

Review

Integrins, membrane-type matrix metalloproteinases and ADAMs: Potential implications for cardiac remodeling

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Abstract

The concept of myocardial remodeling links an initial pathological insult to a progressive geometric change of the ventricle. Currently, our concepts of the remodeling process have evolved to include not only changes in ventricular size and shape, but cellular and molecular remodeling, particularly as the ventricle evolves towards failure. In recent years, much attention has focused on the role of cell–extracellular matrix (ECM) connections in this process. In this review, we will specifically delineate how cell membrane-linked molecules of three classes: integrins, membrane-type matrix metalloproteinases, and ADAMs (*A Disintegrin And Metalloproteinase*) might play crucial roles in myocardial remodeling. These molecules are essential for cell–ECM adhesion, cell signaling, matrix modification, and proteolysis of surface receptors. Our goal is to put forth concepts on how they might interrelate to modulate the remodeling process in the heart. European Society of Cardiology. Published by Elsevier B.V.

Keywords: Metalloproteinases; Membrane-type metalloproteinases; Integrins; ADAMs; Disintegrins; Cardiac remodeling

1. Introduction

The concept of myocardial remodeling links an initial pathological insult to a progressive geometric change of the ventricle. This process may only necessitate a single direct attack on the ventricle and does not necessarily require continued insults. Discussion about remodeling inevitably prompts talk of hypertrophy, dilation and heart failure. Currently, our concepts of the remodeling process have evolved to include not only geometric remodeling, but cellular and molecular remodeling, particularly as the ventricle evolves towards failure [1–3]. Despite dedicated efforts, we still have an incomplete understanding of it. In recent years, much attention has focused on the role of cell-

extracellular matrix connections in remodeling. How these connections are maintained and change with remodeling is the subject of many chapters within the current volume. In this review, we will specifically delineate how cell membrane-linked molecules of three classes: integrins, membrane-type matrix metalloproteinases (MT-MMPs) and ADAMs (*A Disintegrin And Metalloproteinase*) might play crucial roles in this process. These molecules can influence cell–ECM adhesion, cell signaling, matrix modification and even proteolysis of surface receptors. Our goal is to put forth concepts on how they might interrelate to modulate the remodeling process in the heart.

2. Integrins

Integrins are glycoprotein transmembrane receptors which link extracellular matrix (ECM) and the cellular cytoskeleton. They are non-covalently bound heterodimers composed of α and β subunits with a large extracellular

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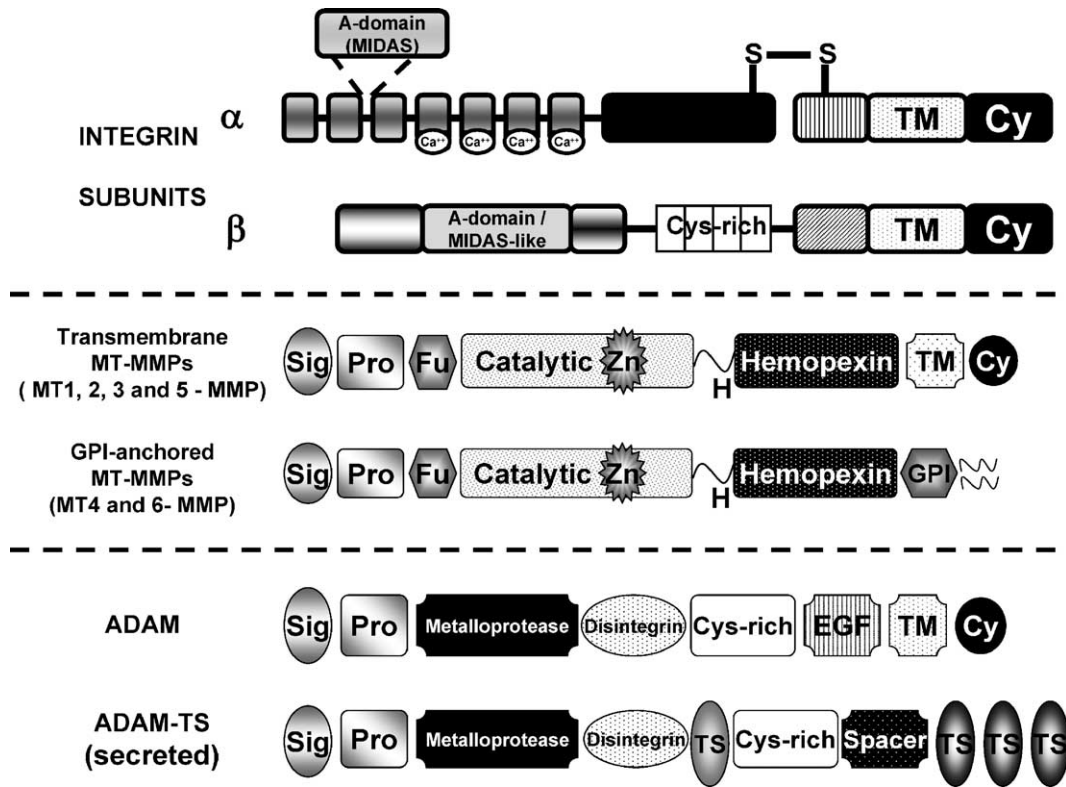


Fig. 1. Domain structure of integrins, MT-MMPs and ADAMS. Abbreviations: MIDAS, metal ion-dependent adhesion site; Cys-rich, cysteine-rich domain; Sig, signal peptide; Pro, propeptide; Fu, furin recognition motif; Catalytic, catalytic domain; Zn, zinc; Hemopexin, hemopexin/vitronectin like domain; TM, transmembrane domain; Cy, cytosolic tail; GPI, glycosylphosphatidyl-inositol; H, proline-rich hinge region; EGF, epidermal growth factor-like domain; TS, thrombospondin motifs.

domain, a single transmembrane span and short cytoplasmic tails (Fig. 1). These molecules orchestrate both cell adhesion and bi-directional intracellular signaling [4]. As multi-functional molecules, integrins are involved in organogenesis, regulation of gene expression, cell proliferation, differentiation, migration and death. Importantly, they function as mechanotransducers, converting mechanical forces to biochemical signals.

Integrins are expressed in most cell types. What makes this class of receptors complex is that one cell can express a variety of integrins and that the expression pattern can change during development or with disease. In the cardiovascular system, integrins are expressed in cardiac myocytes and fibroblasts as well as cells composing the vasculature, blood and neurons. Studies have shown that integrins are involved in heart formation, function and disease. Given space limitations of the current review, the reader is referred to more comprehensive ones by our own group and others on integrin structure, expression and signaling [5–7].

3. Integrin function and the myocardium

In studies which mechanically stretched cardiac fibroblasts, activation of two hypertrophic-related kinases, extracellular signal-regulated kinase (ERK2) and c-Jun-

terminal kinase (JNK1) was demonstrated to occur through cell surface integrins [8]. Integrins were linked to these signaling events by a combination of experiments in which cells were either bound to matrix ligands of integrins (laminin, fibronectin and vitronectin) or where integrin function was inhibited by specific anti-integrin antibodies. Integrins also mediate activation of transforming growth factor β (TGF- β) [9], an important cytokine in the fibrotic response of the heart. TGF- β stimulation of fibroblasts caused increased expression of $\alpha 5 \beta 1$ integrins [10], conversely, overexpression of this integrin heterodimer increased TGF- β expression [11]. Taken together, it is apparent that integrins participate in events of hypertrophic and post-infarct remodeling.

Changes in ECM amount and distribution occur following pathophysiological or growth factor mediated events such as pressure overload, myocardial infarction or following production of substances such as endothelin-1 or angiotensin II (AII). Terracio et al. were some of the first investigators to document the importance of integrins in the myocardium and how their expression was changed with hypertrophy [12]. They showed that with hypertrophy, $\alpha 1$ integrin (a collagen binding subunit when paired with $\beta 1$) increased in parallel with collagen content of the heart itself. Gullberg et al. noted that integrin and PDGF-mediated signaling intersected, in that PDGF-stimulated collagen gel

contraction caused by cardiac fibroblasts, could be partly inhibited by $\beta 1$ integrin antibodies [13]. Sadoshima and Izumo subsequently performed studies which utilized mechanical loading of cultured myocytes to simulate hemodynamic loading of the intact myocardium. They and other investigators showed how the mechanical stimulus induced a variety of intracellular signaling pathways such as phospholipases C, D, and A2, protein kinase C, tyrosine kinases, p21 MAP kinases, and 90 kD S6 kinase [14,15]. Many of these pathways are known to be involved in growth factor and integrin signaling cascades. These same authors also showed that stretch of myocytes provoked paracrine release of factors such as AII which also provoke hypertrophy [16]. AII stimulation of cardiac fibroblasts has been shown to increase expression of $\alpha 8\beta 1$ and also intensify immunomicroscopic expression of $\beta 1$ integrin [17,18].

Several groups, including our own, have shown that the hypertrophic response of cultured myocytes and the intact ventricle can cause increased expression of integrins such as $\alpha 7$ and $\beta 1$; and that integrins (e.g. overexpression of $\beta 1D$ integrin) and ECM ligands for integrin receptors (such as fibronectin) can invoke the hypertrophic response pathway independent of growth factors [19–21]. It has also become clear that there is synergy between growth factor and integrin mediated stimulation of hypertrophy. Much of this overlap may function through focal adhesion kinase (FAK), FAK related kinases (such as Pyk2) and ultimately signal through protein kinase C (PKC) and ERK related pathways [22–29]. Integrins have been shown to utilize FAK, src-Family Kinases (Src), growth factor receptor-bound protein-2 (Grb2) and Ras to induce hypertrophic signals propagated through p38 MAPK [30]. Agents known to induce cardiac myocyte hypertrophy including endothelin-1 (ET-1) and phenylephrine (PE) signal through pathways concomitantly and perhaps synergistically with integrins. As discussed more completely in other sources, integrins have also been shown to interact with a host of other cell surface receptors in the myocardium, including ones which may participate in the remodeling process such as adrenergic, cholinergic and calcium receptors [5,7,31–33]. Thus integrins can function at multiple levels in the remodeling process.

4. Membrane-type matrix metalloproteinases

MMPs are members of a family of zinc endopeptidases that contribute to the degradation of ECM in processes such as tumor expansion, angiogenesis and cardiac remodeling [34–37]. MMPs are capable of digesting ECM and basement membrane proteins, but these are not their only targets as they are also able to cleave other MMPs, an array of other proteases and protease inhibitors, growth factors, growth factor binding proteins, chemokines, cytokines, cell surface receptors and cell adhesion molecules [34,38]. Thereby, MMPs control cell migration, proliferation, and apoptosis [34].

To date 25 different vertebrate MMPs have been identified, of which 22 are found in humans [39]. Although initially classified according to their substrate specificity, the MMP classification is now based on their structure [40]. The MMPs can be segregated into two groups: the soluble type, which are released into the pericellular space, and those anchored to the plasma membrane, the membrane type MMPs (MT-MMPs), a focus of this review. Six distinct members of the MT-MMP subfamily of MMPs have been identified in human tissue [41,42]: MT1-, MT2-, MT3-, MT4-, MT5-, and MT6-. A strict nomenclature of these MT-MMPs has classified them as MMP14, 15, 16, 17, 24 and 25, respectively.

5. MT-MMP structure and classification

The basic domain structure of MMPs includes (1) a signal peptide that directs them to the endoplasmic reticulum, (2) a propeptide with a zinc-interacting thiol (SH) group that maintains the molecule in a latent form (i.e. a zymogen), and (3) a catalytic domain containing the highly conserved Zn^{2+} binding site [43]. With the exception of MMP23 and the matrilysins (MMP7 and MMP26), all other MMPs display a hemopexin/vitronectin-like domain that influences substrate specificity and the binding of the MMPs to their inhibitors, “tissue inhibitors of MMPs” or TIMPs, and a proline-rich hinge region that links the catalytic domain to the hemopexin domain [44] (for more information on MMP structure see Ref. [39]).

The MT-MMPs contain all protein domains characteristic of the more generalized MMP class mentioned above (Fig. 1). The key difference between MT-MMP and the other MMPs is the membrane-anchoring domain of MT-MMPs which allows for a unique cellular localization and also provides for orchestrating a new set of substrate targets, distinct interactions with the TIMPs, and produces a non-conventional regulatory mechanism of these proteases involving enzyme internalization, processing, and ectodomain shedding [45].

On the basis of their method of attachment to the plasma membrane, MT-MMPs may be classified into two groups: transmembrane-type and glycosylphosphatidylinositol (GPI)-type. MT1-, MT2-, MT3- and MT5-MMP are type I transmembrane proteins with a short cytoplasmic tail that is involved in the regulation of intracellular trafficking and activity of these proteases [46–48]. MT4- and MT6-MMP are distinguished in that they are not transmembrane proteins but are bound to the cell surface by a GPI-mediated mechanism [49,50].

All MMPs are produced as zymogens containing a secretory signal sequence and a propeptide whose proteolytic cleavage is required for their activation. Most of the MMPs are activated outside the cell by other MMPs or serine proteinases. An important difference between MT-MMPs and most soluble MMPs is that they are mainly

activated intracellularly. A furin recognition motif localized between the propeptide and the catalytic domain in all six MT-MMPs is cleaved by pro-protein convertases in the *trans*-Golgi network. In this manner it insures that MT-MMPs are active when they reach the cell membrane [38,44].

6. MT-MMP regulation and function

As with the other MMP, MT-MMP function or activity is regulated in several ways: transcriptional, via proenzyme activation and by inhibition [34]. Additionally, MT-MMP activity can be regulated by shedding and endocytosis [45], by factors such as cytokines like interleukin [51], TNF- α [52] or TGF- β [53]; by mechanical stretch [54] and by interactions with ECM proteins like collagen, fibronectin or fibrinogen [38,55,56] which are in turn bound by integrins.

The MT-MMPs can degrade several ECM components as well as other membrane or matrix-bound/pericellular proteins. The spectrum of ECM proteins that can be degraded is broad and includes fibronectin, tenascin, nidogen, aggrecan, perlecan, laminin and native type-I and type-III collagens. Non-ECM proteins cleaved by MT-MMPs include cell adhesion molecules such as CD44 and pro- α v integrin, as well as cytokines like pro-TNF- α [44,57,58].

As noted previously, MMPs are synthesized as latent enzymes that need to be activated. MT-MMPs, like some of the soluble MMPs, serve an important role as activators of other pro-MMPs [59]. One example was shown by Zhou et al. [60] who studied MT1-MMP-deficient mice. They showed that MT1-MMP was an *in vivo* activator of MMP-2 (gelatinase A). This process was regulated by TIMP-2 concentration. MT2-, MT5- and MT6-MMPs can also lead to MMP2 activation [61,62]. This activity is facilitated by α v β 3 integrin. It has been proposed that cross-talk between MT1-MMP and α v β 3 integrin clustered in discrete regions on the cell surface enhances pro-MMP2 activation [63]. This begins to illustrate the complex interactions of membrane-associated molecules which could modulate the remodeling process in heart. MT1-MMP can also activate 1) MMP9 via MMP2 or MMP3 [64] and 2) procollagenase-3 (MMP13), via both MMP2 dependent and independent mechanisms. Showing further interrelationships between the molecules under discussion here, MT4-MMP has been shown to enhance the activation of ADAMTS-4 [65]. Thus MT-MMPs can provoke amplification of a pericellular proteolytic milieu.

7. MT-MMPs in the heart

In the normal heart, MT1-, MT2- and MT3- transcripts have been detected whereas no MT4-, MT5- or MT6-MMP have been shown [41,42,66–69]. In the failing heart, increased expression of MT1-MMP occurs [70]. The mechanical and/or humoral stresses which occur during

pathological processes affect the activity and expression of several MMPs in the heart. This includes activation of MT1-MMP which is regulated in part by the angiotensin type 1 receptor (AT1R) [71,72].

In the heart, MT1-MMP has been the best characterized MT-MMP to date. *In vivo* and *in vitro* experiments have shown the upregulation of this MMP in heart and cardiac cells under stress conditions such as pressure overload [73], myocardial infarction [74], ischemia/reperfusion (I/R) [72], humoral treatments [75] and mechanical stretch [54,76]. Coker et al. [75] showed how MT1-MMP is upregulated in porcine cardiac myocytes after neurohormonal stimulation with factors that have been linked to the development of cardiac hypertrophy and heart failure, e.g. ET-1, AII and Isoproterenol (Iso). In turn, the increased activity of MT1-MMP evoked increased collagenase activity and MMP2 content. This study is in contrast to the one by Menon et al. where MT1-MMP transcript levels did not change in adult rat cardiac myocytes stimulated with Iso [77]. Strain and experimental protocol differences could have lead to this variance. Furthermore, in a recent study, MT1-MMP expression, activity and sub-cellular localization were found to change during I/R [72]. In this study Deschamps and colleagues showed how MT1-MMP activity evaluated in cardiac tissue from pigs was increased in ischemic areas after acute I/R. This was associated with an increase in total MT1-MMP abundance and a concomitant decrease in TIMP-4 as well as TIMP-3. The increased MT1-MMP activity was associated with augmented levels in the endosomal fraction after I/R, suggesting that the increase could be due to changes in trafficking of the enzyme. In the same study, microscopic analysis of isolated porcine LV myocytes showed how MT1-MMP can change its cellular localization during hypoxia and re-oxygenation.

Mechanical stretch has been directly linked to activation of MT1-MMP and MMP2 in several cell types including cardiac myocytes [76,78]. Like the porcine studies above, neonatal rat cardiac myocytes subjected to mechanical stress increased transcript and protein expression of MT1-MMP and MMP2 following stretch. These increases were completely blocked by Losartan, demonstrating that the effect is mediated through the AT1 receptor. In agreement with this result, Deschamps et al. showed that mechanically mediated alterations in MMP activity in the intact heart are partially regulated through the AT1R [71].

Several studies have also shown that MT1-MMP is increased during the transition from compensated hypertrophy to heart failure [73,79]. EMMPRIN (extracellular matrix metalloproteinase inducer) was also upregulated. This likely facilitated an increase in MMP expression as EMMPRIN has been shown to increase MMP2 activation in non-cardiac cells [80,81]. EMMPRIN also forms a complex with α 3 β 1 integrin. This interaction may be another membrane-associated nodal point for activation of MT1-MMP and MMPs in heart [82].

It is generally agreed that mesenchymal cells are the main source of MMPs. In line with this, cardiac fibroblasts are the main producers of MMPs and TIMPs in the myocardium [73]. Polyakova et al. have shown that in patients with heart failure due to aortic stenosis, increases in ECM and activation of numerous MMPs as well as MT1-MMP parallel proliferation of cardiac fibroblasts. More directly, stretch of cardiac fibroblasts was shown to not only regulate fibroblast mediated ECM deposition, proliferation and differentiation [83,84] but also induce MT2-MMP expression in cultured cardiac fibroblasts [54]. More recently, collagen and TGF- β 1 were shown to induce MT1-MMP expression and enhance migration of cardiac fibroblasts [85].

8. ADAMs: classification, structure and function

ADAMs (*A Disintegrin And Metalloproteinase*) belong to a family of zinc transmembrane glycoproteins that have essential functions in cell–cell interactions (such as adhesion and fusion), in signaling, and in proteolysis (also termed ectodomain shedding) of important cytokines, cytokine receptors, and other targets [86]. A related family of ADAMs is the secreted forms, ADAMTSs (TS=thrombospondin motifs) which also bind to the ECM [87]. Like the MMPs, ADAMs also belong to the metzincin subgroup of zinc proteases [88]. A key difference between ADAMs and MMPs lies in the unique integrin receptor-binding disintegrin domain present in ADAMs.

The structure of ADAMs consists of a prodomain, a metalloprotease domain, a disintegrin domain, a cysteine-rich domain, an EGF-like domain, a transmembrane domain and a cytoplasmic tail (Fig. 1). The N-terminal prodomain principally functions to keep the metalloprotease site inactive but also acts as a chaperone for the proper folding of ADAMs' metalloprotease domain [86]. The metalloprotease domain hydrolyses protein substrates such as cytokines and growth factors, as well as their respective receptors. This process is termed ectodomain shedding and ADAMs are often termed “Sheddases”. The disintegrin domain binds matrix ligands of integrin receptors such as fibronectin. 11 ADAM disintegrin domains are known to interact with integrin receptors at the specific location of the “disintegrin loop” found on many ADAM molecules [89]. Among the integrins that bind to the ADAM disintegrin domain are α 4 β 1, α 4 β 7, α 5 β 1, α 6 β 1, α 9 β 1, α v β 3, and α v β 5 [90]. However, the most prominent integrin partner for ADAMs is α 9 β 1 [89]. The exact functions of the cysteine-rich domain and the EGF-like domain are unclear. The cytoplasmic tail of ADAMs is thought to be involved in signaling and may also serve to assemble a group of cytoplasmic adaptor molecules. Thus this multifunctional molecule, like integrins, can participate in “inside-out signaling” of metalloprotease activity; as well as “outside-in” regulation of cell signaling.

9. ADAM family members and expression

To date there have been 40 ADAMs identified in a variety of species. Certain ADAMs are primarily expressed in one tissue, whereas others show a broader expression pattern in several somatic tissues. A total of 14 ADAMs are expressed in a variety of somatic tissues and of those, several (ADAMs 10, 11, 12, 15, 17, and 19) are expressed in muscle [91]. Interestingly, in atrial tissue obtained from patients with atrial fibrillation, it was found that mRNA and protein levels of ADAM10 and ADAM15 were upregulated compared to tissue from patients with no history of atrial fibrillation [92]. This increased expression was thought to be involved in the atrial remodeling that occurs with atrial fibrillation. In addition, although ADAM11 expression was thought to be dominantly in central nervous system tissue where it is involved in adhesion of neurons and axon guidance, it was also found transiently expressed in fetal and perinatal cardiac tissue [93].

10. ADAM function in the heart

Tumor necrosis factor- α converting enzyme or TACE (ADAM17) has been shown to play an important role in myocardial development as shown by studies from ADAM17 $^{\Delta Z^n/\Delta Z^n}$ null mutant mice [94–96]. These mice have multiple abnormalities including a cardiac phenotype characterized by both increased cardiomyocyte size (hypertrophy) and proliferation [94].

ADAM19 is highly expressed in the conotruncus and endocardial cushion regions during cardiogenesis. This ADAM also plays an essential role in cardiac development as ADAM19 null mice display a ventricular septal defect, abnormal aortic and pulmonic valve structures as well as abnormal vasculature [97,98].

In addition to their role in cardiac organogenesis, ADAMs are thought to be involved in cardiac hypertrophy as illustrated through studies of their shedding and subsequent activation of heparin-binding epidermal growth factor-like growth factor (HB-EGF) [99] (Fig. 2). ADAM12 has been linked to the hypertrophic response of cultured neonatal rat cardiomyocytes stimulated with G-protein coupled receptor (GPCR) agonists such as PE, AII, and ET-1. Stimulation with GPCR agonists leads to transactivation of EGFR [100] by HB-EGF following the ectodomain shedding of HB-EGF mediated by ADAM12. Expression of a dominant-negative form of ADAM12 abolished the transactivation of EGFR mediated by GPCR agonists. Use of the protease inhibitor KB-R7785 attenuated hypertrophy caused by pressure overload (using an aortic banding model) as well as that caused by the *in vivo* stimulation by the GPCR agonists PE and AII. These data suggested that shedding of HB-EGF by ADAM12 is a component of the signal transduction pathway leading to cardiac

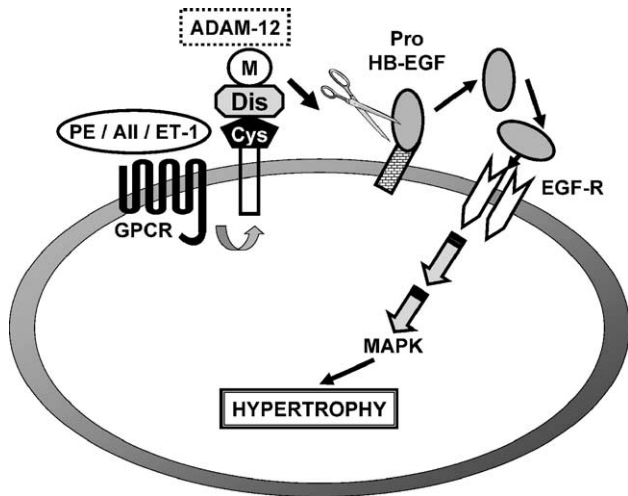


Fig. 2. The role of ADAM 12 in the hypertrophic process. GPCR stimulation by agonists such as phenylephrine (PE), AII or ET-1 leads to ADAM-12 activation. The activated ADAM evokes ectodomain shedding of the heparin-binding epidermal growth factor (HB-EGF), to allow EGF stimulation of its cognate receptor. In turn this activates MAPK signaling and cardiac hypertrophy.

hypertrophy. On the other hand, overexpression of ADAM12 in skeletal muscle of dystrophin-deficient *mdx* mice ameliorated the muscle cell necrosis and inflammation associated with this disease [101]. Although the mechanisms by which this occurred was not entirely clear, ADAM12 acting as an adhesion molecule may reduce damage caused by loss of cell–ECM contact, a phenom-

enon that has been shown to lead to cell necrosis and apoptosis. Alternatively, ADAM12 could benefit the *mdx* muscle by shedding trophic factors such as HB-EGF which may augment cell survival.

Expression of the soluble ADAMTS1 (ADAM with thrombospondin motifs-1) was upregulated in the endothelium as well as the myocardium of the infarcted rat heart. This was particularly evident within 3 h following the onset of the event, and especially in the infarcted zone [102]. The change in expression of ADAMTS1 in this MI model occurred more rapidly than changes in MMP expression which have been also shown to be upregulated after MI. The role that ADAMTS1 plays early after MI is not precisely known. Its function is unlikely to be only that of degradation of ECM components, since its expression occurs so early in the MI time course. In addition to their role in MI, ADAMs have also shown to be involved in the process of ischemic preconditioning. Ischemic preconditioning may activate ADAM17 via GPCR signaling. In turn, ADAM17 may trigger additional signal transduction processes by mediating TNF α shedding [103].

11. Interactions of integrins, MT-MMPs and ADAMs in cardiac remodeling

The interactions of these three classes of membrane-associated molecules in the cardiac remodeling process are

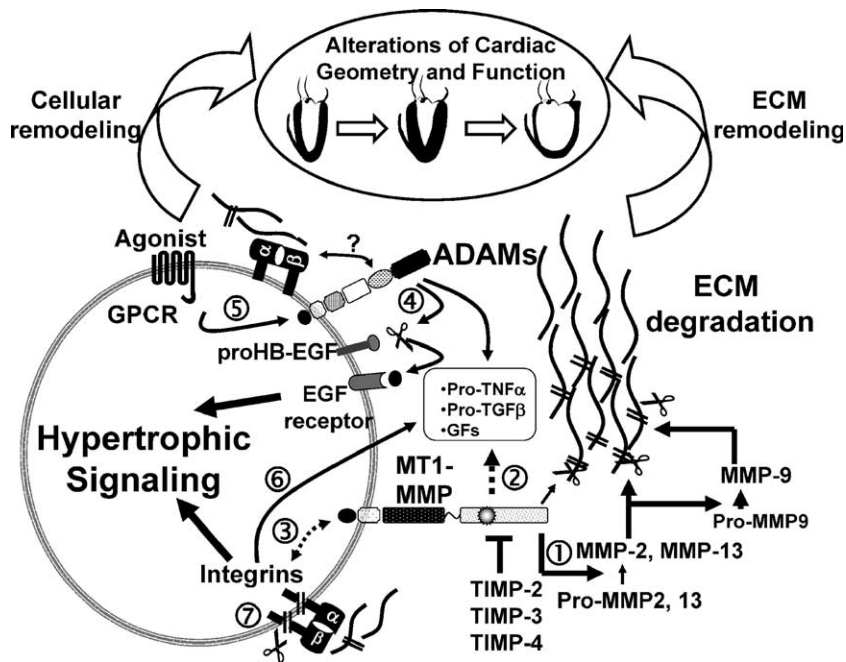


Fig. 3. A global diagram of how membrane associated proteases and integrins might function in the context of the cardiac remodeling process. The MT-MMPs can promote cardiac remodeling through several mechanisms: (1) by activating soluble proMMPs, (2) by shedding or activating growth factors (GFs), cytokines or peptides, and (3) by interacting with integrins. ADAMs may be involved in remodeling (4) through shedding or activation of growth factors including heparin-binding epidermal growth factor (HB-EGF), cytokines or peptides, or (5) by interacting with GPCRs. ADAMs can also participate in remodeling by causing ECM degradation. Integrins can participate in cardiac remodeling by hypertrophic signaling in cardiac myocytes, by (6) activating cytokines such as TGF- β and (7) through shedding of their extracellular segment.

poorly understood. We will present some actual and hypothetical conditions which might impact on myocardial remodeling.

It is important to emphasize that many extracellular proteases are expressed in a latent proenzyme state and that their expression is inducible, perhaps responding to environmental cues during cardiac remodeling [104]. It must also be recognized that through the remodeling process, ECM can alter its own bioactive properties via activation and release of growth factors and other biologically active peptides which are bound within the ECM. To date, little is known as to the dynamic nature of the formation, maintenance, and remodeling of the ECM though it is evident that modulation of cell–matrix and cell–cell adhesion is an important component of the dynamic remodeling process. Integrins, MT-MMPs and ADAMS, as membrane associated molecules, are likely to be important independent or collaborative members of this molecular response pathway. A global view of this is presented in Fig. 3.

One example (Fig. 4, panel A) is demonstrated by the fact that $\alpha v\beta 6$ integrins can bind and activate TGF β 1 latency-associated protein (LAP) [9]. TGF- β is an important cytokine in the fibrotic response of the heart. TGF- β stimulation of fibroblasts in turn causes increased expression of other integrins, e.g. $\alpha 5\beta 1$ and $\alpha 8\beta 1$ [10,18] while conversely, overexpression of integrins increases TGF- β expression [11]. Further, TGF- β 1 has been shown to increase MT1-MMP expression in carcinoma cells [105]. It is known that a) MT1-MMP can induce MMP2 and MMP9 activation, b) that MMP2 and 9 are important proteases which participate in the remodeling process [106,107], c) that MMP2 and 9 can activate TNF- α [108], and d) that TGF- β and TNF- α are also critical modulators of the remodeling process [36]. Given this, one concept of remodeling can implicate a complex interplay between MT-MMPs, integrins, cytokines and the ECM, to modulate matrix production, cell–matrix adhesion and perhaps cell migration of fibroblasts.

Another means of ECM remodeling through interactions between MT-MMPs and integrins might be through molecules like osteopontin (OPN) (Fig. 4, panel B). OPN has been classified as a matricellular protein as it resembles a matrix protein, yet also has cytokine-like properties including modulation of cellular migration and cell-mediated immunity. It is produced by both cardiac fibroblasts and myocytes and is upregulated in the hypertrophic and failing ventricle of humans and animals [109,110]. OPN binds to several integrins which are expressed on the cardiac fibroblast. Work in part by our own group has shown that OPN production is upregulated by AII, that OPN deficient mice have reduced AII-mediated cardiac fibrosis and hypertrophy likely due to the decreased adhesion to ECM and reduced cell proliferation by the OPN^{-/-} cardiac fibroblasts [111]. It is also known that some of the integrins bound by OPN (e.g. $\alpha v\beta 3$) are expressed on fibroblasts and can bind MT1-MMP [63]. When in close proximity on the

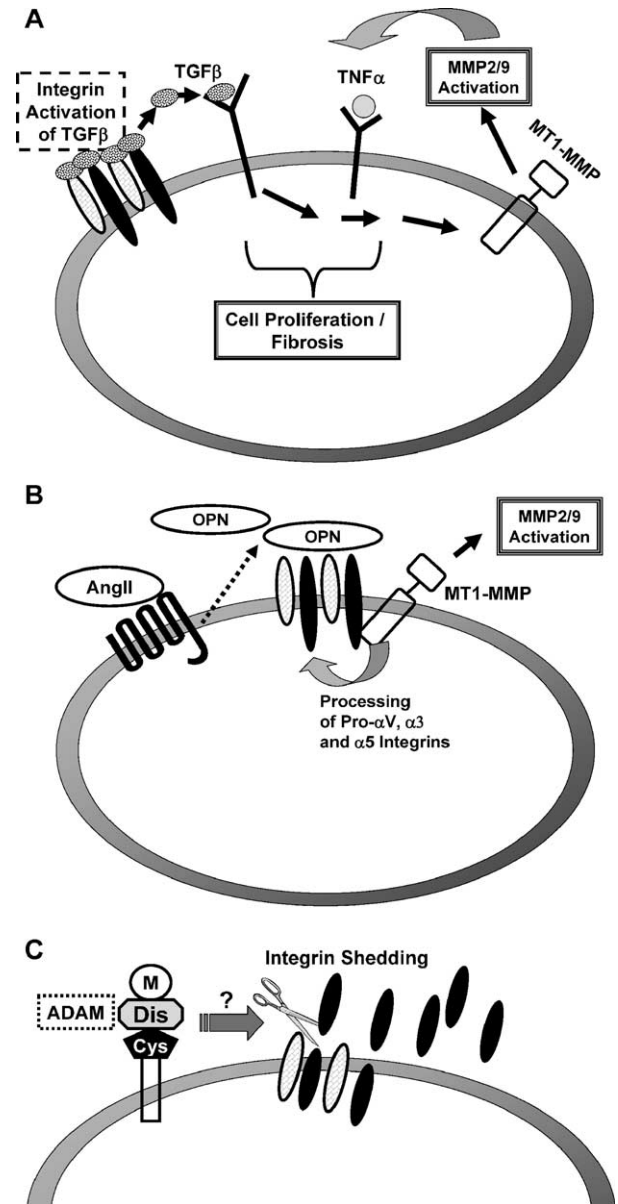


Fig. 4. Detailed examples of actual and hypothetical integrin, MT-MMP and ADAM interactions in the myocardium. **Panel A** — A complex interplay between cytokines, integrin, MT-MMPs and MMPs might modulate matrix production, cell adhesion and cell proliferation. Here integrins bind the inactive or latency-associated protein (LAP) form of TGF- β 1 and cause its activation and also increase expression of TGF- β . TGF- β in turn stimulates expression of integrins and MT1-MMP. MT1-MMP then leads to activation (directly/indirectly) of soluble MMPs and thus TNF- α activation. This combination of events leads to modulation of matrix production, cell adhesion and cell proliferation. **Panel B** — The matricellular protein OPN is upregulated by AII stimulation of cardiac fibroblasts and also binds to fibroblast integrins. Further, some of the integrins bound by OPN can bind and activate MT1-MMP, and lead to activation of soluble MMPs like MMP2 and MMP9. MT1-MMP may also process pro-forms of integrins. Thus a complex interplay of integrins, integrin ligands and MMPs may modulate dynamics of cell adhesion and release. **Panel C** — Shedding of integrin ectodomains may occur during the transition from compensated hypertrophy to heart failure. While the potential role of an ADAM in this process is illustrated, this remains unproven in heart. Shedding of integrins could rapidly “disconnect” cells from the ECM. The role of the shed integrin fragment is currently unknown.

same cell, MT1-MMP may collaborate with $\alpha v\beta 3$ to increase pro-MMP2 activation and possibly alter cell migration. This direct interaction is currently unproven in the myocardium. Additionally, MT1-MMP may process integrins such as pro- αv , $\alpha 3$ and $\alpha 5$. This MT-MMP mediated processing may be a means to regulate ECM–matrix adhesion, alter cell migration and perhaps even integrin signaling in the heart [112]. Again, while this level of regulation is documented in tumor cells, it remains hypothetical in the heart.

Binding of $\beta 1$ integrins to collagen by fibrosarcoma cells can activate Rac1, which in turn alters both MT1-MMP transcript expression, its distribution on the cell surface and then activation of MMP2 [113]. We have studied mice deficient in $\beta 1$ integrins specifically in the cardiac myocyte [114]. These mice develop progressive cardiac fibrosis and heart failure. Heart tissue from these mice showed activation of MT1-MMP and MMP2 vs. littermate control mice at time points which preceded any evidence of significant fibrosis or decrease in cardiac function (Shai, S-Y., Spinale, F. and Ross, R.S., unpublished observations). These results may seem paradoxical when compared to those in the sarcoma cells above. Thus the specific interactive role of integrins and MT-MMPs in the myocardium remains poorly understood.

As mentioned, ADAMs are unique in that they possess dual adhesive and proteolytic domains, and are protein-solubilizing proteases or “sheddas” [115]. With this property, the ADAMs can effectively activate pro-molecules (e.g. ADAM17/TACE mentioned above) or down-modulate cell surface receptors, in essence causing a “switching off” of signals from a cellular receptor whose ectodomain is cleaved and “shed” by the ADAM. This mechanism is appealing in that unlike a progressive down-regulation of gene expression, here, a threshold signal from one receptor sub-type (e.g. from a growth factor receptor or perhaps an integrin) could trigger activation of the “shedase.” The shedase could then cleave the ectodomain of the receptor that was propagating the initial signal. This would result in an unambiguous “off” signal as the receptor would no longer be present. As mentioned, ADAMs can directly interact with integrins. Goldsmith et al. and Ding et al. [116,117] have shown that integrins are shed from the myocyte surface during the evolution of hypertrophy transitioning to heart failure, but the specific role of ADAMs in this process is unknown (Fig. 4, panel C). This process may direct a dynamic modulation of myocyte–matrix adhesion, perhaps allowing changes in cell shape and rigidity. Further, shedding of the integrins would definitively alter signals transmitted from outside-in, through the integrin receptors. These authors have shown integrin shedding to occur from both cardiac fibroblasts and myocytes. Fibroblast shedding could allow for a more proliferative and “fluid” cell which might be required in both hypertrophic and post-infarct remodeling. The function of the shed integrin fragment is not well understood but

could potentially provide for feedback inhibition of the process itself, could block other cell surface intact integrin receptors from binding to ECM and seems to increase myocyte (but not fibroblast) adhesion to ECM (specifically collagen) [116].

12. Conclusion

The concepts of cardiac remodeling have evolved greatly over the last several hundred years. Recent work has begun to focus on the dynamic role of ECM and cell–ECM interactions in this process. The membrane associated molecules discussed in this review all play crucial roles in allowing cell adhesion to ECM, modification of the ECM and importantly, significant molecular remodeling of a host of cell surface and even soluble proteins. While significant advances have been made in the fundamental biology of these molecules, their function and particularly their interaction in the myocardium is poorly understood. We have provided some hypothetical scenarios regarding the functional interactions of the integrins, ADAMs and MT-MMPs. Clearly future studies are required to expand this knowledge base, and detail the true interactions which occur on the myocyte, fibroblast and other cells of the heart. This data could then perhaps allow development of unique therapeutics which could be used to appropriately modify the remodeling process.

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References

- [1] Hoshijima M, Chien KR. Mixed signals in heart failure: cancer rules. *J Clin Invest* 2002;109:849–55.
- [2] Dom GW, Molkenin JD. Manipulating cardiac contractility in heart failure: data from mice and men. *Circulation* 2004;109:150–8.
- [3] Benjamin IJ, Schneider MD. Learning from failure: congestive heart failure in the postgenomic age. *J Clin Invest* 2005;115:495–9.
- [4] Giancotti FG, Ruoslahti E. Integrin signaling. *Science* 1999;285:1028–32.
- [5] Ross RS, Borg TK. Integrins and the myocardium. *Circ Res* 2001;88:1112–9.
- [6] Hynes RO. Integrins: bidirectional, allosteric signaling machines. *Cell* 2002;110:673–87.
- [7] Ross RS. Molecular and mechanical synergy: cross-talk between integrins and growth factor receptors. *Cardiovasc Res* 2004;63:381–90.
- [8] MacKenna DA, Dolfi F, Vuori K, Ruoslahti E. Extracellular signal-regulated kinase and c-Jun NH2-terminal kinase activation by mechanical stretch is integrin-dependent and matrix-specific in rat cardiac fibroblasts. *J Clin Invest* 1998;101:301–10.
- [9] Ma LJ, Yang H, Gaspert A, Carlesso G, Barty MM, Davidson JM, et al. Transforming growth factor-beta-dependent and -independent

- pathways of induction of tubulointerstitial fibrosis in beta6(–/–) mice. *Am J Pathol* 2003;163:1261–73.
- [10] Dalton SL, Scharf E, Davey G, Assoian RK. Transforming growth factor-beta overrides the adhesion requirement for surface expression of alpha(5)beta(1) integrin in normal rat kidney fibroblasts. A necessary effect for induction of anchorage-independent growth. *J Biol Chem* 1999;274:30139–45.
- [11] Wang D, Sun L, Zborowska E, Willson JK, Gong J, Verragharavan J, et al. Control of type II transforming growth factor-beta receptor expression by integrin ligation. *J Biol Chem* 1999;274:12840–7.
- [12] Terracio L, Rubin K, Gullberg D, Balog E, Carver W, Jyring R, et al. Expression of collagen binding integrins during cardiac development and hypertrophy. *Circ Res* 1991;68:734–44.
- [13] Gullberg D, Tingstrom A, Thuresson AC, Olsson L, Terracio L, Borg TK, et al. Beta 1 integrin-mediated collagen gel contraction is stimulated by PDGF. *Exp Cell Res* 1990;186:264–72.
- [14] Sadoshima J, Izumo S. Mechanical stretch rapidly activates multiple signal transduction pathways in cardiac myocytes: potential involvement of an autocrine/paracrine mechanism. *EMBO J* 1993;12:1681–92.
- [15] Yamazaki T, Tobe K, Hoh E, Maemura K, Kaida T, Komuro I, et al. Mechanical loading activates mitogen-activated protein kinase and S6 peptide kinase in cultured rat cardiac myocytes. *J Biol Chem* 1993;268:12069–76.
- [16] Sadoshima J, Xu Y, Slayter HS, Izumo S. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. *Cell* 1993;75:977–84.
- [17] Burgess ML, Carver WE, Terracio L, Wilson SP, Wilson MA, Borg TK. Integrin-mediated collagen gel contraction by cardiac fibroblasts. Effects of angiotensin II. *Circ Res* 1994;74:291–8.
- [18] Thibault G, Lacombe MJ, Schnapp LM, Lacasse A, Bouzeghrane F, Lapalme G. Upregulation of alpha(8)beta(1)-integrin in cardiac fibroblast by angiotensin II and transforming growth factor-beta1. *Am J Physiol Cell Physiol* 2001;281:C1457–67.
- [19] Ross RS, Pham C, Shai SY, Goldhaber JJ, Fenczik C, Glembotski CC, et al. Beta1 integrins participate in the hypertrophic response of rat ventricular myocytes. *Circ Res* 1998;82:1160–72.
- [20] Babbitt CJ, Shai SY, Harpf AE, Pham CG, Ross RS. Modulation of integrins and integrin signaling molecules in the pressure-loaded murine ventricle. *Histochem Cell Biol* 2002;118:431–9.
- [21] Ogawa E, Saito Y, Harada M, Kamitani S, Kuwahara K, Miyamoto Y, et al. Outside-in signalling of fibronectin stimulates cardiomyocyte hypertrophy in cultured neonatal rat ventricular myocytes. *J Mol Cell Cardiol* 2000;32:765–76.
- [22] Laser M, Willey CD, Jiang W, Cooper G, Menick DR, Zile MR, et al. Integrin activation and focal complex formation in cardiac hypertrophy. *J Biol Chem* 2000;275:35624–30.
- [23] Sharp WW, Simpson DG, Borg TK, Samarel AM, Terracio L. Mechanical forces regulate focal adhesion and costamere assembly in cardiac myocytes. *Am J Physiol* 1997;273:H546–56.
- [24] Keller RS, Shai SY, Babbitt CJ, Pham CG, Solaro RJ, Valencik ML, et al. Disruption of integrin function in the murine myocardium leads to perinatal lethality, fibrosis, and abnormal cardiac performance. *Am J Pathol* 2001;158:1079–90.
- [25] Pham CG, Harpf AE, Keller RS, Vu HT, Shai SY, Loftus JC, et al. Striated muscle-specific beta(1D)-integrin and FAK are involved in cardiac myocyte hypertrophic response pathway. *Am J Physiol Heart Circ Physiol* 2000;279:H2916–26.
- [26] Taylor JM, Rovin JD, Parsons JT. A role for focal adhesion kinase in phenylephrine-induced hypertrophy of rat ventricular cardiomyocytes. *J Biol Chem* 2000;275:19250–7.
- [27] Domingos PP, Fonseca PM, Nadruz W, Franchini Jr KG. Load-induced focal adhesion kinase activation in the myocardium: role of stretch and contractile activity. *Am J Physiol Heart Circ Physiol* 2002;282:H556–64.
- [28] Bayer AL, Heidkamp MC, Patel N, Porter MJ, Engman SJ, Samarel AM. PYK2 expression and phosphorylation increases in pressure overload-induced left ventricular hypertrophy. *Am J Physiol Heart Circ Physiol* 2002;283:H695–706.
- [29] Heidkamp MC, Bayer AL, Scully BT, Eble DM, Samarel AM. Activation of focal adhesion kinase by protein kinase C epsilon in neonatal rat ventricular myocytes. *Am J Physiol Heart Circ Physiol* 2003;285:H1684–96.
- [30] Aikawa R, Nagai T, Kudoh S, Zou Y, Tanaka M, Tamura M, et al. Integrins play a critical role in mechanical stress-induced p38 MAPK activation. *Hypertension* 2002;39:233–8.
- [31] Communal C, Singh M, Menon B, Xie Z, Colucci WS, Singh K. beta1 integrins expression in adult rat ventricular myocytes and its role in the regulation of beta-adrenergic receptor-stimulated apoptosis. *J Cell Biochem* 2003;89:381–8.
- [32] Wang YG, Samarel AM, Lipsius SL. Laminin acts via beta1 integrin signalling to alter cholinergic regulation of L-type Ca2+ current in cat atrial myocytes. *J Physiol (Lond)* 2000;526:57–68.
- [33] Cheng Q, Ross RS, Walsh KB. Overexpression of the integrin beta(1A) subunit and the beta(1A) cytoplasmic domain modifies the beta-adrenergic regulation of the cardiac L-type Ca(2+)current. *J Mol Cell Cardiol* 2004;36:809–19.
- [34] Overall CM, Lopez-Otin C. Strategies for MMP inhibition in cancer: innovations for the post-trial era. *Nat Rev Cancer* 2002;2:657–72.
- [35] Lindsey ML. MMP induction and inhibition in myocardial infarction. *Heart Fail Rev* 2004;9:7–19.
- [36] Janicki JS, Brower GL, Gardner JD, Chancey AL, Stewart Jr JA. The dynamic interaction between matrix metalloproteinase activity and adverse myocardial remodeling. *Heart Fail Rev* 2004;9:33–42.
- [37] Li YY, McTiernan CF, Feldman AM. Interplay of matrix metalloproteinases, tissue inhibitors of metalloproteinases and their regulators in cardiac matrix remodeling. *Cardiovasc Res* 2000;46:214–24.
- [38] Zucker S, Pei D, Cao J, Lopez-Otin C. Membrane type-matrix metalloproteinases (MT-MMP). *Curr Top Dev Biol* 2003;54:1–74.
- [39] Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res* 2003;92:827–39.
- [40] Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Cancer* 2002;2:161–74.
- [41] Pei D. Identification and characterization of the fifth membrane-type matrix metalloproteinase MT5-MMP. *J Biol Chem* 1999;274:8925–32.
- [42] Velasco G, Cal S, Merlos-Suarez A, Ferrando AA, Alvarez S, Nakano A, et al. Human MT6-matrix metalloproteinase: identification, progelatinase A activation, and expression in brain tumors. *Cancer Res* 2000;60:877–82.
- [43] Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol* 2001;17:463–516.
- [44] Soumni NE, Noel A. Membrane type-matrix metalloproteinases and tumor progression. *Biochimie* 2005;87:329–42.
- [45] Osenkowski P, Toth M, Fridman R. Processing, shedding, and endocytosis of membrane type 1-matrix metalloproteinase (MT1-MMP). *J Cell Physiol* 2004;200:2–10.
- [46] Jiang A, Lehti K, Wang X, Weiss SJ, Keski-Oja J, Pei D. Regulation of membrane-type matrix metalloproteinase 1 activity by dynamin-mediated endocytosis. *Proc Natl Acad Sci U S A* 2001;98:13693–8.
- [47] Lehti K, Valtanen H, Wickstrom SA, Lohi J, Keski-Oja J. Regulation of membrane-type-1 matrix metalloproteinase activity by its cytoplasmic domain. *J Biol Chem* 2000;275:15006–13.
- [48] Uekita T, Itoh Y, Yana I, Ohno H, Seiki M. Cytoplasmic tail-dependent internalization of membrane-type 1 matrix metalloproteinase is important for its invasion-promoting activity. *J Cell Biol* 2001;155:1345–56.
- [49] Itoh Y, Kajita M, Kinoh H, Mori H, Okada A, Seiki M. Membrane type 4 matrix metalloproteinase (MT4-MMP, MMP-17) is a glycosylphosphatidylinositol-anchored proteinase. *J Biol Chem* 1999;274:34260–6.

- [50] Kojima S, Itoh Y, Matsumoto S, Masuho Y, Seiki M. Membrane-type 6 matrix metalloproteinase (MT6-MMP, MMP-25) is the second glycosyl-phosphatidyl inositol (GPI)-anchored MMP. *FEBS Lett* 2000;480:142–6.
- [51] Origuchi T, Migita K, Nakashima T, Tominaga M, Nakamura H, Nakashima M, et al. IL-1-mediated expression of membrane type matrix-metalloproteinase in rheumatoid osteoblasts. *Clin Exp Rheumatol* 2000;18:333–9.
- [52] Han YP, Tuan TL, Wu H, Hughes M, Garner WL. TNF-alpha stimulates activation of pro-MMP2 in human skin through NF-(kappa)B mediated induction of MT1-MMP. *J Cell Sci* 2001;114:131–9.
- [53] Stawowy P, Margeta C, Kallisch H, Seidah NG, Chretien M, Fleck E, et al. Regulation of matrix metalloproteinase MT1-MMP/MMP-2 in cardiac fibroblasts by TGF-beta1 involves furin-convertase. *Cardiovasc Res* 2004;63:87–97.
- [54] Tyagi SC, Lewis K, Pikes D, Marcello A, Mujumdar VS, Smiley LM, et al. Stretch-induced membrane type matrix metalloproteinase and tissue plasminogen activator in cardiac fibroblast cells. *J Cell Physiol* 1998;176:374–82.
- [55] Galvez BG, Matias-Roman S, Yanez-Mo M, Sanchez-Madrid F, Arroyo AG. ECM regulates MT1-MMP localization with beta1 or alphavbeta3 integrins at distinct cell compartments modulating its internalization and activity on human endothelial cells. *J Cell Biol* 2002;159:509–21.
- [56] Ellerbroek SM, Wu YI, Overall CM, Stack MS. Functional interplay between type I collagen and cell surface matrix metalloproteinase activity. *J Biol Chem* 2001;276:24833–42.
- [57] d'Ortho MP, Will H, Atkinson S, Butler G, Messent A, Gavrilovic J, et al. Membrane-type matrix metalloproteinases 1 and 2 exhibit broad-spectrum proteolytic capacities comparable to many matrix metalloproteinases. *Eur J Biochem* 1997;250:751–7.
- [58] English WR, Puente XS, Freije JM, Knauper V, Amour A, Merryweather J, et al. Membrane type 4 matrix metalloproteinase (MMP17) has tumor necrosis factor-alpha convertase activity but does not activate pro-MMP2. *J Biol Chem* 2000;275:14046–55.
- [59] Knauper V, Will H, Lopez-Otin C, Smith B, Atkinson SJ, Stanton H, et al. Cellular mechanisms for human procollagenase-3 (MMP-13) activation. Evidence that MT1-MMP (MMP-14) and gelatinase A (MMP-2) are able to generate active enzyme. *J Biol Chem* 1996;271:17124–31.
- [60] Zhou Z, Apte SS, Soininen R, Cao R, Baaklini GY, Rausser RW, et al. Impaired endochondral ossification and angiogenesis in mice deficient in membrane-type matrix metalloproteinase I. *Proc Natl Acad Sci U S A* 2000;97:4052–7.
- [61] Morrison CJ, Butler GS, Bigg HF, Roberts CR, Soloway PD, Overall CM. Cellular activation of MMP-2 (gelatinase A) by MT2-MMP occurs via a TIMP-2-independent pathway. *J Biol Chem* 2001;276:47402–10.
- [62] Hernandez-Barrantes S, Bernardo M, Toth M, Fridman R. Regulation of membrane type-matrix metalloproteinases. *Semin Cancer Biol* 2002;12:131–8.
- [63] Deryugina EI, Ratnikov B, Monosov E, Postnova TI, DiScipio R, Smith JW, et al. MT1-MMP initiates activation of pro-MMP-2 and integrin alphavbeta3 promotes maturation of MMP-2 in breast carcinoma cells. *Exp Cell Res* 2001;263:209–23.
- [64] Toth M, Chvyrkova I, Bernardo MM, Hernandez-Barrantes S, Fridman R. Pro-MMP-9 activation by the MT1-MMP/MMP-2 axis and MMP-3: role of TIMP-2 and plasma membranes. *Biochem Biophys Res Commun* 2003;308:386–95.
- [65] Gao G, Plaas A, Thompson VP, Jin S, Zuo F, Sandy JD. ADAMTS4 (aggrecanase-1) activation on the cell surface involves C-terminal cleavage by glycosylphosphatidyl inositol-anchored membrane type 4-matrix metalloproteinase and binding of the activated proteinase to chondroitin sulfate and heparan sulfate on syndecan-1. *J Biol Chem* 2004;279:10042–51.
- [66] Puente XS, Pendas AM, Llano E, Velasco G, Lopez-Otin C. Molecular cloning of a novel membrane-type matrix metalloproteinase from a human breast carcinoma. *Cancer Res* 1996;56:944–9.
- [67] Matsumoto S, Katoh M, Saito S, Watanabe T, Masuho Y. Identification of soluble type of membrane-type matrix metalloproteinase-3 formed by alternatively spliced mRNA. *Biochim Biophys Acta* 1997;1354:159–70.
- [68] Takino T, Sato H, Shinagawa A, Seiki M. Identification of the second membrane-type matrix metalloproteinase (MT-MMP-2) gene from a human placenta cDNA library. MT-MMPs form a unique membrane-type subclass in the MMP family. *J Biol Chem* 1995;270:23013–20.
- [69] Will H, Hinzmann B. cDNA sequence and mRNA tissue distribution of a novel human matrix metalloproteinase with a potential transmembrane segment. *Eur J Biochem* 1995;231:602–8.
- [70] Coker ML, Thomas CV, Clair MJ, Hendrick JW, Krombach RS, Galis ZS, et al. Myocardial matrix metalloproteinase activity and abundance with congestive heart failure. *Am J Physiol* 1998;274:H1516–23.
- [71] Deschamps AM, Apple KA, Leonardi AH, McLean JE, Yarbrough WM, Stroud RE, et al. Myocardial interstitial matrix metalloproteinase activity is altered by mechanical changes in LV Load: interaction with the angiotensin type 1 receptor. *Circ Res* 2005;96:1110–8.
- [72] Deschamps AM, Yarbrough WM, Squires CE, Allen RA, McCleister DM, Dowdy KB, et al. Trafficking of the membrane type-1 matrix metalloproteinase in ischemia and reperfusion: relation to interstitial membrane type-1 matrix metalloproteinase activity. *Circulation* 2005;111:1166–74.
- [73] Polyakova V, Hein S, Kostin S, Ziegelhoeffer T, Schaper J. Matrix metalloproteinases and their tissue inhibitors in pressure-overloaded human myocardium during heart failure progression. *J Am Coll Cardiol* 2004;44:1609–18.
- [74] Wilson EM, Moainie SL, Baskin JM, Lowry AS, Deschamps AM, Mukherjee R, et al. Region- and type-specific induction of matrix metalloproteinases in post-myocardial infarction remodeling. *Circulation* 2003;107:2857–63.
- [75] Coker ML, Jolly JR, Joffs C, Etoh T, Holder JR, Bond BR, et al. Matrix metalloproteinase expression and activity in isolated myocytes after neurohormonal stimulation. *Am J Physiol Heart Circ Physiol* 2001;281:H543–51.
- [76] Wang TL, Yang YH, Chang H, Hung CR. Angiotensin II signals mechanical stretch-induced cardiac matrix metalloproteinase expression via JAK-STAT pathway. *J Mol Cell Cardiol* 2004;37:785–94.
- [77] Menon B, Singh M, Singh K. Matrix metalloproteinases mediate beta-adrenergic receptor-stimulated apoptosis in adult rat ventricular myocytes. *Am J Physiol Cell Physiol* 2005;289:C168–76.
- [78] Wang BW, Chang H, Lin S, Kuan P, Shyu KG. Induction of matrix metalloproteinases-14 and -2 by cyclical mechanical stretch is mediated by tumor necrosis factor-alpha in cultured human umbilical vein endothelial cells. *Cardiovasc Res* 2003;59:460–9.
- [79] Spinale FG, Coker ML, Bond BR, Zellner JL. Myocardial matrix degradation and metalloproteinase activation in the failing heart: a potential therapeutic target. *Cardiovasc Res* 2000;46:225–38.
- [80] Spinale FG, Coker ML, Heung LJ, Bond BR, Gunasinghe HR, Etoh T, et al. A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure. *Circulation* 2000;102:1944–9.
- [81] Suzuki S, Sato M, Senoo H, Ishikawa K. Direct cell-cell interaction enhances pro-MMP-2 production and activation in co-culture of laryngeal cancer cells and fibroblasts: involvement of EMMPRIN and MT1-MMP. *Exp Cell Res* 2004;293:259–66.
- [82] Berditchevski F, Chang S, Bodorova J, Hemler ME. Generation of monoclonal antibodies to integrin-associated proteins. Evidence that alpha3beta1 complexes with EMMPRIN/basigin/OX47/M6. *J Biol Chem* 1997;272:29174–80.
- [83] Lee AA, Delhaas T, McCulloch AD, Villarreal FJ. Differential responses of adult cardiac fibroblasts to in vitro biaxial strain patterns. *J Mol Cell Cardiol* 1999;31:1833–43.

- [84] Atance J, Yost MJ, Carver W. Influence of the extracellular matrix on the regulation of cardiac fibroblast behavior by mechanical stretch. *J Cell Physiol* 2004;200:377–86.
- [85] Guo C, Piacentini L. Type I collagen-induced MMP-2 activation coincides with up-regulation of membrane type 1-matrix metalloproteinase and TIMP-2 in cardiac fibroblasts. *J Biol Chem* 2003;278:46699–708.
- [86] Seals DF, Courtneidge SA. The ADAMs family of metalloproteases: multidomain proteins with multiple functions. *Genes Dev* 2003;17:7–30.
- [87] Porter S, Clark IM, Kevorkian L, Edwards DR. The ADAMTS metalloproteinases. *Biochem J* 2005;386:15–27.
- [88] Stocker W, Grams F, Baumann U, Reinemer P, Gomis-Ruth FX, McKay DB, et al. The metzincins-topological and sequential relations between the astacins, adamalysins, serralyisins, and matrixins (collagenases) define a superfamily of zinc-peptidases. *Protein Sci* 1995;4:823–40.
- [89] White JM. ADAMs: modulators of cell–cell and cell–matrix interactions. *Curr Opin Cell Biol* 2003;15:598–606.
- [90] Bridges LC, Bowditch RD. ADAM-integrin interactions: potential integrin regulated ectodomain shedding activity. *Curr Pharm Des* 2005;11:837–47.
- [91] Primakoff P, Myles DG. The ADAM gene family: surface proteins with adhesion and protease activity. *Trends Genet* 2000;16:83–7.
- [92] Arndt M, Lendeckel U, Rocken C, Nepple K, Wolke C, Spiess A, et al. Altered expression of ADAMs (A Disintegrin And Metalloproteinase) in fibrillating human atria. *Circulation* 2002;105:720–5.
- [93] Rybnikova E, Karkkainen I, Peltto-Huikko M, Huovila AP. Developmental regulation and neuronal expression of the cellular disintegrin ADAM11 gene in mouse nervous system. *Neuroscience* 2002;112:921–34.
- [94] Shi W, Chen H, Sun J, Buckley S, Zhao J, Anderson KD, et al. TACE is required for fetal murine cardiac development and modeling. *Dev Biol* 2003;261:371–80.
- [95] Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, et al. An essential role for ectodomain shedding in mammalian development. *Science* 1998;282:1281–4.
- [96] Zhao J, Chen H, Peschon JJ, Shi W, Zhang Y, Frank SJ, et al. Pulmonary hypoplasia in mice lacking tumor necrosis factor- α converting enzyme indicates an indispensable role for cell surface protein shedding during embryonic lung branching morphogenesis. *Dev Biol* 2001;232:204–18.
- [97] Zhou HM, Weskamp G, Chesneau V, Sahin U, Vortkamp A, Horiuchi K, et al. Essential role for ADAM19 in cardiovascular morphogenesis. *Mol Cell Biol* 2004;24:96–104.
- [98] Kurohara K, Komatsu K, Kurisaki T, Masuda A, Irie N, Asano M, et al. Essential roles of Meltrin beta (ADAM19) in heart development. *Dev Biol* 2004;267:14–28.
- [99] Asakura M, Kitakaze M, Takashima S, Liao Y, Ishikura F, Yoshinaka T, et al. Cardiac hypertrophy is inhibited by antagonism of ADAM12 processing of HB-EGF: metalloproteinase inhibitors as a new therapy. *Nat Med* 2002;8:35–40.
- [100] Daub H, Weiss FU, Wallasch C, Ullrich A. Role of transactivation of the EGF receptor in signalling by G-protein-coupled receptors. *Nature* 1996;379:557–60.
- [101] Kronqvist P, Kawaguchi N, Albrechtsen R, Xu X, Schroder HD, Moghadasszadeh B, et al. ADAM12 alleviates the skeletal muscle pathology in mdx dystrophic mice. *Am J Pathol* 2002;161:1535–40.
- [102] Nakamura K, Hirohata S, Murakami T, Miyoshi T, Demircan K, Oohashi T, et al. Dynamic induction of ADAMTS1 gene in the early phase of acute myocardial infarction. *J Biochem (Tokyo)* 2004;136:439–46.
- [103] Ichikawa Y, Miura T, Nakano A, Miki T, Nakamura Y, Tsuchihashi K, et al. The role of ADAM protease in the tyrosine kinase-mediated trigger mechanism of ischemic preconditioning. *Cardiovasc Res* 2004;62:167–75.
- [104] Rao VU, Spinale FG. Controlling myocardial matrix remodeling: implications for heart failure. *Cardiol Rev* 1999;7:136–43.
- [105] Munshi HG, Wu YI, Mukhopadhyay S, Ottaviano AJ, Sassano A, Koblinski JE, et al. Differential regulation of membrane type 1-matrix metalloproteinase activity by ERK 1/2- and p38 MAPK-modulated tissue inhibitor of metalloproteinases 2 expression controls transforming growth factor- β 1-induced pericellular collagenolysis. *J Biol Chem* 2004;279:39042–50.
- [106] Heymans S, Lupu F, Terclavers S, Vanwetswinkel B, Herbert JM, Baker A, et al. Loss or inhibition of uPA or MMP-9 attenuates LV remodeling and dysfunction after acute pressure overload in mice. *Am J Pathol* 2005;166:15–25.
- [107] Matsumura S, Iwanaga S, Mochizuki S, Okamoto H, Ogawa S, Okada Y. Targeted deletion or pharmacological inhibition of MMP-2 prevents cardiac rupture after myocardial infarction in mice. *J Clin Invest* 2005;115:599–609.
- [108] Gearing AJ, Beckett P, Christodoulou M, Churchill M, Clements J, Davidson AH, et al. Processing of tumour necrosis factor- α precursor by metalloproteinases. *Nature* 1994;370:555–7.
- [109] Graf K, Do YS, Ashizawa N, Meehan WP, Giachelli CM, Marboe CC, et al. Myocardial osteopontin expression is associated with left ventricular hypertrophy. *Circulation* 1997;96:3063–71.
- [110] Hsueh WA, Law RE, Do YS. Integrins, adhesion, and cardiac remodeling. *Hypertension* 1998;31:176–80.
- [111] Collins AR, Schnee J, Wang W, Kim S, Fishbein MC, Brummer D, et al. Osteopontin modulates angiotensin II-induced fibrosis in the intact murine heart. *J Am Coll Cardiol* 2004;43:1698–705.
- [112] Ratnikov BI, Rozanov DV, Postnova TI, Baci PG, Zhang H, DiScipio RG, et al. An alternative processing of integrin α (v) subunit in tumor cells by membrane type-1 matrix metalloproteinase. *J Biol Chem* 2002;277:7377–85.
- [113] Zhuge Y, Xu J. Rac1 mediates type I collagen-dependent MMP-2 activation. Role in cell invasion across collagen barrier. *J Biol Chem* 2001;276:16248–56.
- [114] Shai SY, Harpf AE, Babbitt CJ, Jordan MC, Fishbein MC, Chen J, et al. Cardiac myocyte-specific excision of the β 1 integrin gene results in myocardial fibrosis and cardiac failure. *Circ Res* 2002;90:458–64.
- [115] Dello SP, Rovida E. Transmodulation of cell surface regulatory molecules via ectodomain shedding. *Biol Chem* 2002;383:69–83.
- [116] Goldsmith EC, Carver W, McFadden A, Goldsmith JG, Price RL, Sussman M, et al. Integrin shedding as a mechanism of cellular adaptation during cardiac growth. *Am J Physiol Heart Circ Physiol* 2003;284:H2227–34.
- [117] Ding B, Price RL, Goldsmith EC, Borg TK, Yan X, Douglas PS, et al. Left ventricular hypertrophy in ascending aortic stenosis mice: anoikis and the progression to early failure. *Circulation* 2000;101:2854–62.