Extracellular protease activation and unraveling of the myocardial interstitium: critical steps toward clinical applications

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LV FAILURE AND REMODELING

Congestive heart failure is a complex pathophysiological process in which a significant biological underpinning is left ventricular (LV) failure. Part of the natural advancement to failure is myocardial remodeling, most commonly from adaptation to a pathological stimulus. LV remodeling can be defined as molecular, cellular, and interstitial changes within the myocardium that result in alterations in LV geometry and function (2, 4, 11, 21, 63, 71, 78). In patients with intensely progressive LV remodeling, morbidity and mortality are increased (17, 57, 79). This editorial is focused on the relationship between extracellular proteases and myocardial matrix remodeling. It will also explore basic research targets and analyze critical steps necessary in developing basic research into therapeutic and prognostic realizations. There are a number of underlying factors that contribute to the development and progression of myocardial LV remodeling. Specifically, alterations in myocardial tissue structure occur after myocardial infarction (MI), with the development of cardiomyopathies, and in myocardial hypertrophy (2, 4, 11, 21, 63, 71, 78). Although the initiating stimulus and symptoms may appear comparable among the three etiologies, the cellular remodeling processes are distinctly different and the underlying pathologies diverse. One area of research focus is how the myocardial extracellular matrix (ECM) may contribute to this remodeling process. Of particular note is the activation of extracellular proteases, which cause LV remodeling.

The purpose of this editorial is to place into context the different patterns of myocardial remodeling to that of extracellular protease activity. It is now recognized that the myocardial remodeling process is not a uniform sequence of events but rather a diverse set of molecular and cellular triggers, which are likely to be distinctive to underlying pathological stimuli (16). This editorial attempts to place into context the clinically encountered etiologies of myocardial remodeling (infarction, cardiomyopathy, and hypertrophy) to a unique pattern of extracellular protease activation. However, it must be recognized that summarizing the complex process of myocardial remodeling under these categories fails to address the different magnitude and duration of the pathological stimuli. In an attempt to address the complex issue, this editorial will examine both clinical and relevant animal model data in each of the distinct forms of myocardial remodeling with respect to extracellular protease activation.

MATRIX METALLOPROTEINASES

The matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases that are essential for normal tissue remodeling in processes such as bone growth, wound healing, and reproduction (48, 52, 76, 83). MMPs are responsible for turnover of the ECM, in turn facilitates tissue remodeling. MMPs are synthesized as inactive zymogens and are secreted into the extracellular space in a proenzyme form (48, 52, 76, 83). The pro-MMP binds specific ECM proteins and remains enzymatically quiescent until the propeptide domain is cleaved. Cleavage results in exposure of the zinc active site in the catalytic domain and subsequent activation (49). The disruption of the cysteine-zinc interaction in the MMP active site is essential in the activation of MMPs. This “cysteine switch” hypothesis of MMP activation is likely the mechanism by which most MMPs are activated (49). Instead of a sporadic distribution of pro-MMPs throughout the ECM, there is a specific allotment of these proteolytic enzymes within the extracellular space. Moreover, a large reservoir of recruitable MMPs exists, which upon activation can result in a rapid surge of ECM proteolytic activity.

MMP Classification

MMPs are classified into subgroups according to substrate specificity and/or structure (48, 52, 76, 83). MMPs that have been identified in the myocardium are listed in Table 1. Interstitial collagenase (MMP-1) and collagenase-3 (MMP-13) possess high substrate specificity for fibrillar collagens, whereas the gelatinases (MMP-2 and MMP-9) demonstrate high substrate affinity for basement membrane proteins (48, 52, 76, 83). The substrate portfolio for stromelysin (MMP-3) includes important myocardial ECM proteins such as aggrecan, fibronectin, and fibrillar collagens (48, 52, 76, 83). Furthermore, past in vitro studies have demonstrated MMP-3 can proteolytically process pro-MMP species (47, 49). For example, Murphy and colleagues (47) reported a 12-fold increase in the conversion of pro-MMP-1 to active MMP-1 in the presence of MMP-3. In addition, other MMPs such as MMP-1, MMP-2, and the membrane-type MMPs (MT-MMPs) can also activate pro-MMPs (24, 47-49, 52, 53, 76, 83). MT-MMPs contain a transmembrane domain and are likely activated intracellularly through a proprotein convertase pathway (24, 47-49, 52, 53, 76, 83). Thus, unlike the secretable MMPs, MT-MMPs are activated once positioned in the cell membrane. It has been demonstrated that MT1-MMP degrades fibrillar collagens and a wide range of ECM components as well as proteolytically processes pro-MMP-2 and pro-MMP-13 (24, 47-49, 52, 53, 76, 83). There is emerging evidence that MMPs also degrade nonmatrix substrates, in turn affecting cell proliferation, migration, and apoptosis (43).

MMP Activation/Inhibition

There are presently over 20 members of the MMP family of proteolytic enzymes, and several MMPs are substrate specific for other pro-MMPs. Therefore, activation of a few select enzymes can launch a cascade of proteolytic activity. For example, pro-MMPs are activated not only by MMP-1, MMP-2, MMP-3, and MT-MMP, but also by serine proteases...
Table 1. MMPs identified in human myocardium

<table>
<thead>
<tr>
<th>Class</th>
<th>Number</th>
<th>Substrate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenases</td>
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<td></td>
<td></td>
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<tr>
<td>Interstitial</td>
<td>MMP-1</td>
<td>Collagen I, II, III, VII, gelatin, proteoglycan, glycoprotein</td>
<td>16,48,52,67,76,81,83</td>
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<td>Collagenase 2*</td>
<td>MMP-8*</td>
<td>Collagen I, II, III, aggrecan</td>
<td>16,48,52, 83</td>
</tr>
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<td>Collagenase 3</td>
<td>MMP-13</td>
<td>Collagen I, II, III, gelatin, proteoglycan, pro-MMP-1</td>
<td>16,48,52,67,76,81,83</td>
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<tr>
<td>Gelatinases</td>
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<tr>
<td>Gelatinase A</td>
<td>MMP-2</td>
<td>Gelatins, collagen I, IV, V, VII, elastin, fibronectin, laminin, proteoglycan</td>
<td>16,36,48,52,67,76,81,83</td>
</tr>
<tr>
<td>Gelatinase B</td>
<td>MMP-9</td>
<td>Gelatin, collagen IV, V, XIV, elastin, proteoglycan, glycoprotein</td>
<td>16,36,48,52,67,81,83</td>
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<tr>
<td>Stromelysins</td>
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<td></td>
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</tr>
<tr>
<td>Stromelysin-1</td>
<td>MMP-3</td>
<td>Fibronectin, laminin, collagen III, IV, IX, pro-MMP-1,-7,-9</td>
<td>16,48,49,52,67,76,81,83</td>
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<tr>
<td>Matrilysin*</td>
<td>MMP-7*</td>
<td>Fibronectin, laminin, elastin, gelatin, collagen I, IV</td>
<td>16,48,52,83</td>
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<td>Membrane-type MMPs</td>
<td>MMP-14</td>
<td>Collagen I, II, III, fibronectin, laminin-1, glycoprotein, proteoglycan, pro-MMP-2, -13</td>
<td>14,16,24,48,52,76,81,83</td>
</tr>
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MMP, matrix metalloproteinase. *May exist in the myocardium in states of inflammation and wound healing.
LV Remodeling and MMPs: Animal Models of MI Demonstrating Cause and Effect

A cause-effect relationship between myocardial MMP activation and remodeling has been established through genetic modifications and pharmacological MMP inhibition (18, 55, 61). Altering the expression of certain MMP genes affects tissue remodeling within the MI region as well as influences the degree of post-MI remodeling (18, 55, 61). A recent study by Mukherjee and colleagues (46) utilized MMP inhibition in the setting of post-MI remodeling to evaluate region-specific changes in MMP and TIMP levels. Consistent with previous studies, MMP inhibition attenuated post-MI remodeling. However, as shown in Fig. 2, this study also reports a decrease in the rate of change in regional MI size in the MMP inhibition group, demonstrating that localized MMP activity directly contributes to infarct expansion in later phases of post-MI remodeling (46).

A Unique MMP/TIMP Profile After MI

A unique temporal profile of MMPs and TIMPs has been reported in the post-MI animal model (46, 55, 82). Wilson et al. described a regional imbalance of MMPs and TIMPs following changes in the remote, transition, and infarct regions post-MI (82). Time-dependent changes in myocardial MMP and TIMP levels after MI induction in rats have also been observed and show that differential profiles of MMPs are released throughout LV remodeling post-MI (55). MMP-13, -2, and -9 were elevated early in the post-MI period, whereas a more gradual elevation of MMP-14 (MT1-MMP) followed 16 wk of post-MI. Furthermore, throughout the time course measured, TIMP-1 and -2 increased while TIMP-4 decreased (55). Taken together, alterations in specific MMP and TIMP levels post-MI must be considered, because these certain species warrant further study for target intervention.

A loss of TIMP-mediated control has been reported in LV remodeling following MI (46, 55, 82). In the rat MI model, MMP mRNA levels increased early post-MI but were not associated with a concomitant increase in TIMP mRNA levels (55). In an in vitro system of ischemia and reperfusion, TIMP-1 expression was reduced in the early reperfusion period (4).

These findings suggest a loss of endogenous MMP inhibitory control occurs early in the post-MI period (4).

Identifying proteolytic systems, which promulgate regional geometry changes, offers greater potential for direct therapeutic targeting. However, developing specific targets will be predicated on recognition of the phases of post-MI remodeling. The early phase of post-MI remodeling occurs immediately after an acute myocardial insult. Localized MMP activity contributes to infarct scar formation, and healing is accompanied by neutrophil infiltration into the infarct area (2, 71, 78). With longer post-MI periods, however, rampant MMP activity in the border region of the infarct scar contributes to adverse remodeling and progressive infarct scar expansion (46). Thus targeting the MMP system post-MI must account for both the critical healing phase and the adverse post-MI remodeling phase. To determine the ideal time for MMP inhibitor deployment in the setting of LV remodeling post-MI, it is necessary to couple upstream cues that instigate adverse remodeling with improved imaging modalities.

LV Remodeling and MMPs in Dilated Cardiomyopathy

Remodeling in dilated cardiomyopathy (DCM) is characterized by an increase in the ratio of LV chamber radius to wall thickness, which increases myocardial wall stress and eventually results in progressive LV chamber dilation (84). The ECM undergoes structural realignment, loss of myocyte connections, degradation of the normal collagen fibrillar weave, and abnormalities in collagen cross-linking (20, 78). Markers of collagen degradation have been shown to be increased in DCM patients compared with age-matched control subjects (64). Thus it is likely that changes in ECM structure and function are largely responsible for LV remodeling in DCM.

Whereas the etiologies of DCM are diverse, the general classifications are ischemic, idiopathic (nonischemic), and infectious (84). Myocarditis is an inflammatory cardiomyopathy, most commonly viral or autoimmune in origin (41, 60). The fact that myocarditis often progresses to DCM underscores the potential significance of the inflammatory pathways in ECM remodeling. Furthermore, the inflammatory pathway induces cytokines such as tumor necrosis factor-α (TNF-α), and in DCM there appears to be a unique portfolio of MMPs that emerge and are likely under the control of upstream signals such as TNF-α (81). For example, TNF-α receptor activation occurs in patients with cardiomyopathic disease as evidenced by increased plasma levels of soluble TNF-α receptors (81). Moreover, a relationship has been established between plasma levels of TNF receptors 1 and 2 and plasma MMP-9 levels in patients of cardiomyopathy (Fig. 3) (81).

Clinical Studies of MMPs and TIMPs in Dilated Cardiomyopathy

A number of studies have examined relative MMP and TIMP expression in end-stage human DCM (36, 67, 73, 74). Tyagi and colleagues (74) demonstrated increased in vitro myocardial MMP zymographic activity in DCM samples. Also, it has been observed that myocardial MMP-9 was increased due to either ischemic or nonischemic origins, and MMP-3 was increased in nonischemic DCM myocardial extracts (67, 73). A selective upregulation of certain MMP...
species has been observed in DCM. For example, the collage-
nase MMP-13 is expressed at low levels in normal myocar-
dium but is significantly increased in end-stage DCM (Fig. 4)
(67, 73). Interstitial collagenase (MMP-1), in contrast, is de-
creased (67, 73). In addition, because TIMP-1 binds with less
affinity to MMP-13 than to MMP-1, there is a loss of endog-
enous control as MMP-13 levels increase (32). Furthermore, an
over threefold increase in MT1-MMP has been shown in
cardiomyopathic samples (Fig. 4) (67). Because of its biolog-
ically diverse actions, MT1-MMP is not only able to degrade
surrounding matrix but also is capable of initiating cascades of
proteolytic activity (24, 48, 52, 53, 76, 83). Therefore, the
emergence of certain MMP species within the DCM myocar-
dium may contribute to increased susceptibility of the myocar-
dial fibrillar collagen network to degradation and subsequent
maladaptive myocardial remodeling.

Myocardial TIMP levels appear to be variably expressed
in end-stage DCM (36, 73). Thomas and colleagues (73)
found an increased abundance of TIMP-1 and TIMP-2 in
DCM myocardium samples. In a study by Li and colleagues
(36), TIMP-1 and TIMP-3 levels were reduced in cardio-
myopathic samples, whereas TIMP-2 levels were unchanged
compared with control myocardium. Previous studies of
cardiomyopathic disease have suggested that changes occur
in the stoichiometric ratio of MMPs to TIMPs (36, 67). For
example, in both ischemic and nonischemic DCM, an abso-
lute reduction in MMP-1/TIMP-1 complex formation was
observed (67). Similar to MMPs, TIMPs are encoded by
unique genes and differ in promotor regions (13, 80). Thus
whereas further research is necessary, extracellular stimuli
may induce differential expression of TIMPs in DCM.

LV Remodeling and MMPs in Patients with
Myocardial Hypertrophy

A common cause for symptoms associated with heart failure
is diastolic dysfunction secondary to LV hypertrophy (LVH)
(40, 66). In contrast to LV remodeling post-MI and with
cardiomyopathy, hypertensive heart disease is often character-
ized by an impediment in normal LV filling characteristics.
Whereas the cause of this diastolic dysfunction is multifactor-
ial, changes in the ECM are invariable (57). Increases in
collagen content, as well as alterations in collagen cross-
linking, have been observed in association with LVH (33).

The collagenase MMP-13 is expressed at low levels in normal myocardium but is significantly increased in end-stage DCM (Fig. 4) (67, 73). Interstitial collagenase (MMP-1), in contrast, is decreased (67, 73). In addition, because TIMP-1 binds with less affinity to MMP-13 than to MMP-1, there is a loss of endogenous control as MMP-13 levels increase (32). Furthermore, an over threefold increase in MT1-MMP has been shown in cardiomyopathic samples (Fig. 4) (67). Because of its biologically diverse actions, MT1-MMP is not only able to degrade surrounding matrix but also is capable of initiating cascades of proteolytic activity (24, 48, 52, 53, 76, 83). Therefore, the emergence of certain MMP species within the DCM myocardium may contribute to increased susceptibility of the myocardial fibrillar collagen network to degradation and subsequent maladaptive myocardial remodeling.

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MMPs and TIMPs in an Animal Model of DCM

A model of heart failure that has reported a relationship between LV remodeling in DCM and MMP activity is the pacing-induced cardiomyopathy model (12, 68, 69). After the pacing protocol in pigs was instituted, MMP activity measured by an in vitro assay was increased (12, 68, 69). Not only was an increased abundance of myocardial MMP-2 and MMP-3 observed, but MMP activity was also shown to coincide with the onset of LV remodeling and dilation (69). Because LV remodeling preceded significant defects in myocardial contractility, activation of MMPs may be an early event in the progression to cardiomyopathy. In the murine myocarditis model, an upregulation of MMP-3 and MMP-9 mRNA and protein has been reported along with a downregulation of TIMP-1 and TIMP-4 mRNA and protein (35). Upregulated MMP levels in this model also correlated to increased expression of several cytokines (35).

LV Remodeling and MMPs in Patients with Myocardial Hypertrophy

A common cause for symptoms associated with heart failure is diastolic dysfunction secondary to LV hypertrophy (LVH) (40, 66). In contrast to LV remodeling post-MI and with cardiomyopathy, hypertensive heart disease is often characterized by an impediment in normal LV filling characteristics. Whereas the cause of this diastolic dysfunction is multifactorial, changes in the ECM are invariable (57). Increases in collagen content, as well as alterations in collagen cross-linking, have been observed in association with LVH (33).
There is evidence to support such observations from biochemical modification of the ECM (9, 75). For example, interfering in advanced glycated end products in collagen directly affects diastolic properties (9, 75). There are two distinct patterns of LVH that occur in response to persistent load: pressure overload hypertrophy (POH) and volume overload hypertrophy (VOH). The patterns of myocardial remodeling differ significantly between these two overload states and are briefly detailed below (11, 50, 70, 78).

LVH and MMPs in Patients

In POH, accumulation of myocardial fibrillar collagen influences passive compliance properties of the ventricle and results in diastolic dysfunction (11, 23, 78). Past studies have documented reduced MMP plasma levels in patients with systemic hypertension and LVH (33, 39). For example, decreased plasma levels of MMP-1 were reported in hypertensive patients with hypertrophy, and reduced plasma levels of MMP-9 were observed in untreated hypertensive patients (33, 39). The ratio of TIMP-1 to MMP-1 was also markedly increased in patients of severe LVH (26, 33, 39). Taken together, these studies suggest an initial decrease in MMPs and increase in TIMPs during POH will favor matrix accumulation.

In contrast to patterns of collagen accumulation in POH, LV remodeling with volume overload is characterized by excessive ECM degradation and LV dilation. Unlike collagen accumulation in POH, chronic VOH states display disruption of normal fibrillar collagens, which may be due to enhanced proteolytic activity of myocardial MMPs (23, 33, 50, 70). It is possible that early initiation of MMPs facilitates LV dilation. Specific profiles and time-dependent changes of MMPs and TIMPs in patients with VOH remain unknown.

LV Remodeling and MMPs in Hypertrophy: Animal Models of Overload

As hypertrophy progresses to decompensation and eventual LV failure, time-dependent changes in the activation of myocardial MMPs are likely to occur. In fact, several studies (34, 45) have demonstrated such changes in myocardial MMP levels throughout the development of POH. In the spontaneously hypertensive rat (Fig. 5), the development of compensated hypertrophy is associated with an increase in TIMP-4 levels, which would imply a net reduction in MMP activity (54). However, over time, MMP-2 and MMP-9 levels increase and TIMP levels fall, favoring myocardial remodeling and changes in the ECM related to decompensation and failure (34, 45). Additionally, Iwanaga et al. (29) reported disparate MMP and TIMP levels in the compensation stage of LVH compared with the transition to CHF stage. Whereas net MMP-2 and TIMP activity remained unchanged at the compensation stage, MMP-2 activity increased significantly and surpassed that of the TIMPs as LVH decompensation progressed to LV failure (29).

It is probable that both physical and chemical stimuli influence LV remodeling in POH, and the effects are likely time dependent (29, 50). For example, an animal model of acute pressure overload resulted in increased myocardial MMP-9 expression and zymographic activity (50). With prolonged pressure overload, MMP-9 zymographic activity began to normalize and was accompanied by changes in TIMP-1 levels (50). Furthermore, it has been demonstrated in an animal model of POH that relieving the pressure of the overload stimulus directly affected MMP and TIMP levels (77). Therefore, the driving stimulus to LV remodeling in overload states is likely wall stress.

In volume overload states, such as mitral regurgitation or aortocaval fistula, increased myocardial MMP levels and zymographic activity have been observed (8, 15, 50). Rat models of volume overload have shown not only an increase in MMP-2 and MMP-9 zymographic activity, which was associated with changes in LV function and geometry, but also an attenuation in LVH and adverse LV remodeling following MMP inhibition with a concomitant maintenance of normal LV function (8, 10). Taken together, these LVH studies suggest that 1) changes in myocardial MMP and TIMP levels likely contribute to the LV remodeling process given a pressure or volume overload stimulus; 2) different patterns of MMP and TIMP expression occur depending on the type and duration of overload states; and 3) increased levels of MMPs and TIMPs may be decreased with pharmacological inhibition or alleviation of the overload stimulus.

![Fig. 5](http://ajpheart.physiology.org/)

**Fig. 5.** Left ventricular (LV) cross sections taken from the level of the papillary muscles and prepared with a Mason’s trichrome stain. Sections shown are from a 13-mo-old wild-type rat, a 13-mo-old spontaneously hypertensive heart failure (SHHF) rat, and a 13-mo-old SHHF rat treated with the MMP inhibitor PD-166793 during months 9–13. [ Modified from Peterson et al. (54).]
**FUTURE CLINICAL DIRECTIONS AND THERAPEUTIC STRATEGIES**

**Modifying MMPs Post-MI**

Animal studies have clearly demonstrated the modification of progressive LV dilation and dysfunction post-MI through the use of MMP inhibition (46, 55, 61, 85). The clinical application of broad-spectrum MMP inhibitors, however, may be problematic (25, 59). Specifically, broad-spectrum MMP inhibition has been associated with musculoskeletal side effects, which suggests that broad-spectrum inhibition may interfere with normal tissue turnover (25, 59). Therefore, the specific MMP types causative in the adverse LV remodeling process must be identified. A study by Lindsey et al. (38) deployed selective MMP inhibition, which effectively spared MMP-1, in a rabbit model of post-MI ventricular remodeling and reported that progressive LV dilation was prevented. Thus a proof-of-concept has been established in which selective MMP inhibition is a practical pathway to modify LV remodeling post-MI. Along with selectivity, optimal timing must also be considered for interventions in post-MI remodeling. The acute, early phase of remodeling immediately after MI is essential for infarct scar formation and immune cell infiltration, and it is important to recognize the necessity for the wound-healing response post-MI. For example, past clinical studies that interfered with the early acute inflammatory response were associated with adverse outcomes (65). Differentiation of this acute critical healing phase from that of the adverse remodeling phase is essential. Thus, in targeting the MMP system, proteolytic cascades as well as their initiating events and temporal profiles must be carefully considered in properly deploying MMP inhibition.

**Modifying MMPs in Cardiomyopathy**

The development and progression of cardiomyopathic disease is a multifactorial process, but there are likely underlying processes that may influence MMPs and have beneficial effects on myocardial remodeling. Specifically, mechanical signals such as wall stress may be an important determinant in patients of cardiomyopathy. Figure 6A, from a study by Li et al. (37), depicts MMP-2 and MMP-9 levels before and after mechanical support with the LV assist device. Although MMP-2 remained unchanged, MMP-9 was reduced in 26 of 30 patients after long-term LV-assisted support (Fig. 6B) (37). Thus, with load as a promulgating process, physical stimuli are effective in modifying MMP levels in patients with cardiomyopathy. The modification of inflammatory pathways is another therapeutic target in cardiomyopathy because elevated levels of inflammatory cytokines have been reported in cardiomyopathy patients (42). Therefore, in cardiomyopathy, both mechanical and biological signals are operative, which likely modify MMP and TIMP release.

**Modifying MMPs in Myocardial Hypertrophy**

Current pharmacological approaches are focused on neurohormonal pathways. However, it may be possible to target the myocardium and ECM specifically. A recent study by Badenhorst and colleagues (3) used collagen cross-link breakers to modify myocardial compliance properties. Furthermore, it may be possible to selectively activate MMPs in hypertrophy, which may alleviate the accumulation of the ECM. For example, serine protease activation of MMPs has been shown to reduce fibrillar collagen and decrease elastic stiffness (72). MMP intervention in LVH will likely be entirely different from...
that in remodeling post-MI and in cardiomyopathy. The previous two disease states suggest inhibition of selective MMPs will attenuate LV remodeling, whereas in LVH, MMP activation may be necessary to restore the normal balance between ECM synthesis and degradation. Although directly modifying MMP levels may have beneficial effects on myocardial compliance, research must continue to favorably alter the myocardium without introducing unintended side effects.

A Need for Further Clinical and Basic Research

Developing pharmacological strategies that interfere with upstream signaling cascades involved in MMP transcription may improve our understanding of the complex myocardial remodeling process and the specific role of MMPs. For example, cytokine interruption, as with TNF-α neutralizing proteins, may be a useful pharmacological tool in identifying the signaling pathways obligatory for MMP species induction (14). Ideally, through targeting specific bioactive molecules or blocking nuclear binding sites, MMPs implicated in adverse remodeling could be inhibited while necessary basal expression of beneficial MMP levels could continue. Gene delivery systems provide potential for local modification of MMPs and TIMPs. Because genes can be selectively introduced into the myocardium in the form of naked deoxyribonucleic acid or as adenoviral vectors, gene delivery holds therapeutic promise for several CHF processes (1, 5, 30, 44). Emerging evidence also suggests that nonmatrix substrates of MMPs influence cell function. For example, the ability of MMP-7 to cleave multiple nonmatrix substrates, such as cell surface-bound Fas ligand, β2-integrin, and pro-TNF-α, renders it significant in numerous pathways (43). Thus more clinically applicable strategies specific to each disease state and time course can be realized through acknowledging and targeting upstream signals of MMPs, as well as their various nonmatrix substrates. In consideration of the divergent physical and biochemical pathways involved in LV remodeling, defining the molecular triggers of MMP and TIMP expression and targeting the upstream mechanisms responsible may prove to be an important therapeutic paradigm for heart failure treatment.

As outlined in the previous sections, three distinct etiologies give rise to the presentation of heart failure. Whereas these disease states give rise to similar symptoms, the myocardial remodeling process is distinctly different post-MI in cardiomyopathy and in hypertension and hypertrophy. In post-MI remodeling and cardiomyopathic disease states, structural alterations within the ECM occur, which result in mechanical disadvantage of surviving myocytes. In contrast, remodeling in hypertension and hypertrophy is characterized by excessive matrix accumulation and abnormalities in compliance. The factors that drive ECM remodeling are numerous. However, a specific pattern of MMPs and TIMPs appear to occur in these three disease states (Fig. 7). Therefore, cellular and molecular triggers, which in turn give rise to changes in the ECM, likely hold therapeutic promise.

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