Short Conceptual Overview

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Matrix metalloproteinases: an emerging role in regulation of actin microfilament system

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Abstract: Matrix metalloproteinases (MMPs) are implicated in many physiological and pathological processes, including contraction, migration, differentiation, and proliferation. These processes all involve cell phenotype changes, known to be accompanied by reorganization of actin cytoskeleton. Growing evidence indicates a correlation between MMP activity and the dynamics of actin system, suggesting their mutual regulation. Here, data on the influence of MMPs on the actin microfilament system, on the one hand, and the dependence of MMP expression and activation on the organization of actin structures, on the other hand, are reviewed. The different mechanisms of putative actin-MMP regulation are discussed.

Keywords: actin cytoskeleton; extracellular matrix; matrix metalloproteinases; smooth muscle actin.

Introduction

Matrix metalloproteinases (MMPs) are zinc- and calcium-dependent endopeptidases that can degrade all the extracellular matrix (ECM) structural elements. They play important roles in many physiological processes, such as embryonic development, morphogenesis, reproduction, and tissue remodeling (1–4), as well as different pathologies (5–8). These processes all involve changes in cell phenotype, which are typically accompanied by actin cytoskeleton dynamics. This review is aimed to highlight interdependence between actin microfilament system and MMPs in different cell types and speculate on their mutual regulation.

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General structure of MMPs

MMPs all share a number of common features and include several domains. The N-terminal signal domain enhances protein export across the cell membrane into extracellular space. Propeptide domain binding with Zn^{2+} in active site maintains MMP molecule in latent form. The majority of MMPs release as inactive proenzymes. Hydrolytic removal of propeptide domain and release of the Zn^{2+}-binding center is followed by the activation of MMP. Endopeptidase activity of MMPs is provided by the catalytic domain that includes two Zn^{2+} ions and three Ca^{2+} ions (9).

Digestion of ECM by MMPs

All MMPs are able to degrade at least one component of the ECM. The different members of this family are specialized in degrading different sets of matrix proteins, although their substrate specificities may overlap. To date about 30 types of MMPs are described and classified into several groups based on their matrix substrate specificities and amino acid sequence similarity, i.e. collagenases (MMP-1, -8, and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, and -11), matrilysins (MMP-7 and -26), membrane-type MMPs (MMP-14, -15, -16, -17, -24, and -25), enamelysin (MMP-20), and others (MMP-19, -21, -23, -27, and -28) (10, 11). Collagenases cleave interstitial collagens I, II, and III and other ECM molecules and soluble proteins. Gelatinases (MMP-2 and MMP-9) readily digest gelatin (11). They also digest a number of other ECM molecules including type IV, V, and XI collagens, laminin, aggrecan core protein, etc. MMP-2 further digests collagens I, II, and III. The membrane-bound MT-MMPs may digest collagens on or near the cell surface. All MT-MMPs, except MT4-MMP (MMP-17), can activate proMMP-2. For a detailed description of ECM-dependent activities of different MMPs, see the review by Nagase et al. (11).

Non-matrix substrates for MMPs

Although MMPs were initially described as ECM-remodeling proteases, data indicate that their role is not limited to matrix digestion. MMPs can also cleave a variety of non-matrix proteins including cytokines, growth factors, lipoproteins, and clotting factors, leading to their shedding, activation or inactivation (12). Moreover, it was shown that some MMPs may be involved in direct N-cadherin shedding, thereby inducing proliferative phenotype in cells. For example, MMP9 and MMP12, but not MMP2 or MMP14, were shown to cause N-cadherin shedding and activating the β-catenin signaling pathway on vascular smooth muscle cells (VSMCs) and promote their proliferation (13). Moreover, Goldsmith et al. (14) proposed a role for MMPs in integrin shedding. The authors have shown that, in neonatal rat cardiac fibroblasts, but not in myocytes, inhibition of MMPs leads to a clear dose-dependent inhibition of shedding of the extracellular β_1-integrin domain into the extracellular environment. However, the function of the shed β_1-integrin fragment was not defined. The authors suggest that it may provide a feedback signal to regulate receptor distribution on the cell surface or bind to specific ECM components in turn enhancing or inhibiting some cellular functions (14).

Besides a lot of studies relating the extracellular role of MMPs, their intracellular action is also contemplated. In cardiomyocytes, the activity of MMPs in mitochondria was shown (15), where the mitochondrial accumulation of MMP-9 was related to arrhythmia and impaired contractility (16, 17). MMP-2 was further detected in the nuclei of heart and liver cells (18). Moreover, a truncated yet active fragment of MMP-3 was localized to the nuclei of several human cancer cell lines (19). However, the biological role for MMPs within the nucleus remains unclear. Some authors credit it with nuclear matrix degradation (20).

A further role for MMPs in myofibril degradation is proposed. In the hearts exposed to oxygen stress-induced ischemic reperfusion injury MMP-2 was shown to be involved in digestion of sarcomeric proteins, including α-actinin (21), troponin I (15), myosin light chain-1 (22), myosin light chain-2 (23), and titin (24). Sarcomeric protein degradation led to contractile dysfunction, which was protected by the inhibition of MMP-2 action (25). In normal skeletal muscle, MMP-2 was detected in Z-lines of the sarcomeres, in the nuclear membrane, and in mitochondria (26).

Therefore, MMPs are likely to act as intracellular proteases, modulating different cell functions. However, mechanisms targeting active MMPs to intracellular compartments and the mechanisms of their intracellular activation are not fully understood. It is believed that intracellular MMPs may be splice variants lacking a signal sequence or MMPs with an ineffective signal sequence to target them to the endoplasmic reticulum (25, 27).

The ECM-independent functions of MMPs are discussed in greater detail in Ref. (28).

Regulation of MMPs

MMPs are tightly regulated at several levels including transcriptional, post-transcriptional, and post-translational. The expression of most MMPs is primarily regulated at transcriptional level, with the different MMPs having varying temporal and spatial expression patterns (29). The expression of MMPs can be up-regulated in different cells in response to many factors including proinflammatory cytokines and growth factors (10). Various exogenous and endogenous stimuli may also regulate MMPs at post-transcriptional level by stabilizing and/or destabilizing mRNA transcripts (30). The stabilization of MMP-1 and -3 transcripts by phorbol esters and epidermal growth factor in fibroblasts and stabilization of MMP-13 transcripts in osteoblasts by platelet-derived growth factor and glucocorticoids as well as destabilization by transforming growth factor beta (TGF-β) were shown (31, 32). Several studies indicate that MMP-2 activity is also regulated via non-proteolytic post-translational modifications of the full-length zymogen, by S-glutathiolation, S-nitrosylation, and phosphorylation (33–36). In addition, MMP activity may be regulated directly by their endogenous inhibitors named tissue inhibitors of metalloproteinases (TIMMPs), which can reversibly bind to activated MMPs (32, 37, 38).

Correlation between MMPs and actin cytoskeleton organization

Many cellular functions such as migration, contraction, proliferation, and differentiation are associated with MMP dynamics. Significantly, these functions are characterized by distinct cellular phenotypes, dependent considerably on the organization of actin microfilament system. Increasing evidence describes a correlation between MMP activity and the dynamics of actin structures in different cell types. It was shown, e.g. that MMPs are influenced by actin polymerization. Induced production of MMP-9 in SNB19 glioma cells and constitutive expression of MMP-9 in HT1080 fibrosarcoma cells were lost

following treatment of these cells with an inhibitor of actin polymerization cytochalasin-D. However, treatment with cytochalasin-D did not affect MMP-2 expression in HT1080 cells (39). According to another study, disruption of actin cytoskeleton organization in human trabecular meshwork cells, induced by direct inhibitors of actin polymerization cytochalasin D, and latrunculin A, was followed by the activation of MMP-2 and the reduction in pro-MMP-2, suggesting that MMP-2 is regulated via proteolytic activation of its latent form. This increase in active MMP-2 correlated with the increased expression of MT1-MMP, the activator of MMP-2, and with decreases in protein levels of the MMP inhibitors TIMP-1 and TIMP-2 (40). MMP-2 activation was regulated by actin cytoskeleton organization in human palmar fascial fibroblasts as well (41). The additional study demonstrates that MMP-9 is suppressed by an alteration in cell shape and actin disruption in melanoma cells (42). Moreover, actin cytoskeleton remodeling is shown to be a critical regulator of MT1-MMP trafficking, and disruption of the actin cytoskeleton potently affects the MT1-MMP cell surface accumulation (43, 44).

Taken together, these data indicate that expression and/or activation of different MMPs may be regulated by actin polymerization/depolymerization process, where, in most cases, polymerized actin is likely to down-regulate MMP-2 and up-regulate MMP-9.

MMPs and contractility

In VSMCs, changes in MMP-2 mRNA expression were shown to inversely relate to changes in mRNA levels for smooth muscle actin (α-SM actin) (45). In these cells, α-SM actin is the predominating actin isoform (46) and is a key marker of contractile phenotype, which is often referred to as differentiated. Induced VSMC de-differentiation, involving changes in the actin cytoskeleton with decreased level of α-SM actin expression resulted in up-regulation of MMP-2 expression (45).

In fibroblasts, transition to myofibroblast phenotype, characterized by the expression of high levels of contractile proteins, particularly α-SM actin was shown to suppress the expression of MMP-2. Factors that promote cell tension and favor the expression of contractile proteins, including serum factors, TGF-β, pro-contractile GPCR ligands, or culturing fibroblasts in collagen lattices under tension, down-regulated MMP-2. Jasplakinolide, that promotes F-actin assembly, also suppressed MMP-2 gene expression (47). Suppression described could be overcome by forcing the disassembly of F-actin, either through the addition of F-actin depolymerizing agents or by culturing cells in non-attached 3-D lattices that prevent force generation. However, the loss of contractility alone was not sufficient to promote MMP-2 up-regulation. Stimulating cells with the actin depolymerizing agent, latrunculin B, in the absence of serum factors, caused contractile protein down-regulation but did not up-regulate MMP-2 expression, suggesting several mechanisms involved in MMP-2 regulation in these cells.

α-SM actin is not always considered to be a marker of a differentiated state. For example, the visceral smooth muscle cells express higher levels of α-SM actin when de-differentiated, which is contrary to what occurs in VSMCs (48). Notably, in these cells, γ-SM actin is the predominating variant of actin in contrast to VSMCs, where α-SM actin is the main actin isoform (46).

In cardiomyocytes, differentiated contractile status is associated with α-cardiac actin expression, while α-SM actin up-regulation corresponds to a less contractile phenotype and is considered to be a de-differentiation marker of these cells (49). Recently we have shown that reorganization of myofibrillar apparatus in neonatal rat cardiomyocytes in culture is characterized by the loss of contractility and α-SM actin expression (50) and is accompanied by MMP-2 production (51).

It appears therefore that, in different cell types, more contractile phenotype, associated either with α-SM actin up-regulation or with α-SM actin down-regulation, generally corresponds to MMP-2 depletion.

MMPs in migration

Some authors suggest contractile vs. migratory phenotype to be mutually exclusive (47). Transition to migratory phenotype in different cell types includes actin cytoskeleton reorganizations (Figure 1), such as lamellipodia formation (52). For smooth muscle cells, the ability to alter their phenotype from a contractile to a migratory state is shown to be accompanied by proliferation (53). During this phenotypic modulation, VSMCs down-regulate a set of contractile proteins, including α-SM actin, and up-regulate genes involved in cell migration, ECM deposition, and cell growth (54, 55).

Migration is accompanied by MMP-2 expression in the majority of cells. MMP-2 is therefore typically referred to as pro-migratory protease. Up-regulation of MMP-2 was linked to migration and proliferation of different smooth muscle cells (56–59), as well as myoblast migration (60). Increased MMP-2 activity stimulated melanoma cell

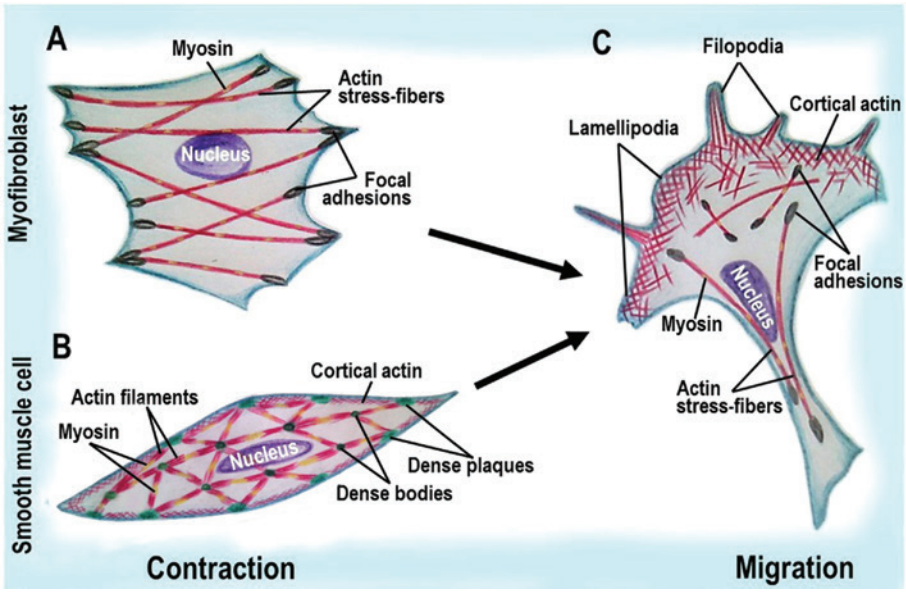

FIgure 1: Schematic diagram illustrating contraction vs. migration phenotype in fibroblasts and smooth muscle cells.
(A) contractile fibroblasts, myofibroblasts, are characterized by the formation of myosin-containing actin contractile stress fibers.
(B) in contracting smooth muscle cells, actin assembles into myosin-containing actin contractile apparatus and cortical actin network.
(C) migration of both fibroblasts and smooth muscle cells is accompanied by a similar reorganization of actin microfilament system, including lamellipodia and filopodia formation.

migration (61) as well as migration and invasion of endometriotic cells (62). In contrast, inhibited MMP-2 activity and expression blocked migration, and invasion of human fibrosarcoma cells (63).

In general, MMP-2 activation accompanies migration and inversely correlates with contractile activity.

MMPs in differentiation

Interdependent dynamics of actin and MMPs may be further observed during the differentiation process. For example, muscle cell differentiation is known to be accompanied by significant actin rearrangements with actin isoform switching as cells progress from their non-muscle precursors (64). Cardiogenic differentiation of the human heart L9TB progenitor cells was shown to include the decreased expression of MMP-1 and increased expression of MMP-2 and MMP-9 compared to non-differentiating cells, with MMP-9 up-regulation observed at the early stage of differentiation only. MMP-2 expression at the later differentiation stages might be surprising in view of data described above, as MMP-2 is expected to be incompatible with the differentiated contractile phenotype. However, its expression through the whole differentiation period is likely to be accountable for the fact that fully differentiated cells were not obtained in this study (65). The role of MMPs was shown in the cardiac differentiation of embryonic stem cells as well (66). Moreover, MMP changes were shown in the differentiation of chondroblasts, osteoblasts, and adipoblasts, derived from adult mesenchymal stem cells (67).

Actin-MMP mutual regulation

Data described demonstrate a strong relation between actin system dynamics and MMP activity in different cell types and various processes, which may suggest actin-MMP mutual regulation. Although the regulation mechanisms have not been determined, relevant knowledge allows their contemplation.

As cytoskeleton changes often precede MMP modulation, actin microfilament dynamics might be linked to the expression of MMP genes. A role for actin in gene expression is well known [for a review see ref. (68)]. The best known actin-regulated transcription factor is serum response factor (SRF), which controls the expression of many cytoskeleton-associated genes in response to changes in actin dynamics. The signal from the actin cytoskeleton to SRF is mediated by the megakaryoblastic leukemia 1 (MKL1) transcription coactivator (also known as MAL or MRTF-A) (69). There is also evidence that polymerized actin could regulate the expression of

specific genes (70, 71). Dynamics of cytoplasmic actin can further regulate the activity of transcription factors, and thus indirectly influence nuclear events. For example, presequence protease 2 (PREP2) (72) and Yin-Yang1 (YY1) (73) are transcription factors, bound to actin filaments in the cytoplasm, and depolymerization of actin filaments releases them to the nucleus to activate transcription. It is in addition well accepted for the actin cytoskeleton to affect gene expression via NF-κB. Regulation of NF-κB by actin polymerization is supported by NF-κB activation following disruption of the actin cytoskeleton in human intestinal epithelial cells (74). Altogether, actin can control gene expression by regulation of the localization and activity of transcription factors, in both the cytoplasm and the nucleus.

This allows us to assume a possible involvement of actin microfilament system in the regulation of MMP expression and thereby ECM remodeling, as MMPs are key modulators of ECM.

It is well accepted that deformation of the ECM, in turn, can affect cell actin cytoskeleton and thereby alter cell shape, motility, and function. ECM is shown to influence the actin cytoskeleton organization in non-muscle cells (75–77) and smooth muscle cells (78), as well as myofibrillar apparatus in striated muscle cells (79, 80). The interaction between ECM and actin cytoskeleton is provided by integrin receptors (Figure 2), which are transmembrane heterodimers capable of transmitting mechanical signals from ECM to anchored cells and transfer them into the intracellular stimuli, leading to the alteration of the cell phenotype (81, 82). This process is known as mechanotransduction, which differs from those involved in adhesion (83). So, it would be reasonable to suggest that the actin system dynamics are regulated by MMPs via ECM remodeling followed by the integrin-mediated mechanotransduction.

On the other hand, some data suggest a direct interaction between MMPs and integrins. For example, integrin shedding by MMPs was proposed in the cardiovascular system (14). Moreover, MMP-2 in its active form was able to directly bind with integrin $\alpha_v\beta_3$ on the surface of invasive cells (84), suggesting regulatory relationships between these two molecules.

Another regulation mechanism may involve the MMP-induced release of different stimulating factors from ECM. MMP-3, e.g. was shown to release TGF-β from the ECM by proteolytic cleavage of the latent TGF-β binding protein (85), where TGF-β is known to stimulate α-SM actin expression (86).

Interestingly, it is α-SM actin that was shown to provide a mechanical linkage between mechanosensory

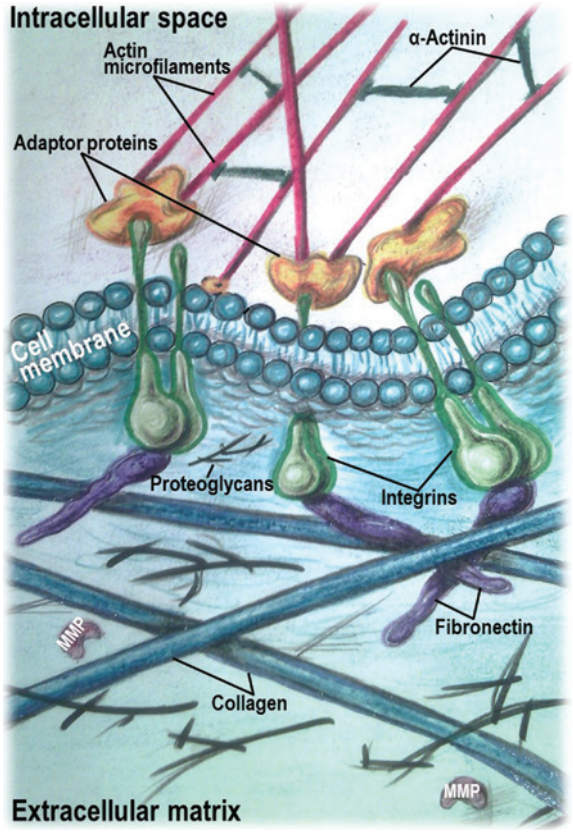

Figure 2: Schematic diagram illustrating a linkage between the extracellular matrix and the actin cytoskeleton by integrins. The extracellular domain of integrins interacts with the extracellular matrix components, while the cytoplasmic tail binds to actin microfilaments through adaptor cytoskeletal proteins.

elements and appropriate targets required for mechanotransduction (87). In myofibroblasts, cell-generated traction forces, associated with α-SM actin, were shown to contribute to matrix remodeling (87). Our recent study suggests that α-SM actin can modulate the synthesis of ECM by cardiomyocytes, which in turn suppresses α-SM actin expression (50). This evidence implies a feedback regulation between ECM and actin system dynamics. The involvement of MMPs in this process is supported by the recent data (88), suggesting that mesenchymal stem cell function is controlled by MMP activity, which in turn is regulated by mechanical stimulation of cells. In this regard, MMP regulation by mechanical stimuli, applied to the cells, is well described (89–94). Moreover, it was shown that type VIII collagen signals through β_1-integrin receptors to allow optimal configuration of the cytoskeleton by stress-fiber formation and thereby facilitates MMP-2-dependent cell migration (95).

Thus, an increasing body of data suggests that actin system dynamics is involved in regulation of MMP

expression and activation, which in turn may regulate actin structure organization and isoform expression.

Conclusions

Processes, strongly regulated by actin system dynamics, such as migration, contraction, proliferation, and differentiation, involve MMP changes in both muscle and non-muscle cells, normal or transformed. The obvious correlation between actin organization and expression, on the one hand, and MMP expression and activity, on the other hand, suggests their mutual regulation. The mechanisms underlying are not clear but are likely to be mediated by integrin mechanotransduction. Investigation of these mechanisms may shed light on cell adaptation to the extracellular environment during key physiological and pathological processes via actin-ECM feedback regulation, which is becoming apparent.

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List of abbreviations

ECM	extracellular matrix
MMP	matrix metalloproteinase
SM actin	smooth muscle actin
TGF-β	transforming growth factor beta
VSMC	vascular smooth muscle cell

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