bioactive peptides. Furthermore, fibronectin binds to integrins which activate a profibrotic pathway that leads to extracellular matrix deposition.³⁷ While laminin and fibronectin play a role in determining receptor to ligand interaction within the myocardial interstitium, these glycoproteins have been over looked in the context of heart failure.

Matrix Signaling and Associative Proteins

It is becoming recognized that the myocardial interstitium is comprised of a vast array of non-structural proteins. Specifically, these proteins influence collagen fibril assembly and morphology as well as regulating cell to extracellular matrix signaling. Some illustrative examples of the wide portfolio of matrix proteins are provided below.

SPARC—Secreted protein and rich in cysteine, SPARC (also known as osteonectin), is a matricellular protein that serves as an accessory protein made of three modular domains which regulate matrix assembly into mature fibrils, specifically collagen types I and III.^{38–39} In a transgenic mouse model, SPARC gene deletion is associated with impaired collagen production and collagen fibril disorganization. Overall, there is an inefficiency of incorporation of collagen into fibrils in the absence of SPARC, which results in premature myocardial rupture.⁴⁰ With overexpression of SPARC, enhanced collagen deposition is noted with increased formation of mature fibers that leads to ventricular hypertrophy.^{39, 41}

Thrombospondin—Thrombospondin (TSP) is a family of glycoproteins that participate in the communication between the cardiomyocyte and the myocardial interstitium in both embryogenesis and cardiac disease states such as POH and DCM.^{42–44} Specifically, TSP appears to modulate cell-to-matrix interactions through the coalescence of membrane proteins and signaling molecules at specific contact points on the cell surface.^{42, 45–46} One

of the most important functions of TSP is its downstream induction of fibrillar collagen expression and synthesis.^{44, 46} In a murine model with gene deletion of TSP, multiple processes were affected in the interstitium including decreased collagen cross-linking and increased matrix protease activity.⁴⁷ Ultimately, the lack of TSP caused a decrease in collagen content, and combined with the decrease in collagen cross-linking, LV dilation occurred with increasing rates of myocardial rupture.⁴³

Galectin-3—The beta-galactoside binding protein, galectin-3, has been identified as an interstitial chaperone protein that regulates extracellular matrix growth, structure and function in cardiac disease such as in POH.^{48–49} Expression and activation of galectin-3 is stimulated by cardiac inflammation, specifically the macrophages and neutrophils. Galectin-3 binds to a number of interstitial ligands that include fibrillar collagens, basement membranes, and integrins, and this in turn affects collagen synthesis and degradation.⁴⁹

Transforming Growth Factor—As a family of four regulatory cytokine (beta1, beta2, and beta3), transforming growth factor (TGF) plays an important role in stimulating production of extracellular matrix in the myocardium.^{50–53} For the purposes of this chapter, TGF will be referred to in general terms. TGF is released in an inactive form in the interstitial space where it is activated by proteolytic cleavage and has been shown to influence a wide array of processes including inflammation, apoptosis, cardiac development and myocardial remodeling.^{50–53} Active TGF binds to TGF type I and type II receptors and results in downstream activation of a variety of events, which prototypically include fibrillar collagen expression.^{50–51} In a transgenic model of TGF over-expression, increased collagen I and III deposition occurred whereas in a mouse MI model, inhibition of TGF decreased collagen deposition and increased LV dilation.^{54–55} Thus, TGF appears to be a critical signaling molecule in maintaining normal extracellular matrix homeostasis as well as regulating increased collagen expression in myocardial remodeling during cardiac disease.

Matrix Metalloproteinases—The *matrix metalloproteinases (MMPs)* are a family of zinc dependent myocardial interstitium proteases which play a number of roles in myocardial remodeling.^{56–61} Over 25 distinct human MMPs have been identified and characterized; expression of MMPs has been shown to be ubiquitous in tissue remodeling processes.^{58–61} The identifications of specific MMPs in cardiac disease states are listed in Table 1. Historically, it was thought that MMPs were only involved in proteolysis of the myocardial interstitium; however, it is now well understood that MMPs possess a large portfolio of biological functions pertaining to myocardial remodeling.^{60–62} Initially, MMPs are synthesized as inactive zymogens that are secreted as proenzymes into the myocardial interstitium. The proenzyme form then binds specific myocardial interstitium proteins and remains enzymatically quiescent until the pro-peptide domain is cleaved. While the MMPs were initially thought to be secreted only in a soluble, pro-enzyme form, a unique sub-family of MMPs, the membrane-type matrix metalloproteinases (MT-MMPs), are a fully active enzyme once inserted into the cell membrane after secretion.⁵⁶ Since the MT-MMPs are inserted into the cell membrane already activated, it can serve as a localized, pericellular site of myocardial interstitium proteolytic activity. Multiple clinical studies of cardiac disease have shown a clear cause and effect relationship between MMPs and myocardial interstitial remodeling and ventricular dysfunction, which will be discussed in later sections of this chapter.

Tissue Inhibitors of Matrix Metalloproteinases—A critical control point of MMP activity is through the inhibition of the activated enzyme by the actions of a group of specific MMP inhibitors termed tissue inhibitors of matrix metalloproteinases (TIMPs).^{63–65} In general, TIMPs are low molecular weight proteins that bind to the catalytic domain of

active MMPs and thereby prevent access to substrates. Historically, it has been thought that the predominant role of TIMPs is the inhibition of active MMPs; however, studies have demonstrated TIMPs to also be involved in MMP activation along with actions independent of MMPs.^{66–67}

EXTRACELLULAR REMODELING IN CARDIAC DISEASE

The etiologies that give rise to heart failure are diverse as are the structural and functional changes of prototypical etiologies. Stylized summations of the structural changes are depicted in Figure 3 as seen in POH, DCM, and MI.

Myocardial Remodeling with Pressure Overload Hypertrophy

Matrix Remodeling and LV Function—In addition to myocyte hypertrophy, the hallmark of myocardial structural remodeling with POH is extracellular matrix accumulation.^{68–74} Moreover, prolonged POH is associated with significantly increased collagen accumulation between individual myocytes and myocyte fascicles, and the highly organized architecture of the myocardial interstitium is replaced with a thickened, poorly organized structure. Clinical studies of POH showed increased myocardial interstitial matrix accumulation and with increased LV stiffness.^{71–74} For example, increased collagen accumulation in LV myocardial samples taken from patients with POH secondary to aortic stenosis and is associated with increased myocardial stiffness.⁷¹ As shown in the histopathologic images of Figure 2A, amplification of matrix accumulation occurs and causes the fundamental pathophysiological change seen in POH, myocardial stiffness, which gives rise to impairments in diastolic filling as demonstrated in Figure 2B.^{75–76} Therefore, in POH, the structural abnormalities within the matrix leads to impaired LV filling and increased filling pressures such as increased LV end diastolic pressures and left atrial pressures. In summation, changes in the matrix can directly contribute to the progression of symptoms of heart failure in patients with POH.

Changes in Myocardial Interstitium Determinants in POH—The preponderance of studies evaluating myocardial biopsies obtained from patients with POH, irrespective of aortic stenosis or hypertensive heart disease, uniformly shows increased accumulation of collagen.^{43, 70–71, 75, 77} Furthermore, changes in critical determinants that effect collagen levels are altered in the remodeling process that occurs with POH. Myocardial samples from patients with POH secondary to aortic stenosis demonstrate increases in the matrix signaling molecule TSP; therefore, parallel induction of TSP occurs to increase collagen deposition.⁴³ A number of studies present increases in myocardial expression of TGF in patients with POH secondary to aortic stenosis, and the increase in TGF positively correlate with levels of collagen I and III in patients with POH.^{70, 77} Moreover, dynamic changes in MMP and TIMP levels have been reported. For example, Fielitz et al. identified robustly increased levels of TIMPs which would in turn favor greater inhibition of MMP induced matrix degradation.⁶⁸ Thus, as stylized in Figure 3C, increased induction of profibrotic signaling molecules and inhibition of collagen breakdown promotes matrix remodeling by favoring increased collagen accumulation.

Changes in Matrix Determinants Detected in the Plasma in POH—Collagen-derived peptides, such as PIP and PIIP, enter the circulation in quantities that likely reflect collagen synthesis and can be measured in the plasma.^{78–79} For example, Diez and colleagues measured increased levels of PIP and PIIP with no change in levels of the marker for collagen degradation in patients with POH secondary to hypertension.⁷⁹ Plasma levels of the signaling molecule galectin-3 were increased in patients with POH.⁴⁸ Moreover, it has been widely demonstrated that plasma levels of TIMP-1 are increased in

POH secondary to hypertension.^{80–81} The disproportionate increase in TIMP levels promotes inhibition of MMP activated interstitial collagen turnover due to a shift in the overall ratio of MMPs to TIMPs.^{80–81} In summation, plasma profiling has identified that determinants of synthesis, signaling proteins, and inhibitors of collagen degradation are all increased and correlate with collagen accumulation in the setting of POH.

Myocardial Remodeling with DCM

Myocardial Interstitial Remodeling and LV Function—In contrast to POH, the underlying pathophysiology of DCM is LV dilation and reduced systolic performance. DCM is a diverse classification of primary myocardial disease states, which uniformly causes an increase in LV chamber radius compared to wall thickness.^{58–59} With respect to the myocardial matrix in patients with DCM, changes in normal structure and composition occur, which can result in a loss of appropriate alignment of cardiomyocyte fascicles, which in turn may contribute to LV dilation. In general, a heterogeneous matrix remodeling process occurs in DCM which results in structural discontinuity and in turn the loss of normal matrix cellular support, such as the matrix-myocyte interfaces. The failure of a cohesive matrix-myocyte interface would in turn defeat normal transduction of myocyte shortening to myocardial ejection. Thus, significant disruptions in the normal matrix architecture can contribute to both LV dilation and decreased systolic performance.

Changes in Myocardial Interstitium Determinants in DCM—In DCM, a dysregulation between matrix synthetic and degradative pathways occur, which results in defective matrix architecture.^{63–65, 82–86} Multiple studies have identified that collagen expression and collagen content are increased in DCM.^{17, 84, 87} However, defects in collagen cross-linking occur with the development of DCM, which increases susceptibility to proteolysis and matrix instability. In several reports, the matrix signaling molecule TSP was decreased in patients with end-stage DCM.^{43, 88} The reduction of TSP results in a loss of normal matrix signaling and the synthetic pathways of collagen. TGF expression is simultaneously augmented in DCM, which underscores the differential changes occurring within the myocardial interstitium.^{43, 88} Increased post-translational modification and degradation of collagen in DCM is also taking place within the myocardial matrix as exemplified by the alterations in MMP and TIMP levels. More specifically, increases in MMP-2, MMP-3, MMP-9, MMP-13, and MT1-MMP occur with concurrent decreases in MMP-1, TIMP-2, TIMP-3, and TIMP4 in DCM. The overall change in ratio of MMPs to TIMPs shifts favoring MMP mediated matrix proteolysis.^{56–57, 63–65} Therefore, in summary, there appears to be an increase in matrix profibrotic signaling coupled with an increase in interstitial proteolytic pathways, which would create a futile cycle in terms of matrix accumulation and stability in patients with DCM. The resulting architecture of the defective myocardial interstitium is depicted in Figure 3D.

Changes in Matrix Determinants Detected in the Plasma in DCM—DCM is the most common etiology for patients undergoing cardiac transplantation, and as such, myocardial sampling can be readily performed. Thus there have been few studies which have focused primarily on plasma profiling for extracellular matrix remodeling. However, in conjunction with myocardial biopsies, Bruggink et al. evaluated plasma samples and measured increased levels of PIP and PIIP in both the myocardium and the plasma before and after implantation of a LV assist device in patients with end-stage DCM.⁸⁹

Myocardial Remodeling with Ischemic Heart Disease

Myocardial Interstitial Remodeling and LV Function—It is now recognized that a number of structural events occur within the myocardial interstitium following MI which involves both the MI and non-MI regions.^{56–57, 90–93} The LV remodeling process after MI

occurs in two phases, the acute phase and the chronic remodeling phase. The acute phase involves myocyte necrosis, an influx of inflammatory cells, and interstitial remodeling primarily within the MI region. In addition, a new region emerges, the border zone region, which consists of viable myocytes, an influx of inflammatory cells, and proliferating fibroblasts, which results in a site of continuous matrix turnover.^{90, 93–94} In the chronic adaptive phase, the MI region undergoes increased matrix accumulation and scar formation. However, the border zone region continues to undergo both matrix accumulation and proteolysis.^{90, 93–94} This type of matrix instability is not dissimilar to that described in patients with DCM. The structural changes that occur within the MI and border zone regions can result in dyskinetic contraction patterns. This dyskinesia can cause abnormal stress and strain patterns during the cardiac cycle, continued matrix turnover, and potentially yield MI expansion and LV dilation.^{57, 90–94} This post-MI remodeling process is exemplified in Figure 4A, whereby LV dilation occurs in patients as a function of time post-MI. Despite uniform standards of pharmacologic therapy, LV remodeling occurs in a majority of patients post-MI underscoring the need for matrix specific therapeutic interventions. The dynamic changes occurring in the different regions of the myocardium promote significant architectural changes that are depicted in a stylized manner in Figure 3E.

Changes in Myocardial Interstitium Determinants in Ischemic Heart Disease—

While clinical studies have documented a relationship between plasma levels of matrix signaling proteins and the progression of ischemic heart disease secondary to MI, few have evaluated the structure and function of the myocardial interstitium directly.^{90–92, 56–57, 95} Using a microdialysis system, dynamic changes in interstitial MMP activity were demonstrated in patients during and following a period of myocardial arrest and subsequent reperfusion.⁹⁵ This study underscores that rapid and time specific changes within the human myocardial interstitium occur with respect to determinants of matrix remodeling.

Changes in Matrix Determinants Detected in the Plasma in Ischemic Heart Disease—

A large number of studies have been performed which clearly demonstrate time specific changes in plasma profiles of the synthetic and degradative matrix pathways post-MI.^{18, 90–92, 96–97, 56–57, 98–101} One example demonstrated both PIIP and the plasma marker for collagen degradation, CITP, were increased in patients at the onset of the MI.⁹⁰ The acute elevation in these determinants of collagen composition suggest that there is a simultaneous increase in collagen synthesis and degradation, which is consistent with the acute phase of post-MI remodeling. A number of studies have provided data to demonstrate that increased plasma levels of MMPs were measured post-MI.^{96–97, 102–105} For example, increased levels of MMP-8 and MMP-9 were demonstrated in the plasma three days after MI, whereby MMP-8 levels subsequently decreased and MMP-9 levels remained elevated for six months.⁹⁴ Concurrently, TIMP-1 plasma levels were increased with no change in levels of TIMP-2 and TIMP-4 for 6 months after MI.⁹⁷ Overall, the post-MI ratio of MMP levels to TIMP levels shifted in favor of a heightened matrix proteolytic state. For example, the ratio of MMP-9 levels to TIMP-4 levels increased by over 200% for 6 months post-MI, as illustrated in Figure 4B.¹⁰⁵ Thus, the plasma signature in patients post-MI suggests a heterogeneity in matrix remodeling which includes both prosynthetic and degradative pathways that can culminate in a heterogeneous matrix as stylized in Figure 3E.

CLINICAL APPLICATION OF THE MYOCARDIAL INTERSTITIUM

The Myocardial Interstitium and the Diagnostic and Prognostic Potential in Heart Failure

One potential clinical application in the context of developing heart failure is to monitor myocardial interstitial remodeling through plasma profiling determinants of matrix synthesis and degradation. For example, one study demonstrated that plasma levels of PIP and PIIP

can be utilized in determining prognosis in patients with heart failure.¹⁰⁶ Higher plasma levels of these collagen synthesis markers were associated with increased hospitalization and mortality. In patients presenting with acute dyspnea, levels of the matrix signaling molecule galectin-3 were increased in those patients with an underlying myocardial etiology, which may hold diagnostic relevance.^{48–49} In addition, increased plasma galectin-3 was associated with increased hospitalizations and mortality in patients with heart failure.⁴⁸ Plasma levels of TIMP-1 have also been evaluated as a diagnostic tool in determining the transition to heart failure in POH secondary to hypertension.^{103, 107} For example, a specific cassette of matrix determinants, which included TIMP-1, can be predictive for the development of heart failure in patients with POH.¹⁰⁷ Plasma levels of MMPs and TIMPs have demonstrated potential prognostic utility with respect to cardiovascular events and mortality.¹⁰⁸ For example, the degree of LV dilation post-MI, which is a predictor of outcomes, has been associated with the magnitude of change in plasma MMP-9 (Figure 4C).¹⁰⁵ In another example, patients from the Framingham Heart Study demonstrated a relationship between increased plasma TIMP-1 levels with morbidity and mortality in heart failure.¹⁰⁸ Thus, plasma profiling of matrix signaling molecules and matrix proteases may have a role in monitoring the progression and predicting outcomes of patients in heart failure.

With respect to therapeutic interventions in heart failure, plasma profiling myocardial matrix structural proteins and proteases may reflect the efficacy of therapy. In a sub study of the Eplerenone Post-Acute MI Heart Failure Efficacy and Survival Study (EPHESUS), selective aldosterone receptor antagonists resulted in clear changes in markers of collagen synthesis and degradation, which were associated with a decrease in all-cause mortality and the composite end point of cardiovascular death or heart failure hospitalization in patients post-MI.¹⁰⁹ In patients with POH secondary to hypertension, angiotensin-converting enzyme inhibitors (ACE inhibitors) have been demonstrated to decrease plasma levels of TIMP-1.⁷⁹ In patients with end-stage heart failure secondary to DCM, LV assist device placement resulted in a time-dependent increased in plasma levels of PIP and PIIP and decreased levels of MMP-9.^{85, 89} These findings suggest that a shift in matrix synthesis and degradation occurs, whereby LV assist devices promote a stabilization of the collagen matrix.

The myocardial interstitium is not a passive entity, but rather a complex and dynamic microenvironment which represents an important structural and signaling system within the myocardium. Future clinical research focused upon the molecular and cellular mechanisms which regulate the extracellular matrix structure and function will likely contribute to an improved understanding of the LV remodeling process in heart failure as well as yield novel diagnostic, prognostic, and therapeutic targets.

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Figure 1.

Transmission and scanning electron microscopy (EM) were performed on papillary muscle samples which had been fixed at a maximum length preload. The images are of normal myocardium and normal myocardium treated with plasmin, a serine protease that activates matrix metalloproteinases to cleave interstitial proteins including fibrillar collagen. In Panel A, the top left transmission EM depicts intact sarcolemma with individual myofibrils. The bottom left scanning EM of normal myocardium depicts a fine fibrillar collagen weave within the interstitium. The bottom right scanning EM image shows the myocardium after treatment with plasmin, and it demonstrates a significant loss of fibrillar collagen. The top right transmission EM shows that there were no gross changes in sarcolemma architecture or evidence of myocyte injury. B) The normal myocardium treated with plasmin develops less

force at a specific muscle length when compared to untreated myocardium. Overall, plasmin treatment moved the developed force versus muscle length relationship downward. C) The graph demonstrates that there was no change in cardiomyocyte shortening extent with plasmin treatment of normal cardiomyocytes, which lays further evidence to support the concept that extracellular matrix degradation does not affect the function of the isolated cardiomyocyte. The figure was reproduced and modified from reference 21.

Figure 2.

A) Histopathologic images of normal myocardium compared to myocardium that has undergone extracellular matrix remodeling secondary to pressure overload hypertrophy. Note the significant collagen accumulation in the myocardium affected by POH (white and blue areas). The images were reproduced and modified from reference 68. B) The graph illustrates the relationship between pressure and volume of the LV during diastole in both normal patients and patients with POH. With the same diastolic volume during filling, the graph illustrates that patients with POH have increased diastolic pressures in comparison to control patients. This indicates that there is a decrease in compliance of the myocardium in with long-standing POH. The figure was adapted from reference 69.

Figure 3.

Panel A depicts normal myocardial interstitium organization as seen by scanning EM. The schematic illustration depicts the extracellular matrix surrounding the cardiomyocytes in B) normal myocardium, C) POH, D) DCM, and E) MI. B) In the normal myocardium, the interstitium forms a highly organized continuum between cardiomyocytes to provide a structural support system and a functional depot for a wide array of non-collagen matrix proteins, signaling molecules, and other cell types such as fibroblasts. C) In POH secondary to aortic stenosis or hypertension, the schematic illustrates the diffuse collagen accumulation that occurs along with an increase in fibroblast proliferation that leads to myocardial matrix accumulation and diastolic dysfunction. D) In DCM, the schematic demonstrates the increase in extracellular matrix turnover with the hallmarks of increased fibrillar collagen and decreased collagen cross-linking. E) In ischemic heart disease secondary MI, the myocardial remodeling process is region dependent and not uniform with both collagen accumulation (the infarct region) and degradation occurring (the border zone).

Figure 4.

A) The graph demonstrates the relationship between time after a MI versus the LV end diastolic volume. Compared to patients without an MI (Normal Range), there is a significant increase in LV end diastolic volume after a MI. B) After a MI, there is a significant increase in the ratio of MMP-9 levels to TIMP-4 levels compared to patients without an MI (range of ratio illustrated by the two dashed lines). C) When the percent change in MMP-9 levels from day 1 to day 5 is compared to the percent change in LV end diastolic volume 1 month after a MI, it is noted that there is a significant increase in the percent change in LV end diastolic volume with an increase in MMP-9 from day 1 to day 5. The graphs were reproduced and modified from reference 94.

Table 1

Studies Evaluating MMPs and TIMPs in Different Cardiac Diseases

Classification	MMP/TIMP	POH	MI	DCM
Collagenase	MMP-1	79		63, 64, 85
	MMP-8	107	95, 102	
Gelatinase	MMP-2	103, 107	95, 98, 99	63, 64, 87
	MMP-9	103	95, 98, 99, 101, 105	63, 64, 65, 87
Stromelysins	MMP-3		95	63, 64
Membrane Type	MMP-14	103		64, 87
Tissue Inhibitors	TIMP-1	79, 80, 81, 103	105, 108	63, 65, 85
	TIMP-2	103	105	63, 65
	TIMP-3			65, 85, 87
	TIMP-4	107	105	65