

## Myocardial extracellular matrix remodeling in ischemic heart failure

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### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. The Myocardial Extracellular Matrix
  - 3.1. Structural and Functional Roles of Myocardial Fibrillar Collagen
  - 3.2. Alterations in Myocardial Fibrillar Collagen
4. Regulation of Myocardial Fibrillar Collagen: The Matrix Metalloproteinases
  - 4.1. Regulation of Matrix Metalloproteinases
  - 4.2. Interplay of Fibrillar Collagen and Matrix Metalloproteinases
5. Matrix Metalloproteinases and Ischemic Heart Failure
6. Matrix Metalloproteinase Inhibition as Treatment for Ischemic Heart Failure
7. Conclusions and Perspective
8. Acknowledgments
9. References

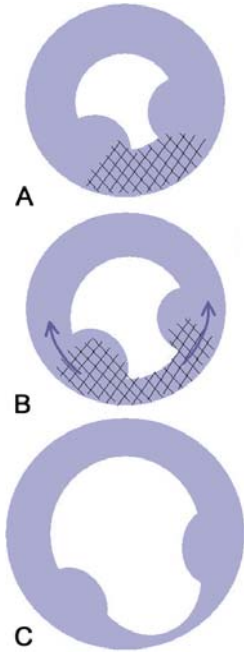
## 1. ABSTRACT

Left ventricular (LV) remodeling is a process whereby structural alterations attempt to compensate altered hemodynamic load. In the chronic setting this process becomes maladaptive, self-sustaining and is associated with worsened survival. The extracellular matrix (ECM) of the heart, once believed an inert scaffold for cardiomyocytes, is now known to play an important role in LV remodeling. The enzyme system primarily responsible for ECM turnover is the matrix metalloproteinases (MMPs), and these enzymes are robustly altered in cardiovascular pathologies, including myocardial infarction (MI) and ischemic heart failure. A cause-and-effect relationship has been established between MMPs and LV remodeling post MI, as MMP inhibition prevents LV dilation and preserves cardiac function in animal models of infarction. In spite of this, initial clinical experience with MMP inhibition post MI has been disappointing. This review examines the structural and functional roles of the myocardial ECM, the evidence for MMP involvement in LV remodeling, and recent investigations into MMPs as prognostic markers and therapeutic targets.

## 2. INTRODUCTION

Structural alterations in the left ventricle have in recent years been referred to as “left ventricular remodeling”. This remodeling process originates as an adaptive mechanism, enabling the heart to compensate for acute changes in hemodynamic load. Over time, however, remodeling becomes maladaptive and is associated with adverse clinical events and worsened survival prognosis (1). While remodeling is often viewed as a gross structural event involving the size and shape of the left ventricle, it is predominantly a cellular process involving myocytes and the interstitium in a coordinated process that accounts for the gross structural changes observed (2).

LV remodeling after myocardial infarction plays a major role in the progression to heart failure (Figure 1). At the time of infarction, acute distension of the viable myocardium and the operation of the Frank-Starling mechanism, as well as augmentation of chronotropic and inotropic activity through adrenergic receptor stimulation tend to maintain pump function with the abrupt loss of contractile tissue. These acute compensatory mechanisms,



**Figure 1.** Cross-sectional schematic of the LV (mid-papillary level), demonstrating the process of post myocardial infarction remodeling. At the time of infarction (A), acute compensatory mechanisms (such as adrenergic receptor stimulation) tend to maintain cardiac function. Within hours to days, however, the infarcted myocardium begins to expand (B), followed by global remodeling (C) (days to months).

however, are inadequate to maintain stroke volume when the non-contractile regions involve more than approximately 20% of the LV circumference (1).

Augmenting cavity size by long-term dilation can restore stroke volume despite a persistently depressed ejection fraction. Within hours to days, the area of myocardium affected by the infarction begins to expand and become thinner, and within days to months, global remodeling will occur (3). But through the operation of Laplace's law, this dilation would augment diastolic and systolic wall stress and thereby stimulate further ventricular enlargement. Myocyte hypertrophy may also be stimulated to offset the increased ventricular wall stress, however the extent of cavity dilation is often out of proportion to the augmentation in mass. When the cumulative loss of myocardium is large, a vicious cycle can be created in which dilation initiated to maintain pump function continues, that is, "dilation begets more dilation".

The process of LV remodeling and the progression of heart failure was originally believed to arise from alterations in intrinsic properties of the cardiomyocytes themselves, and indeed a multitude of phenotypic changes are observed in the remodeled myocardium. Cardiomyocytes, however, constitute less than one third of the cells in the myocardium (4). A substantial part of myocardial volume is extracellular

space, which is largely filled by an intricate network of macromolecules constituting the extracellular matrix (ECM). While the ECM was once thought to serve as a relatively inert scaffold to stabilise the physical structure of tissues, it is now clear that the matrix is a dynamic entity, which has a far more active and complex role. Evidence accumulated in recent years provides compelling affirmation for the importance of the matrix in the pathophysiologic expressions of various cardiovascular diseases, including ischemic heart failure.

### 3. THE MYOCARDIAL EXTRACELLULAR MATRIX

The myocardial ECM consists of macromolecules, primarily produced locally by fibroblasts, and includes a fibrillar collagen network, a basement membrane and proteoglycans. The fibrillar collagen network strengthens the matrix and ensures the structural integrity of adjoining myocytes. It provides the means by which myocyte shortening is translated into overall ventricular pump function and contributes to myocardial diastolic stiffness (5). In the heart, collagen type I, a fibrillar collagen with the tensile strength of steel, and collagen type III, also a fibrillar collagen, are the most abundant phenotypes (4). The basement membrane surrounds the myocyte and is attached to the sarcolemma as well as to the fibrillar collagen network. It is postulated that myocyte adherence to basement membrane may be a major determinant in maintenance of cell shape and positional integrity within the ventricular wall (6). Proteoglycans are composed of a protein core to which polysaccharide chains called glycosaminoglycans are covalently bound. These negatively charged molecules possess significant osmotic activity and therefore attract water and cations (7). The proteoglycan molecules in connective tissue thus form a highly hydrated, gel-like "ground substance" in which the fibrous proteins are embedded. The polysaccharide gel resists compressive forces on the matrix while permitting the rapid diffusion of nutrients, metabolites, and hormones between the blood and the tissue cells (8). Qualitatively, the composition of the ECM is similar in all tissues. Quantitatively, however, it is unique, and reflects the physiology of that particular tissue.

#### 3.1. Structural and Functional Roles of Myocardial Fibrillar Collagen

The myocardial fibrillar collagen weave forms the scaffold upon which myocytes are arranged, thus fibrillar collagen is the primary determinant of tissue architecture and ventricular size and shape. In the normal heart, the number and location of intermyocyte connections prevents slippage of adjacent myocytes, either laterally or longitudinally (9). It has been consistently demonstrated that degradation of collagen leads to ventricular dilation and sphericalisation (10-12).

In addition, because of its anatomic relation to the cardiac myocytes, myofibrils and muscle fibres and bundles, it has been hypothesised that the fibrillar collagen matrix coordinates the transmission of force generated by myocytes to the ventricular chamber. Collagen holds myocytes in a

given region at essentially the same length at the end of diastole (9) thereby imparting an equivalent preload, ensuring homogenous contraction of cells. Furthermore, Baicu *et al* demonstrated that systolic performance is impaired in isolated papillary muscles, but not isolated individual cardiomyocytes, following plasmin-induced collagen degradation (13).

Increases in interstitial collagen, a relatively inelastic material, will result in the myocardium becoming stiffer. A positive correlation between ventricular stiffness and collagen content has been established in nonhuman primates with experimental hypertension, rats with genetic, perinephretic or renovascular hypertension, and rats with myocardial fibrosis secondary to perinephritis and/or isoproterenol administration (12). To exclude the possible contribution of myocardial hypertrophy often observed concurrently with fibrosis, Narayan *et al* (14) demonstrated that prevention of myocyte hypertrophy in spontaneously hypertensive rats with hydralazine did not reduce the abnormal accumulation of collagen, nor the elevated passive myocardial stiffness. A comparison of diastolic function in hypertensive patients and trained athletes provides further support that excess myocardial collagen and not hypertrophy is responsible increased ventricular stiffness, as diastolic function is normal or even enhanced in the athlete, despite a significant increase in LV mass.

### 3.2. Alterations in Myocardial Fibrillar Collagen

It is now well recognised that myocardial fibrillar collagen plays an important role in determining the size and shape of the cardiac chambers, as well as ventricular diastolic and systolic function. Abnormal modifications of the collagen matrix, therefore, will in turn alter myocardial mechanical properties and ventricular function. In general, the matrix is altered by either a degradation of collagen, producing a reduction in collagen concentration characterised by a disruption and disappearance of fibrillar collagen, or an increase in collagen concentration because of reparative fibrosis and/or reactive fibrosis. Reparative fibrosis, or replacement fibrosis, is scarring that preserves the structural integrity of the tissue following myocyte necrosis. Reactive fibrosis is the synthesis of interstitial collagen fibres and the thickening of existing fibres at sites distant to myocyte cell loss.

Alterations in the fibrillar collagen network differ between the various cardiac pathologies. Pressure overload hypertrophy, for example, is associated with a rise in collagen synthesis in proportion to the increase in myocardial mass (15). Direct and indirect evidence of enhanced collagen degradation have also been observed (16, 17), however the rate of collagen degradation is not comparable to the increment in collagen synthesis and the result is an interstitial fibrosis. Decompensated volume overload hypertrophy, on the other hand, is characterised by grossly dilated, compliant cardiac chambers, with a high accumulation of interstitial collagen. It has been hypothesised that these changes are the result of increased collagen degradation and disruption of the collagen weave, accompanied by increased collagen deposition that is inadequately developed and poorly cross-linked and thus unable to provide the necessary structural and functional support (18).

Development of heart failure following myocardial infarction is accompanied by alterations in the extracellular matrix at both the site of infarction and in non-infarcted areas of myocardium (19). Following infarction and cell necrosis/apoptosis, the infarcted zone undergoes a long-term phase of reparative collagen deposition, that is, scar formation. This early stage of collagen synthesis is particularly important in the prevention of ventricular rupture as the ECM serves as a structural backbone to maintain integrity of the infarcted area. Depending on the species, the process of scar formation is completed within weeks to months, however the scar remains a dynamic entity that has constant and indefinite turnover of its connective tissue (20, 21).

While interstitial fibroblasts are responsible for collagen synthesis in the normal myocardium, phenotypically transformed fibroblasts, termed myofibroblasts, are responsible for fibrogenesis at sites of infarction. A hallmark of myofibroblasts is their expression of alpha smooth muscle actin filaments, and these cells are not residents of normal myocardial tissue, except heart valve leaflets. In experimental myocardial infarction in rats, myofibroblasts first appear at the site of infarction as early as day 3, become evident at week 1 and remain abundant for months and years thereafter (22, 23). Myofibroblasts present in other forms of wound healing such as the skin, disappear (via apoptosis) as soon as healing is complete, however the continuous mechanical stress caused by ongoing contraction and relaxation may explain their persistence in the heart.

Studies by this laboratory (19) have described the replacement and interstitial fibrosis observed in ischemic heart failure using an ovine model of coronary microembolisation. Significant replacement and interstitial fibrosis were observed in the infarcted LV, and also in the non-infarcted RV (although to a lesser extent). Volders *et al* (24) reported similar findings in humans; anterior, posterior or lateral LV infarcts have increased reactive collagen deposition in the non-infarcted interventricular septum and right ventricular subendocardial region when compared to both non-hypertensive hypertrophied and control hearts.

Concomitant with the activation of collagen synthesis is the activation of collagen degradation. Sato *et al* (25) found that after only 20 minutes of occlusion of the left anterior coronary artery the collagen network became irregularly arranged and disruption of collagen fibrils appeared in the subendocardium. After 2 hours of occlusion, entire collagen struts had disappeared and collagen fibrils had separated from the basement membrane.

## 4. REGULATION OF MYOCARDIAL FIBRILLAR COLLAGEN: THE MATRIX METALLOPROTEINASES

The amount of myocardial collagen depends on the balance between collagen degradation and deposition. While the turnover of fibrillar collagen in the normal heart is a relatively slow process (the half-life of collagen type I is ~100 days (26)), turnover of collagen in cardiac disease is greatly upregulated. One of the major enzyme systems

involved in the regulation of collagen turnover is the matrix metalloproteinases, or MMPs.

The MMPs constitute a family of zinc-dependant enzymes capable of degrading a wide spectrum of ECM proteins. The MMPs have been demonstrated to play a pivotal role in ECM remodeling across many tissue types, and it is now recognised that MMPs are expressed in the myocardium and play an important role in LV remodeling and various cardiac pathologies. MMPs are secreted into the extracellular space by a number of cell types, including fibroblasts, smooth muscle cells, endothelial cells and cardiomyocytes (27-29). All major cell types within the myocardium thus have the potential to synthesise MMPs and participate in LV collagen remodeling.

Twenty-five different human MMPs have been identified, which may be divided into sub-groups including interstitial collagenases, gelatinases, stromelysins and membrane-type MMPs (MT-MMPs). While this classification of MMPs was originally determined by substrate specificity, it is now recognised that a great deal of substrate cross-over exists between MMP classes and species.

### 4.1. Regulation of Matrix Metalloproteinases

The regulation of MMPs occurs at numerous levels, including transcription, activation and endogenous inhibitory control. All MMPs, with the exception of MT-MMPs, are secreted into the extracellular space in a latent, or proenzyme state (proMMP). In the normal heart, MMPs are predominantly present as latent proenzymes (30), thus a pool of recruitable MMPs exists within the ECM and provides a means for the rapid induction of proteolytic activity. Activation of proMMPs is achieved through enzymatic cleavage of the propeptide domain by serine proteases, such as plasmin, as well as other MMP species. Cleavage results in a conformational change and exposure of the catalytic domain to the ECM substrate.

Another important control point of MMP activity is through the presence of an endogenous class of low-molecular weight molecules called tissue inhibitors of metalloproteinases (TIMPs). Four different TIMP species have been identified and all bind to activated MMPs in a 1:1 stoichiometric ratio. Furthermore, certain TIMPs bind to proMMPs and thereby form proMMP-TIMP complexes. The functional significance of these proMMP-TIMP complexes remains incompletely understood, but they may actually facilitate MMP activation. For example, TIMP-2 forms a complex with MT-MMPs which enhances the activation of proMMP-2 (31). TIMP-1, which binds with great affinity to activated MMPs, is the most ubiquitous inhibitor. TIMP-4 appears to have predominant distribution within the myocardium, (32), however the significance of TIMP-4 myocardial expression remains unclear. In addition to binding to MMPs, TIMPs appear to influence cell growth and metabolism *in vitro*. Thus, TIMPs may have multiple biological effects with respect to MMP activity within the myocardium, which would be relevant to the LV remodeling process.

MMP mRNA expression can be influenced by a variety of chemical agents, neurohormones, corticosteroids

and cytokines. Inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1 beta) and tumour necrosis factor-alpha (TNF-alpha) have been found to decrease collagen expression and increase total MMP activity in cultured cardiac fibroblasts (33). Specifically, IL-1 beta was found to increase MMP-2 and MMP-3 at the mRNA level, suggesting increased activity was due, at least in part, to increased transcription.

Mechanical load also affects MMP expression. Unloading of the left ventricle during LVAD support decreases MMP-1 and MMP-9 expression and increases TIMP-1 and TIMP-3 expression (34). Although MMP-2, MMP-3, TIMP-2 and TIMP-4 remained unchanged in this study, Guo *et al* (35) found increased MMP-2 in cell lysates of mechanically unloaded cardiac fibroblasts. In addition, associations between functional parameters and MMPs following myocardial infarction have been made in both animal and human studies (36, 37). Whether alterations in mechanical load affect expression of these matrix enzymes directly (for example through integrins) or whether autocrine and paracrine signals are required (such as growth factors) remains incompletely investigated. Evidence for involvement of both mechanisms exists (38, 39).

### 4.2. Interplay of Fibrillar Collagen and Matrix Metalloproteinases

MMPs not only play a role in the degradation of matrix components, but may also modulate collagen synthesis. Digestion of ECM proteins by enzymes such as MMPs may release peptides which by themselves constitute new signals for the surrounding tissue. One such molecule, or "matrikine" is the tripeptide glycyl-histidyl-lysine (GHK), which is derived from ECM proteins (including several collagen  $\alpha$  chains) during their partial degradation and has been found to stimulate collagen synthesis in a potent and dose-dependent manner (40). In addition, collagen itself has been shown to activate certain MMP species. Type I collagen is a known matrix effector for MMP-2 activation in various cell types, including rat cardiac fibroblasts (41). These phenomena may explain why certain pathologies, including heart failure, demonstrate increased MMPs accompanied with increased fibrosis, and why therapies targeting one aspect often result in reductions to both (42, 43).

## 5. MATRIX METALLOPROTEINASES AND ISCHEMIC HEART FAILURE

In 1975, Monfort and Perez-Tamayo first demonstrated the presence of collagenase in the normal myocardium (44). In 1996, Tyagi *et al* (45) found collagenase activity to be approximately 30-fold higher in infarcted LV from explanted failing hearts than normal atrial tissue from donor hearts.

It has now been robustly demonstrated that MMPs are overexpressed in both the acutely remodeling ventricular tissue after myocardial infarction, and in chronic, non-ischemic ventricular myocardium undergoing gradual dilation. It is less certain, however, which

## Matrix remodelling post MI

**Table 1.** Summary of alterations in MMPs and TIMPs (gene or protein) post MI described in representative laboratory and clinical studies

	Animal Studies				Human
	MI Evolution & Early infarct healing		Late healing & scar formation	Chronic LV remodeling	End-stage Ischemic HF
	0-72h post MI	72h-2w post MI	2-6w post MI	>6w post MI	
<b>MMP-1 (57-61, 69-71)</b>					
Infarcted LV	↑ ↔	↑ ↔	↔	↓	↑ ↓ ↔
Remote LV	↑ ↔	↔	↑ ↔	↔	
<b>MMP-2 (57-64, 67-69)</b>					
Infarcted LV	↑ ↓ ↔	↑ ↔	↑ ↔	↑	↔
Remote LV	↑ ↔	↑	↑	↑ ↓ ↔	
<b>MMP-3 (59-61, 67)</b>					
Infarcted LV	↑ ↔	↑	ND	↓	↔
Remote LV	ND	ND	ND	↔	
<b>MMP-7 (59, 64)</b>					
Infarcted LV	ND	ND	ND	↑ ↓	ND
Remote LV	ND	ND	ND	↔	
<b>MMP-8 (59, 62, 63)</b>					
Infarcted LV	↑ ↔	↔	↔	↑ ↔	ND
Remote LV	↔	↔	↔	↔	
<b>MMP-9 (32, 49, 57-65, 67, 69)</b>					
Infarcted LV	↑ ↔	↑ ↔	↑ ↔	↑ ↓ ↔	↑
Remote LV	↔	ND	↑	↑ ↔	
<b>MT1-MMP (59, 61, 66, 68)</b>					
Infarcted LV	↑	ND	ND	↑	↑
Remote LV	↔	ND	ND	↔	
<b>TIMP-1 (32, 58-61, 64, 67-71)</b>					
Infarcted LV	↑ ↓	↑ ↓ ↔	↑	↑ ↓ ↔	↑ ↓ ↔
Remote LV	↔	↑	↑ ↓	↔	
<b>TIMP-2 (32, 59, 63, 69, 70)</b>					
Infarcted LV	↑ ↔	↑	↑	↑ ↓	↔
Remote LV	↑ ↔	↑ ↔	↑ ↔	↑ ↓	
<b>TIMP-3 (32, 59, 70)</b>					
Infarcted LV	↑ ↔	↑	↑	↓	↓
Remote LV	↔	↔	↔	↓	
<b>TIMP-4 (32, 59, 64, 68, 69)</b>					
Infarcted LV	ND	ND	ND	↓ ↔	↓ ↔
Remote LV	ND	ND	↔	↓ ↔	

Source: 32, 49, 57-71, ↑: increased, ↓: decreased, ↔: unchanged, ND: not determined.

particular MMP species are activated and at what time-point, especially since human studies are confounded by co-morbidities, polypharmacy and duration of the disease. Table 1 summarises a representative series of studies

investigating MMP and TIMP alteration post MI, highlighting the complexity and contradiction involved with formulating a model of this disease process. Nonetheless, a cause-and-effect relationship has been

established between MMP induction and LV remodeling, as broad spectrum MMP inhibition in animal models of myocardial infarction has consistently demonstrated reduction of LV dilation and preservation of cardiac function (42, 46-48).

Some MMP species, such as MMP-9, are thought to be involved in the early stages of remodeling following myocardial infarction (36, 49). Yet while MMP-9 knockout mice are partially protected against LV rupture and dilation post infarction (50, 51), evidence of impaired inflammatory cell migration, scar formation and infarct revascularisation suggests MMP induction is not entirely pathological and is required, to some extent, for effective infarct healing (50). An alternative to MMP gene knockout, is the use of TIMP gene therapy. A study by Jayasankar *et al* demonstrated TIMP-1 gene transfer following coronary ligation in rats lead to a preservation of cardiac geometry and function after 6 weeks (52).

Recent interest in MMPs and ischemic heart failure progression has expanded from therapeutic targets alone, to include diagnosis and prognosis following myocardial infarction. Measurements of MMPs in plasma originated as a surrogate marker of activity in the myocardium to enable serial measurements over time. As expected, plasma levels of MMPs and TIMPs were abnormal in patients following myocardial infarction (53) and with chronic ischemic heart failure (54). More recently, associations between plasma MMP levels following myocardial infarction and measures of LV function have been reported. Squire *et al* (37) observed peak MMP-9 levels on admission correlated significantly with end-diastolic and end-systolic LV volumes, inversely with LV wall motion index and directly with plasma N-BNP levels. Interestingly, MMP-2 demonstrated a strong inverse relationship with LV volumes both during and after admission. These results emphasise that subtypes of MMPs are likely to vary in distribution of expression, time-course of induction and functional/structural roles.

## 6. MMP INHIBITION AS TREATMENT FOR ISCHEMIC HEART FAILURE

The first clinical trial, PREMIER (Prevention of MI Early Remodeling), has been carried out to investigate the potential of MMP inhibition in the prevention of LV remodeling following myocardial infarction (55). The MMP inhibitor employed was PG-116800, which has high affinity for target MMP-13 and for MMPs -2, -3, -8, -9 and -14 but low affinity for MMP-1 and MMP-7, which are associated with musculo-skeletal side-effects. Patients (n=250) were randomised to PG-116800 or placebo for 90 days following myocardial infarction associated with an ejection fraction of <40% (treatment commenced within 48h of MI). The primary endpoint for the study was LV end-diastolic volume index change at 90 days post MI. While PG-116800 was well tolerated by patients, no benefit in LV remodeling was demonstrated. The progression of LV remodeling in the study was related to initial LV end-diastolic volume, the region of origin and the time from admission to percutaneous coronary intervention (PCI).

The failure of MMP inhibition to show benefit in this study is surprising considering the resounding evidence in animal studies. While MMP inhibitor trials in cancer treatment also failed to show any benefit, this was attributed to their application in advanced cancer, rather than early stages when MMPs are more likely to be involved (56). However the reason behind the failure of PREMIER is unclear. One difference between the majority of animal studies performed and the clinical situation is the addition of reperfusion therapy. It is possible that the ability of reperfusion itself to prevent LV remodeling disguises any effect of MMP inhibition, particularly since time to PCI was related to LV dilation while MMP inhibition was not. Nonetheless, it is expected that further study of agents targeting MMPs in ischemic heart failure will proceed.

## 7. SUMMARY AND PERSPECTIVE

The molecular alterations that accompany LV remodelling following MI are complex. It is evident that MMPs and TIMPs are involved in the remodelling process, and that a specific portfolio of these enzymes is expressed according to time after MI, proximity to infarcted zone and species of animal studied. The inflammatory and neurohormonal response to MI will also influence MMPs, as will the ensuing hemodynamic load on the heart. The use of MMP plasma profiling in the clinical situation may assist in tracking LV remodeling post MI, however the ubiquitous expression of MMPs in the body and their involvement with diverse pathologies (such as cancer, arthritis and atherosclerosis) may confound such measurements. Therapies targeting MMPs to prevent LV remodelling post MI have now reached clinical trial but so far have failed to demonstrate significant benefit. Further research is essential to elucidate more definitively the subtypes of MMPs and TIMPs involved in the remodeling process, and at what time point they are best targeted. The ability of MMP regulation to confer additional protection over coronary reperfusion and current standard therapy also needs consideration.

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## 9. REFERENCES

1. Pfeffer, M. A. & E. Braunwald: Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation.*, 81, 1161-72 (1990)
2. Anand, I. S. & J. N. Cohn: Introduction. *Journal of Cardiac Failure.*, 8, S247 (2002)
3. Huang, Y., S. N. Hunyor, L. Jiang, O. Kawaguchi, K. Shirota, Y. Ikeda, T. Yuasa, G. Gallagher, B. Zeng & X. Zheng: Remodeling of the chronic severely failing ischemic sheep heart after coronary microembolization: functional, energetic, structural, and cellular responses. *American Journal of Physiology - Heart & Circulatory Physiology*, 286, H2141-50 (2004)

## Matrix remodelling post MI

4. Cleutjens, J. P.: The role of matrix metalloproteinases in heart disease.[comment]. *Cardiovascular Research.*, 32, 816-21 (1996)
5. Weber, K. T.: Cardiac interstitium in health and disease: the fibrillar collagen network. *Journal of the American College of Cardiology.*, 13, 1637-52 (1989)
6. Terracio, L. & T. K. Borg: Factors affecting cardiac cell shape. *Heart Failure*, 4, 114-24 (1988)
7. Kuettnner, K. E. & J. H. Kimura: Proteoglycans: an overview. *Journal of Cellular Biochemistry.*, 27, 327-36 (1985)
8. Alberts, B., A. Johnson, J. Lewis, M. Raff, K. Roberts & P. Walter: Molecular Biology of the Cell. Garland Science, New York (2002)
9. Caulfield, J. B. & T. K. Borg: The collagen network of the heart. *Laboratory Investigation.*, 40, 364-72 (1979)
10. O'Brien, L. J. & C. M. Moore: Connective tissue degradation and distensibility characteristics of the non-living heart. *Experientia.*, 22, 845-7 (1966)
11. Caulfield, J. B., P. Norton & R. D. Weaver: Cardiac dilatation associated with collagen alterations. *Molecular & Cellular Biochemistry.*, 118, 171-9 (1992)
12. Janicki, J. S. & G. L. Brower: The role of myocardial fibrillar collagen in ventricular remodeling and function. *Journal of Cardiac Failure.*, 8, S319-25 (2002)
13. Baicu, C. F., J. D. Stroud, V. A. Livesay, E. Hapke, J. Holder, F. G. Spinale & M. R. Zile: Changes in extracellular collagen matrix alter myocardial systolic performance. *American Journal of Physiology - Heart & Circulatory Physiology.*, 284, H122-32 (2003)
14. Narayan, S., J. S. Janicki, S. G. Shroff, R. Pick & K. T. Weber: Myocardial collagen and mechanics after preventing hypertrophy in hypertensive rats. *American Journal of Hypertension.*, 2, 675-82 (1989)
15. Skosey, J. L., R. Zak, A. F. Martin, V. Aschenbrenner & M. Rabinowitz: Biochemical correlates of cardiac hypertrophy. V. Labeling of collagen, myosin, and nuclear DNA during experimental myocardial hypertrophy in the rat. *Circulation Research.*, 31, 145-57 (1972)
16. Bonnin, C. M., M. P. Sparrow & R. R. Taylor: Collagen synthesis and content in right ventricular hypertrophy in the dog. *American Journal of Physiology.*, 241, H708-13 (1981)
17. Doering, C. W., J. E. Jalil, J. S. Janicki, R. Pick, S. Aghili, C. Abrahams & K. T. Weber: Collagen network remodelling and diastolic stiffness of the rat left ventricle with pressure overload hypertrophy. *Cardiovascular Research.*, 22, 686-95 (1988)
18. Gunja-Smith, Z., A. R. Morales, R. Romanelli & J. F. Woessner, Jr.: Remodeling of human myocardial collagen in idiopathic dilated cardiomyopathy. Role of metalloproteinases and pyridinoline cross-links.[comment]. *American Journal of Pathology.*, 148, 1639-48 (1996)
19. Ikeda, Y., C. Yutani, Y. Huang, K. Masuda, T. Yuasa, O. Kawaguchi & S. N. Hunyor: Histological remodeling in an ovine heart failure model resembles human ischemic cardiomyopathy. *Cardiovascular Pathology*, 10, 19-27 (2001)
20. Sun, Y. & K. T. Weber: Infarct scar: a dynamic tissue. *Cardiovascular Research.*, 46, 250-6 (2000)
21. Cleutjens, J. P., W. M. Blankesteijn, M. J. Daemen & J. F. Smits: The infarcted myocardium: simply dead tissue, or a lively target for therapeutic interventions. *Cardiovascular Research.*, 44, 232-41 (1999)
22. Sun, Y. & K. T. Weber: Angiotensin converting enzyme and myofibroblasts during tissue repair in the rat heart. *Journal of Molecular & Cellular Cardiology.*, 28, 851-8 (1996)
23. Willems, I. E., M. G. Havenith, J. G. De Mey & M. J. Daemen: The alpha-smooth muscle actin-positive cells in healing human myocardial scars. *American Journal of Pathology.*, 145, 868-75 (1994)
24. Volders, P. G., I. E. Willems, J. P. Cleutjens, J. W. Arends, M. G. Havenith & M. J. Daemen: Interstitial collagen is increased in the non-infarcted human myocardium after myocardial infarction. *Journal of Molecular & Cellular Cardiology.*, 25, 1317-23 (1993)
25. Sato, S., M. Ashraf, R. W. Millard, H. Fujiwara & A. Schwartz: Connective tissue changes in early ischemia of porcine myocardium: an ultrastructural study. *Journal of Molecular & Cellular Cardiology.*, 15, 261-75 (1983)
26. Swynghedauw, B.: Molecular mechanisms of myocardial remodeling. *Physiological Reviews.*, 79, 215-62 (1999)
27. Galis, Z. S., M. Muszynski, G. K. Sukhova, E. Simon-Morrissey, E. N. Unemori, M. W. Lark, E. Amento & P. Libby: Cytokine-stimulated human vascular smooth muscle cells synthesize a complement of enzymes required for extracellular matrix digestion. *Circulation Research.*, 75, 181-9 (1994)
28. Tyagi, S. C., S. Kumar & G. Glover: Induction of tissue inhibitor and matrix metalloproteinase by serum in human heart-derived fibroblast and endomyocardial endothelial cells. *Journal of Cellular Biochemistry.*, 58, 360-71 (1995)
29. Coker, M. L., M. A. Doscher, C. V. Thomas, Z. S. Galis & F. G. Spinale: Matrix metalloproteinase synthesis and expression in isolated LV myocyte preparations. *American Journal of Physiology.*, 277, H777-87 (1999)

30. Tyagi, S. C., L. Matsubara & K. T. Weber: Direct extraction and estimation of collagenase (s) activity by zymography in microquantities of rat myocardium and uterus. *Clinical Biochemistry*, 26, 191-8 (1993)
31. Spinale, F. G., H. Gunasinghe, P. D. Sprunger, J. M. Baskin & W. C. Bradham: Extracellular degradative pathways in myocardial remodeling and progression to heart failure. *Journal of Cardiac Failure*, 8, S332-8 (2002)
32. Li, Y. Y., A. M. Feldman, Y. Sun & C. F. McTiernan: Differential expression of tissue inhibitors of metalloproteinases in the failing human heart. *Circulation*, 98, 1728-34 (1998)
33. Siwik, D. A., D. L. Chang & W. S. Colucci: Interleukin-1beta and tumor necrosis factor-alpha decrease collagen synthesis and increase matrix metalloproteinase activity in cardiac fibroblasts *in vitro*. *Circulation Research*, 86, 1259-65 (2000)
34. Li, Y. Y., Y. Feng, C. F. McTiernan, W. Pei, C. S. Moravec, P. Wang, W. Rosenblum, R. L. Kormos & A. M. Feldman: Downregulation of matrix metalloproteinases and reduction in collagen damage in the failing human heart after support with left ventricular assist devices.[comment]. *Circulation*, 104, 1147-52 (2001)
35. Guo, C. & L. Piacentini: Type I collagen-induced MMP-2 activation coincides with up-regulation of membrane type 1-matrix metalloproteinase and TIMP-2 in cardiac fibroblasts. *The Journal of Biological Chemistry*, 278, 46699-708 (2003)
36. Rohde, L. E., M. Aikawa, G. C. Cheng, G. Sukhova, S. D. Solomon, P. Libby, J. Pfeffer, M. A. Pfeffer & R. T. Lee: Echocardiography-derived left ventricular end-systolic regional wall stress and matrix remodeling after experimental myocardial infarction. *Journal of the American College of Cardiology*, 33, 835-42 (1999)
37. Squire, I. B., J. Evans, L. L. Ng, I. M. Loftus & M. M. Thompson: Plasma MMP-9 and MMP-2 following acute myocardial infarction in man: correlation with echocardiographic and neurohumoral parameters of left ventricular dysfunction. *Journal of Cardiac Failure*, 10, 328-33 (2004)
38. Butt, R. P. & J. E. Bishop: Mechanical load enhances the stimulatory effect of serum growth factors on cardiac fibroblast procollagen synthesis. *Journal of Molecular & Cellular Cardiology*, 29, 1141-51 (1997)
39. Nawata, J., I. Ohno, S. Isoyama, J. Suzuki, S. Miura, J. Ikeda & K. Shirato: Differential expression of alpha 1, alpha 3 and alpha 5 integrin subunits in acute and chronic stages of myocardial infarction in rats. *Cardiovascular Research*, 43, 371-81 (1999)
40. Maquart, F. X., L. Pickart, M. Laurent, P. Gillery, J. C. Monboisse & J. P. Borel: Stimulation of collagen synthesis in fibroblast cultures by the tripeptide-copper complex glycyl-L-histidyl-L-lysine-Cu<sup>2+</sup>. *FEBS Letters*, 238, 343-6 (1988)
41. Borg, K. T., W. Burgess, L. Terracio & T. K. Borg: Expression of Metalloproteinases by Cardiac Myocytes and Fibroblasts *In vitro*. *Cardiovascular Pathology*, 6, 261-9 (1997)
42. Yarbrough, W. M., R. Mukherjee, G. P. Escobar, J. T. Mingoia, J. A. Sample, J. W. Hendrick, K. B. Dowdy, J. E. McLean, A. S. Lowry, T. P. O'Neill & F. G. Spinale: Selective targeting and timing of matrix metalloproteinase inhibition in post-myocardial infarction remodeling. *Circulation*, 108, 1753-9 (2003)
43. Hayashi, M., T. Tsutamoto, A. Wada, T. Tsutsui, C. Ishii, K. Ohno, M. Fujii, A. Taniguchi, T. Hamatani, Y. Nozato, K. Kataoka, N. Morigami, M. Ohnishi, M. Kinoshita & M. Horie: Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction.[comment]. *Circulation*, 107, 2559-65 (2003)
44. Montfort, I. & R. Perez-Tamayo: The distribution of collagenase in normal rat tissues. *Journal of Histochemistry & Cytochemistry*, 23, 910-20 (1975)
45. Tyagi, S. C., S. E. Campbell, H. K. Reddy, E. Tjahja & D. J. Voelker: Matrix metalloproteinase activity expression in infarcted, noninfarcted and dilated cardiomyopathic human hearts. *Molecular & Cellular Biochemistry*, 155, 13-21 (1996)
46. Rohde, L. E., A. Ducharme, L. H. Arroyo, M. Aikawa, G. H. Sukhova, A. Lopez-Anaya, K. F. McClure, P. G. Mitchell, P. Libby & R. T. Lee: Matrix metalloproteinase inhibition attenuates early left ventricular enlargement after experimental myocardial infarction in mice. *Circulation*, 99, 3063-70 (1999)
47. Lindsey, M. L., J. Gannon, M. Aikawa, F. J. Schoen, E. Rabkin, L. Lopresti-Morrow, J. Crawford, S. Black, P. Libby, P. G. Mitchell & R. T. Lee: Selective matrix metalloproteinase inhibition reduces left ventricular remodeling but does not inhibit angiogenesis after myocardial infarction. *Circulation*, 105, 753-8 (2002)
48. Yarbrough, W. M., R. Mukherjee, T. A. Brinsa, K. B. Dowdy, A. A. Scott, G. P. Escobar, C. Joffe, D. G. Lucas, F. A. Crawford, Jr. & F. G. Spinale: Matrix metalloproteinase inhibition modifies left ventricular remodeling after myocardial infarction in pigs. *Journal of Thoracic & Cardiovascular Surgery*, 125, 602-10 (2003)
49. Deten, A., H. C. Volz, W. Briest & H. G. Zimmer: Cardiac cytokine expression is upregulated in the acute phase after myocardial infarction. Experimental studies in rats. *Cardiovascular Research*, 55, 329-40 (2002)



50. Heymans, S., A. Luttun, D. Nuyens, G. Theilmeier, E. Creemers, L. Moons, G. D. Dyspersin, J. P. Cleutjens, M. Shipley, A. Angellilo, M. Levi, O. Nube, A. Baker, E. Keshet, F. Lupu, J. M. Herbert, J. F. Smits, S. D. Shapiro, M. Baes, M. Borgers, D. Collen, M. J. Daemen & P. Carmeliet: Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure.[comment]. *Nature Medicine.*, 5, 1135-42 (1999)
51. Ducharme, A., S. Frantz, M. Aikawa, E. Rabkin, M. Lindsey, L. E. Rohde, F. J. Schoen, R. A. Kelly, Z. Werb, P. Libby & R. T. Lee: Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. *Journal of Clinical Investigation.*, 106, 55-62 (2000)
52. Jayasankar, V., Y. J. Woo, L. T. Bish, T. J. Pirolli, M. F. Berry, J. Burdick, R. C. Bhalla, R. V. Sharma, T. J. Gardner & H. L. Sweeney: Inhibition of matrix metalloproteinase activity by TIMP-1 gene transfer effectively treats ischemic cardiomyopathy. *Circulation*, 110, 11180-6 (2004)
53. Tziakas, D. N., G. K. Chalikias, J. T. Parissis, E. I. Hatzinikolaou, E. D. Papadopoulos, G. A. Tripsiannis, E. G. Papadopoulou, I. K. Tentis, S. M. Karas & D. I. Chatseras: Serum profiles of matrix metalloproteinases and their tissue inhibitor in patients with acute coronary syndromes. The effects of short-term atorvastatin administration. *International Journal of Cardiology*, 94, 269-77 (2004)
54. Wilson, E. M., H. R. Gunasinghe, M. L. Coker, P. Sprunger, D. Lee-Jackson, B. Bozkurt, A. Deswal, D. L. Mann & F. G. Spinale: Plasma matrix metalloproteinase and inhibitor profiles in patients with heart failure. *Journal of Cardiac Failure.*, 8, 390-8 (2002)
55. Cleland, J. G., A. P. Coletta, N. Freemantle, P. Velavan, L. Tin & A. L. Clark: Clinical trials update from the American College of Cardiology meeting: CARE-HF and the remission of heart failure, Women's Health Study, TNT, COMPASS-HF, VERITAS, CANPAP, PEECH and PREMIER. *European Journal of Heart Failure*, 7, 931-6 (2005)
56. Zucker, S., J. Cao & W. T. Chen: Critical appraisal of the use of matrix metalloproteinase inhibitors in cancer treatment. *Oncogene*, 19, 6642-50 (2000)
57. Herzog, E., A. Gu, T. Kohmoto, D. Burkhoff & J. S. Hochman: Early Activation of Metalloproteinases after Experimental Myocardial Infarction Occurs in Infarct and Non-infarct Zones. *Cardiovascular Pathology*, 7, 307-312 (1998)
58. Cleutjens, J. P., J. C. Kandala, E. Guarda, R. V. Guntaka & K. T. Weber: Regulation of collagen degradation in the rat myocardium after infarction. *Journal of Molecular & Cellular Cardiology.*, 27, 1281-92 (1995)
59. Wilson, E. M., S. L. Moainie, J. M. Baskin, A. S. Lowry, A. M. Deschamps, R. Mukherjee, T. S. Guy, M. G. St John-Sutton, J. H. Gorman, 3rd, L. H. Edmunds, Jr., R. C. Gorman & F. G. Spinale: Region- and type-specific induction of matrix metalloproteinases in post-myocardial infarction remodeling. *Circulation.*, 107, 2857-63 (2003)
60. Coker, M. L., J. L. Zellner, A. J. Crumbley & F. G. Spinale: Defects in matrix metalloproteinase inhibitory stoichiometry and selective MMP induction in patients with nonischemic or ischemic dilated cardiomyopathy. *Annals of the New York Academy of Sciences.*, 878, 559-62 (1999)
61. Spinale, F. G., M. L. Coker, L. J. Heung, B. R. Bond, H. R. Gunasinghe, T. Etoh, A. T. Goldberg, J. L. Zellner & A. J. Crumbley: A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure.[comment]. *Circulation.*, 102, 1944-9 (2000)
62. Deten, A., H. C. Volz, A. Holzl, W. Briest & H. G. Zimmer: Effect of propranolol on cardiac cytokine expression after myocardial infarction in rats. *Molecular & Cellular Biochemistry*, 251, 127-37 (2003)
63. Deten, A., A. Holzl, M. Leicht, W. Barth & H. G. Zimmer: Changes in extracellular matrix and in transforming growth factor beta isoforms after coronary artery ligation in rats. *Journal of Molecular & Cellular Cardiology*, 33, 1191-207 (2001)
64. Gaertner, R., M. P. Jacob, F. Prunier, E. Angles-Cano, J. J. Mercadier & J. B. Michel: The plasminogen-MMP system is more activated in the scar than in viable myocardium 3 months post-MI in the rat. *Journal of Molecular & Cellular Cardiology*, 38, 193-204 (2005)
65. Etoh, T., C. Joffs, A. M. Deschamps, J. Davis, K. Dowdy, J. Hendrick, S. Baicu, R. Mukherjee, M. Manhaini & F. G. Spinale: Myocardial and interstitial matrix metalloproteinase activity after acute myocardial infarction in pigs. *American Journal of Physiology - Heart & Circulatory Physiology.*, 281, H987-94 (2001)
66. Deschamps, A. M., W. M. Yarbrough, C. E. Squires, R. A. Allen, D. M. McClister, K. B. Dowdy, J. E. McLean, J. T. Mingoia, J. A. Sample, R. Mukherjee & F. G. Spinale: Trafficking of the membrane type-1 matrix metalloproteinase in ischemia and reperfusion: relation to interstitial membrane type-1 matrix metalloproteinase activity. *Circulation*, 111, 1166-74 (2005)
67. Romanic, A. M., C. L. Burns-Kurtis, B. Gout, I. Berrebi-Bertrand & E. H. Ohlstein: Matrix metalloproteinase expression in cardiac myocytes following myocardial infarction in the rabbit. *Life Sciences*, 68, 799-814 (2001)
68. Mukherjee, R., T. A. Brinsa, K. B. Dowdy, A. A. Scott, J. M. Baskin, A. M. Deschamps, A. S. Lowry, G. P. Escobar, D. G. Lucas, W. M. Yarbrough, M. R. Zile & F. G. Spinale: Myocardial infarct expansion and matrix

## Matrix remodelling post MI

metalloproteinase inhibition. *Circulation.*, 107, 618-25 (2003)

69. Podesser, B. K., D. A. Siwik, F. R. Eberli, F. Sam, S. Ngoy, J. Lambert, K. Ngo, C. S. Apstein & W. S. Colucci: ET (A)-receptor blockade prevents matrix metalloproteinase activation late postmyocardial infarction in the rat. *American Journal of Physiology - Heart & Circulatory Physiology*, 280, H984-91 (2001)

70. Sun, Y., J. Q. Zhang, J. Zhang & S. Lamparter: Cardiac remodeling by fibrous tissue after infarction in rats. *Journal of Laboratory & Clinical Medicine.*, 135, 316-23 (2000)

71. Barton, P. J., E. J. Birks, L. E. Felkin, M. E. Cullen, M. U. Koban & M. H. Yacoub: Increased expression of extracellular matrix regulators TIMP1 and MMP1 in deteriorating heart failure. *Journal of Heart & Lung Transplantation*, 22, 738-44 (2003)

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