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Matrix Metalloproteinase Therapy in Heart Failure

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Opinion Statement

Milestones in the progression to heart failure following myocardial infarction (MI) are changes in LV geometry and function- termed post-MI remodeling. Critical to this adverse remodeling process are changes in the expression, synthesis, and degradation of myocardial extracellular matrix (ECM) proteins. The myocardial ECM is not a passive entity, but rather a complex and dynamic microenvironment which represents an important structural and signaling system within the myocardium. In particular, basic and clinical studies have provided conclusive evidence that abnormal and persistent activation of the ECM degradation pathway, notably through the matrix metalloproteinases (MMPs), contribute to adverse post-MI remodeling. This review examines recent clinical studies which provide further support to the hypothesis that a specific portfolio of MMPs are both diagnostic and likely contributory to LV remodeling and the progression to heart failure post-MI. Future translational and clinical research focused upon the molecular and cellular mechanisms which regulate ECM structure and function will likely contribute to an improved understanding of the post- MI LV remodeling and yield novel therapeutic targets.

Introduction

With a prolonged cardiovascular stress or pathophysiological stimuli, a cascade of compensatory structural events occurs within the myocardium. This process occurs as a continuum and has been defined as myocardial remodeling. This remodeling process has been demonstrated within the myocardial compartment in most cardiac disease states which give rise to heart failure (HF); notably following myocardial infarction (MI), with hypertrophy, or cardiomyopathic disease. Thus, interventions which directly alter the LV myocardial remodeling process hold therapeutic promise in the setting of HF. A number of cellular and extracellular factors likely contribute to the complex process of myocardial remodeling. For example, myocardial remodeling following MI includes changes in coronary vascular structure and function, myocyte loss, hypertrophy of remaining myocytes, and increased size and number of non-myocyte cells; all of which result in non-uniform changes in LV myocardial wall geometry. While myocardial remodeling is accompanied by changes in the cellular constituents of the LV myocardium, significant alterations in the structure and composition of the extracellular matrix (ECM) occurs.¹⁻⁵ Moreover, it has become increasingly evident that the myocardial ECM is not a static structure, but rather a dynamic entity which may play a

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fundamental role in myocardial adaptation to a pathological stress and thereby facilitate the remodeling process.¹⁻¹⁰ Therefore, identification and understanding of the biological systems responsible for ECM synthesis and degradation within the myocardium holds particular relevance in the progression of HF. The purpose of this review is to briefly examine a fundamental proteolytic pathway which likely contributes to myocardial ECM remodeling following MI with respect to critical translational and clinical studies. This review will examine only one ECM proteolytic pathway which is evoked following only one cardiac disease state. Thus, the multifactorial nature of myocardial remodeling in general terms, and how ECM remodeling more specifically, can affect other cardiac disease states which can give rise to HF will not be addressed. Nevertheless, it is hoped that this short review will provide a prototypical example of how insight into an ECM proteolytic pathway with respect to recent translational and clinical studies hold relevance to our understanding, and eventually the development of diagnostic and therapeutics for this adverse myocardial remodeling process.

Heterogeneous ECM remodeling following MI

The LV remodeling process, which occurs in the post-MI period, can be considered to occur in 2 phases: the acute healing phase, and the chronic adaptive phase. In the acute phase of MI healing, myocyte necrosis and replacement fibrosis occurs. In the chronic adaptive phase, changes within the MI region as well as in the non-infarcted region occur. Within the MI region, fibroblasts proliferate and form an extracellular matrix which provides a support structure for infarct scar maturation. This extracellular matrix within the MI region also provides a means to tether viable myocyte fascicles and thereby forms a substrate to resist deformation from the intracavitary stresses generated during the cardiac cycle. Failure of this extracellular support has been associated with LV wall thinning and slippage of myocyte fascicles. This adverse remodeling process has been termed “infarct expansion” and occurs in the absence of additional myocyte injury or alterations in LV loading conditions. The extent of LV remodeling which occurs post-MI, with subsequent myocardial remodeling, are the strongest predictors for the development of HF.^{11,12} In contrast to the MI region, it has been postulated that an acceleration of ECM degradation occurs within the myocardium surrounding the MI (border zone) and may facilitate the infarct expansion process. These events within the myocardial ECM occur in a time and region dependent manner following MI. Thus, different patterns of ECM remodeling can be taking place simultaneously in the post-MI period — where enhanced ECM accumulation is occurring within the MI region and increased degradation is occurring within the border zone. The mechanisms and stimuli which determine the balance between ECM synthesis and degradation are likely to be different within each region of the LV following MI. Thus, elucidating the molecular mechanisms which locally control ECM synthesis and degradation in the post-MI period will likely yield specific therapeutic strategies which will facilitate the wound healing response, but attenuate the adverse myocardial remodeling which gives rise to infarct expansion and LV failure. One such underlying molecular pathway is likely to involve the emergence of an ECM proteolytic pathway.

Matrix Metalloproteinases- Definition and Function

The matrix metalloproteinases (MMPs) are a family of zinc dependent proteases which play a role in a number of tissue remodeling processes and have been clearly identified to be expressed within the human myocardium and upregulated following the development of HF.^{1,3,4,9,13} The MMPs were historically classified into sub-groups based upon substrate specificity and/or structure, and an informal nomenclature for some of the individual MMPs arose from these initial substrate studies. However, there is significant overlap in MMP proteolytic substrates and a more rigid numerical classification is now utilized. Important MMPs in the context of this review include the collagenases such as MMP-1 and MMP-13, the stromelysins/matrilysins which include MMP-3/MMP-7, the gelatinases which include MMP-9 and

MMP-2, and the membrane-type MMPs (MT-MMPs). Taken together, once the MMPs are activated, these enzymes can degrade all ECM components and therefore, it is important that the activity of these enzymes is kept under tight control. One important control point of MMP activity is through a group of specific MMP inhibitors termed tissue inhibitors of matrix metalloproteinases (TIMPs).^{1,6,13} There are four known TIMP species which are low molecular weight proteins that can complex non-covalently with high efficiency to MMPs in a 1:1 molar ratio. Therefore, these inhibitory proteins are an important endogenous system for regulating MMP activity *in vivo*. TIMPs are expressed in a variety of cells, where TIMP-4 is associated with a high level of expression in cardiovascular tissue.^{14,15}

Matrix Metalloproteinases and MI- Proof of Concept Translational Studies

Experimental studies have provided mechanistic evidence that increased expression and activation of MMPs contribute to the post-MI remodeling process.^{6,7,8,10,16-18} For example, it has been demonstrated that manipulating MMP expression in transgenic mice can alter tissue remodeling within the MI region as well as influence the degree of post-MI remodeling.^{6-8,16} These past studies suggest that prolonged activation of MMPs within the MI region may cause ECM instability and failure of proper scar formation. Prolonged activation or an acceleration of MMP expression within the viable post-MI myocardium may contribute to the process of infarct expansion. Neutrophils have been demonstrated to release several species of MMPs including MMP-8 and MMP-9.¹ Thus, the induction of MMP-9 following MI is likely the result of liberated MMP-9 from endogenous and exogenous cell types. The putative role for MMP-9 induction to contribute to the post-MI remodeling process has been exemplified in transgenic mouse studies.⁸ However, it is unlikely that a single MMP type is responsible for the adverse post-MI remodeling process. For example, gene deletion of MMP-2 has also been demonstrated to cause favorable effects on LV geometry and function in the early post-MI period.¹⁶ In addition to the induction of a large portfolio of MMPs in the post-MI period, a loss of MMP inhibitory control also appears to play an important role in the adverse LV remodeling process. Pharmacological MMP inhibition deployed in various animal models of MI have invariably demonstrated a favorable effect on the early post-MI remodeling process.^{1,7,16-18} Moreover, gene deletion of TIMPs have been shown to cause accelerated post-MI LV remodeling.^{6,19} These findings provided proof of concept/translational demonstration that increased MMP expression and activation coupled with a loss of endogenous MMP inhibitory control occurs early in the post-MI period and contributes to post-MI remodeling.

Matrix Metalloproteinases and MI- Recent Clinical Observations

While pre-clinical studies provide a means to directly measure myocardial MMP/TIMP levels during the progression of post-MI remodeling, a surrogate approach must be utilized for studying this proteolytic pathway in post-MI patients. The most common surrogate approach is to measure relative MMP/TIMP levels in the plasma using an immunological based method. In fact, the most actively studied cardiovascular disease state with respect to plasma profiling MMPs/TIMPs is during and following MI.²⁰⁻³² A summary of the directional changes in MMP/TIMP profiles that have been reported in clinical studies with acute coronary syndromes/MI is shown in Figure 1. One of the first uniform observations is that there is a temporal pattern of changes in MMPs and TIMPs following MI. For example, MMP-2 and MMP-3 levels increase early (hours-days) following MI, but then return to referent control levels at longer (weeks-months) post-MI intervals.^{20,23,26-28} One of the more uniform changes following MI is a robust increase in relative MMP-9 levels, and this change in MMP-9 levels has been associated with adverse post-MI remodeling.^{20,22-25,27,30} Thus, a unique temporal MMP signature appears to become manifest in patients post-MI. While relative MMP levels are increased in the plasma, there does not appear to be a concordant increase in TIMP levels. For example, relative TIMP-1 levels do not match the increase in MMP-9 levels post-MI, resulting

in an elevated MMP-9/TIMP-1 ratio.^{20,22} The temporal pattern for TIMP-4, which is robustly expressed within the cardiovascular system, was examined in patients up to 6 months following MI.²² In this study, a robust increase in plasma MMP-9 was observed early in the post-MI period, and was accompanied by a relative reduction in TIMP-4 levels. One potential net effect of this relative reduction in MMP inhibitory control in this post-MI period would be an increase in overall matrix degradation. Indeed, changes in plasma levels of MMPs in the post-MI period are emerging as an independent predictor of the degree of adverse LV remodeling and progression to CHF.^{22,23,28,31,32}

With respect to clinical studies which have examined MMP/TIMP profiles and published over the past year, there are several that are notable.²⁸⁻³² Kelly and colleagues examined relative MMP-3 levels in over 300 patients following MI and demonstrated that the early increase in relative plasma MMP-3 levels was associated with poor prognosis as defined as death and development of severe heart failure.²⁸ Indeed, this past study developed a cut-point in plasma MMP-3 levels which was associated with worse long term survival rates when examined by a Kaplan-Meier analysis. In a study by Gurbel et al,³⁰ relative MMP-3 levels were higher in patients at increased risk for an acute coronary syndrome. MMP-3 degrades a large portfolio of ECM proteins, and more importantly proteolytically processes inactive, pro-MMPs to an active MMP.¹ Thus, the emergence of this MMP type during and following MI may result in the degradation of a number of ECM molecules as well as promulgate an MMP activation cascade. Orn and colleagues reported a study in which plasma MMP-2/-9 profiles and contrast enhanced MRI measurements were performed for up to 4 years post-MI.³¹ In this study, there was no relationship between changes in LV geometry post-MI to MMP-2 levels, whereas an early relationship was observed for MMP-9. These studies underscore the importance for identifying and recognizing the biological role that individual MMPs play in the post-MI remodeling process, and to identify which MMP types may hold prognostic utility. Furthermore, measuring several MMP types and placing these values in context to MMP/TIMP stoichiometry may also be of importance.^{22,32} In a study by Elmas and colleagues, increased levels of TIMP-1 was strongly associated with an increased incidence of ventricular fibrillation in patients post-MI.³² These findings emphasize the importance of recognizing that post-MI remodeling is a highly heterogeneous process, where increased collagen accumulation may occur within the MI region, whereas concomitant fibrosis/degradation may be occurring in the border zone. Thus, localized changes in relative MMP/TIMP levels would cause a shift in the balance of ECM turnover, which in turn would cause realignment of myocytes and conduction tissue, which in turn could contribute to a pro-arrhythmogenic substrate. Finally, in a study by Sabatine et al, 1565 subjects were profiled with respect to an MMP type protease called “*a* disintegrin-like and metalloproteinase with thrombospondin motifs” or ADAMTS.²⁹ In this study, genotyping was performed for an ADAMTS-1 polymorphism, and it was identified that in men homozygous for the 227^{Pro} allele was associated with a 2-fold increase risk of MI. While not conclusively shown by this genotyping study, these findings suggest that induction of ECM proteolytic enzymes may play an important role in coronary vascular remodeling as well as myocardial remodeling. More importantly, this past study demonstrated that the increased risk of MI which was associated with the ADAMTS-1 polymorphism could be reduced by statin therapy.²⁹ This observation suggests that clinically available pharmacological agents can modify the induction of ECM proteolytic enzymes. Finally, some recent studies have identified that a transmembrane protein that induces the expression of specific MMPs *in vitro*,^{1,3} is upregulated following MI and may play an important role in MMP induction in the post-MI period.^{33,34} The nomenclature of this protein is primarily that of the extracellular matrix metalloproteinase inducer protein (EMMPRIN). A past clinical study has clearly demonstrated an upregulation of EMMPRIN in platelets following MI.³⁴ Moreover, a recent study has demonstrated that increased EMMPRIN levels, and subsequently increased EMMPRIN signaling can occur in platelets and monocytes which in turn can cause platelet and monocyte degranulation.³³ Therefore, EMMPRIN may also be an important contributory

factor in the up-regulation of various MMPs in the context of myocardial remodeling. Thus, it may be possible in future studies to utilize specific MMP/TIMP plasma profiles not only for risk assessment, but also as a biomarker of pharmacological efficacy with respect to adverse post-MI remodeling.

The studies outlined herein utilized immunologic based assays on blood samples, and thereby determined total relative abundance. However, the interpretation of these results with respect to net proteolytic activity which may occur in the myocardium is at best an indirect determination and must be done with extreme caution. Since multiple protein structures of an MMP type can exist within the plasma, then the sensitivity and the specificity of the immunological reagents utilized must be carefully scrutinized. In many of the clinical reports outlined in the previous section, these analytical considerations were variable, or not presented. This makes interpretation of plasma MMP/TIMP profiles difficult with respect to standardizing to referent control values. Since it is becoming apparent that plasma MMP/TIMP profiling may hold relevance with respect to prognosis and diagnosis, then standardization of analytical methods and establishing reference normal concentrations for sub-populations of patients would be an important advancement for clinical research. Another important consideration for MMP/TIMP profiling is the blood sampling procedure and preparation. For example, a recent report identified a large discrepancy between TIMP-1 levels measured in serum as opposed to plasma; and the difficulty in interpretation between the two methods.³⁵ The final and probably one of the most important considerations and limitations of plasma MMP/TIMP profiling is that of the actual source of the analytes. MMPs and TIMPs are synthesized within a wide variety of tissue types and therefore changes in plasma MMP/TIMP levels may not necessarily reflect changes occurring within the myocardium. This is of a particular concern in patients that are encumbered by multiple disease processes such as rheumatological disorders or cancer. Many of the clinical studies performed to date have attempted to control for these potential confounding factors through the use of exclusion criteria, however this will remain a concern with larger, broad based studies.

Clinical Studies and Matrix Metalloproteinase Inhibition- Lessons Learned and The Road Ahead

Due to the fact that MMPs play a prominent role in tissue remodeling processes, a large push was made to develop pharmacological MMP inhibitors. Initially, these pharmacological compounds exhibited inhibitory effects across a wide range of MMP types, and therefore were generically termed “broad spectrum” MMP inhibitors. Preclinical studies of the broad spectrum MMP inhibitors were uniformly successfully in several animal models of LV remodeling.^{1,5,7,16,17} However, concerns arose whether and to what degree these broad spectrum MMP inhibitors may affect closely related proteases (ie such as ADAMTS). Moreover, it was postulated that the inhibition of certain MMPs, such as MMP-1 may significantly contribute to the development of a musculoskeletal syndrome (MSS) or the “frozen joint” syndrome. Accordingly, more selective MMP inhibitors were developed which could be pharmacologically titrated to avoid inhibition of certain MMP types; particularly MMP-1. The most advanced of these “selective” MMP inhibitors in terms of cardiovascular disease was the Procter and Gamble compound (PGE530742/PGE7113313), which advanced to clinical evaluation and therefore was assigned a new identification number: PG116800.^{18,36} The target of this clinical evaluation was post-MI patients and the study was entitled Selective Matrix Metalloproteinase Inhibitor to Prevent Ventricular Remodeling After Myocardial Infarction (Prevention of Myocardial Infarction Early Remodeling-PREMIER). The PREMIER study enrolled post-MI patients primarily from international study centers (Poland, Canada). Patients were randomized to an active treatment arm consisting of selective MMP inhibition or placebo. Initially, the study design called for a 200 mg dose to be given orally twice daily for the entire study interval of 180 days. However, due to historical concerns regarding the risk of MSS, the

dosing regimen was altered following initial launch of the study.³⁶ Specifically, patients randomized to PG116800 were treated with 200 mg orally once per day for the study period. The echocardiographic determined LV end-diastolic volume at baseline (initial post-MI measurement at time of randomization) was compared to that obtained at 90 days and was the primary response variable. As a composite, LV end-diastolic volumes increased slightly from baseline (~10%) at 90 days. The relative degree of LV dilation, as a function of baseline values was 8.4% in the PG11680 group and 10.3% in the placebo group which did not reach statistical significance by t-test ($p=0.31$). Thus, the outcomes from this clinical study utilizing a selective MMP inhibitor in post-MI patients appeared equivocal. The initial outfall from this study was the closure of a number of development programs for MMP inhibitors, and darkened the future for developing pharmacological strategies for MMP inhibition in the clinical context of cardiovascular disease. However, if this initial clinical study is carefully evaluated, there are several important concerns that should be recognized which include an inadequate dosing regimen, a minimal change in the primary response variable, and experimental design issues. With respect to the dosing regimen, it is unlikely that this study achieved significant therapeutic efficacy of PG11680 in a large number of patients. Specifically, if the pharmacokinetics from the preclinical studies of this compound are considered, then the single daily dose used in this clinical study fell well below an effective inhibitory concentration of any MMP type.¹⁸ Another means by which to compare the dosing regimens for PG11680 in the pre-clinical MI studies and the clinical study would be to normalize the dose on a body weight basis (mg of drug/kg body weight). If this is considered, then the clinical dose was approximately 4-fold lower than that reported to be effective for achieving a LV remodeling effect observed in the preclinical studies.¹⁸ In the PREMIER study, the relative magnitude of post-MI remodeling as a function of changes in LV end-diastolic volume was modest and based upon the initial power estimates, it would be necessary for PG11680 to reduce the change in LV end-diastolic volume during the post-MI period by 80% when compared to placebo values. The small change in LV end-diastolic volume in this study is somewhat perplexing as other clinical studies, with smaller MI sizes, report much greater changes in LV volumes over a similar observation period.^{22, 25-27} In the PREMIER study, MMP inhibition was instituted within 24 hours of the onset of the MI, and therefore was in place during the initial wound healing period. Therefore, in addition to the dosing regimen, the timing of selective MMP inhibition also varied from the pre-clinical post-MI studies.

There are important lessons that can be taken away from the PREMIER study, which would be relevant to future strategies to modulate MMP activity. First, these results underscore the importance of properly translating preclinical studies into clinical therapeutics. Second, this study emphasizes the complexity and diversity of the MMP system. An important future direction would be to define the specific portfolio of MMPs which are specifically expressed within the different wound healing phases of the post-MI period and to develop selective targeting strategies to inhibit these MMP species. The biophysical stimuli which contribute to the local expression of myocardial MMPs is likely to be a complex and dynamic process determined by the summation of a number of extracellular signals. While a number of therapeutic interventions are likely to be developed which will directly modulate the myocardial extracellular environment, it is important to recognize that the temporal sequence and pattern of myocardial ECM remodeling are a heterogeneous process with respect to time and region in the post-MI period. Early induction and activation of MMPs may be essential for the wound healing response post-MI and exogenous MMP pharmacological inhibition may actually worsen myocardial viability in the acute MI period. However, persistently increased myocardial MMP activation following an established MI may contribute to the maladaptive process of infarct expansion. Thus, interventional strategies targeted at modulating the myocardial ECM must be time and disease specific. Further advancements in through interrogating the myocardial ECM,³⁷ as well as directly imaging myocardial MMP activity,¹⁰ are likely to provide the necessary tools to address this complex issue.

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	Acute Coronary Syndrome/ Myocardial Infarction	
	Directional Change	References
MMP-1	→	22,24
MMP-2	↑ Early ↓ Late	20, 25, 23, 26
MMP-3	↑ Early → Late	28, 22
MMP-7	→	
MMP-8	↑ ↑	22
MMP-9	↑ ↑ ↑	30, 20, 22, 24, 25, 23, 27
MMP-13	→	
TIMP-1	↓ Early ↑ Late	22, 25

Figure 1.

Profiling of matrix metalloproteinases (MMPs) and the tissue inhibitors of the MMPs (TIMPs) have been performed in a number of clinical studies in patients following acute coronary syndromes/myocardial infarction (MI). The generalized changes in the predominant types of MMPs in the early (days) and late stages (months) post-MI are shown. The arrows indicate the relative change in terms of a baseline or referent control value. Robust changes in MMP-8 and MMP-9 occur during and following an MI; and these MMP types are prototypically induced in a wound healing/inflammatory cascade. In contrast, other MMP types and TIMP-1 tend to show temporal profiles which likely reflect the dynamic changes occurring during the LV remodeling response following MI.