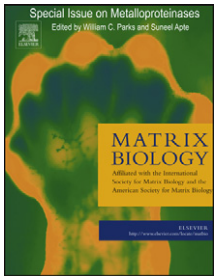
Review



Extracellular regulation of metalloproteinases

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Abstract

Matrix metalloproteinases (MMPs) and adamalysin-like metalloproteinase with thrombospondin motifs (ADAMTSs) belong to the metzincin superfamily of metalloproteinases and they play key roles in extracellular matrix catabolism, activation and inactivation of cytokines, chemokines, growth factors, and other proteinases at the cell surface and within the extracellular matrix. Their activities are tightly regulated in a number of ways, such as transcriptional regulation, proteolytic activation and interaction with tissue inhibitors of metalloproteinases (TIMPs). Here, we highlight recent studies that have illustrated novel mechanisms regulating the extracellular activity of these enzymes. These include allosteric activation of metalloproteinases by molecules that bind outside the active site, modulation of location and activity by interaction with cell surface and extracellular matrix molecules, and endocytic clearance from the extracellular milieu by low-density lipoprotein receptor-related protein 1 (LRP1).

Introduction

Matrix metalloproteinases (MMPs) and adamalysin-like metalloproteinases with thrombospondin motifs (ADAMTSs) degrade extracellular matrix (ECM) macromolecular components. Both MMPs and ADAMTSs are multi-domain proteinases, with the human genome containing 23 MMPs and 19 ADAMTSs. They are considered to play important roles in many physiological processes including embryonic development, morphogenesis, tissue remodelling, cell growth, migration and apoptosis [1,2] and pathological conditions such as inflammation, rheumatoid arthritis, osteoarthritis, cardiovascular diseases, nephritis, chronic wounds, pulmonary diseases, cancer and fibrosis [3]. The activity of these enzymes is tightly regulated by a number of mechanisms, and their activity is often not readily detected in steady state tissues. Expression is regulated transcriptionally by factors such as growth factors, hormones, inflammatory cytokines, UV irradiation, cell–cell and cell–matrix contacts, and the half-lives of their transcripts may be post-transcriptionally regulated by microRNAs [4]. Once translated, MMPs and ADAMTSs are produced as inactive zymogens (pro-MMPs). Many of the MMPs and ADAMTSs are secreted from the cell in this zymogen form, and are then activated extracellularly by other proteinases. The membrane-bound MMPs (MT-MMPs) and ADAMTSs are activated intracellularly by proprotein convertases such as furin. The activity of mature metalloproteinases is then regulated by endogenous inhibitors such as α_2-macroglobulin (α_2M) in blood plasma or body fluids and tissue inhibitors of metalloproteinases (TIMPs) in the tissue [5].

In addition to these well-recognized regulatory mechanisms, several secreted MMPs and ADAMTSs are known to bind to the ECM or to interact with specific cell surface molecules or receptors. More recently, some of the MMPs, ADAMTSs and TIMPs have been found to be very short-lived in the extracellular space, as they are rapidly endocytosed

by the cells that produce them. These new findings add further complexity to the regulation of metalloproteinase activity and ECM degradation. In this mini-review, we focus on the effect of allosteric activators on proMMP activation, and extracellular trafficking of MMPs and ADAMTSs.

Activation of proMMPs through allosteric sites

ProMMPs are kept in an inactive state by coordination of the catalytic zinc ion by the sulfhydryl group of the Cys residue in the conserved PRCGXPD sequence of the pro-peptide domain, called the 'cysteine switch' [6]. This interaction prevents H_2O from interacting with Zn^{2+} in the active site and thus blocks catalytic activity. Disruption of the cysteine switch Zn^{2+}-Cys interaction can activate proMMPs, and can be triggered by (i) step-wise cleavage of the prodomain by proteolytic enzymes (ii) oxidation of the cysteine switch by reactive oxidants or SH-reactive agents such as mercurial compounds and (iii) by structural perturbation by chaotropic agents and denaturants such as sodium dodecyl sulfate, low pH and heat treatment [7,8]. Hypochlorous acid generated by myeloperoxidase in macrophages and neutrophils has been shown to oxidatively activate and subsequently inactivate proMMP-1 and proMMP-7 [9,10]. S-nitrosylation also activates proMMP-9 [11].

In addition, a number of reports have shown that ECM components and cell surface molecules can promote proMMP activation. Binding of such components to allosteric sites on the proMMPs is thought to induce conformational changes that disrupt the cysteine switch. For example, insoluble elastin is able to bind to proMMP-2 and proMMP-9, probably through the three repeats of the fibronectin type II (FNII) domain that are attached to the catalytic domain. This interaction leads to auto-activation of proMMP-2, followed by autocatalytic inactivation of the mature enzyme [12]. However, elastin binding does not promote proMMP-9 activation, even when potential activator proteases are added [12]. ProMMP-9 can be allosterically activated by binding to gelatin, without removal of the pro-domain [13]. In both proMMP-2 and proMMP-9, the third domain of the three FNII repeats interacts with the pro-domain and the catalytic domain [14,15]. Gelatin, elastin and type IV collagen bind to these FNII domains, and may thus disturb the molecular interaction between the pro- and catalytic domains, facilitating the activation of proMMP-2 and proMMP-9.

ProMMP-7 can be activated on the cell surface by interaction with the C-terminal extracellular loop of the transmembrane tetraspanin CD151 [16] or with highly sulfated glycosaminoglycans (GAGs) [8]. Heparin, chondroitin-4,6-sulfate and dermatan sulfate augment intermolecular autolytic activation of proMMP-7, while heparan sulfate, less sulfated chondroitin sulfate and chondroitin-2,6-sulfate are ineffective.

Activation of proMMP-2 by MT3-MMP is enhanced by melanoma-specific chondroitin sulfate proteoglycan, leading to an increase in cell invasion in vitro [17]. The chondroitin sulfate chain of the proteoglycan binds to the catalytic domain of MT3-MMP and the hemopexin domain of proMMP-2. Activation can also be enhanced by the addition of isolated chondroitin-4-sulfate, but not by chondroitin-6-sulfate, hyaluronan or heparin. As with proMMP-7 activation, a specific sulfation pattern has been shown to be essential for MT3-MMP-mediated proMMP-2 activation.

A fraction of proMMP-9 secreted by the leukemic macrophage cell-line THP-1 is covalently linked to the core protein of a chondroitin sulfate proteoglycan. Activation of proMMP-9 in this complex is uniquely induced by Ca^{2+}, but not by mercurial compounds [18]. This involves sequential intramolecular release of the prodomain, cleavage of the proteoglycan core protein, truncation of a part of the hemopexin domain and release of active MMP-9.

The hemopexin domain of proMMP-9 can also bind to hemin and βhematin, which induces autoproteolytic processing of the pro-peptide and subsequent activation by MMP-3 [19].

Regulation by location

At the cell surface

Various mechanisms focus and modulate metalloproteinase activity in the extracellular environment (Fig. 1). For example, MMP-1 is considered to be a soluble collagenase, but it binds to the I domain of α2 integrins [20]. α2β1 integrin binds native collagen I with high affinity, clustering this integrin at contact points in migrating keratinocytes. MMP-1 binding to α2β1 integrin thus enables focal cleavage of collagen; weakening adhesion to the matrix and allowing keratinocyte migration [21]. MMP-1, collagen and α2β1 integrin thus coordinate together to drive and regulate keratinocyte migration during re-epithelialization. Similarly, proMMP9 has been shown to associate with α5 and β5 integrins and to co-localise with β5 at the leading edge of invading cells [22]. No specific effect on enzyme activity has been demonstrated in this case, but this is clearly an efficient localisation mechanism to focus enzyme function where it is required.

Emmprin (CD147, basigin) is a cell membrane MMP regulator originally identified as an MMP-inducer. It is a transmembrane glycoprotein with two Ig-like domains that interacts with a number of other membrane proteins, including caveolin, cyclophilin 60 and monocarboxylate transporters, as well as proMMP-1 and

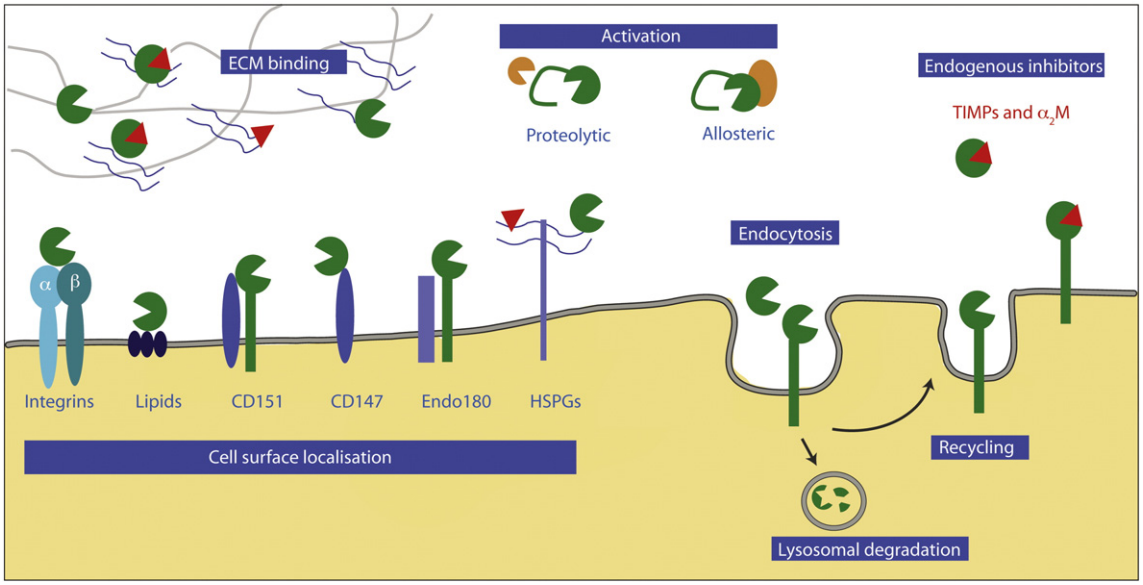

Fig. 1. Extracellular regulation of metalloproteinases: Metalloproteinases (shown in green) are regulated in the extracellular environment by a number of mechanisms, including binding to the ECM, proteolytic and allosteric activation, interaction with endogenous inhibitors (shown in red), interaction with a variety of cell surface molecules, and endocytic trafficking.

active MMP-1 [23,24]. Although the activity of emmprin-bound MMP-1 has not been examined, this may be another way to specifically regulate pericellular collagenolytic activity.

MMP-7 binds to cell surface cholesterol sulfate and induces adhesion of colon cancer cells by cleavage of cell surface proteins [25]. This lipid interaction promotes the proteolytic activity of MMP-7 toward particular substrates such as fibronectin and laminin-332 in the pericellular ECM [26]. The cholesterol sulfate-binding site is located on the opposite side of MMP-7 to that bearing the catalytic cleft [27], which is thought to position the enzyme in a manner that enables it to cleave protein substrates both on the cell surface and in the pericellular ECM.

MT1-MMP colocalizes with β1 integrin in some cell types and this appears to regulate its function. Plating of endothelial cells on β1 integrin-interacting matrices such as collagen I, fibronectin and fibrinogen leads to the upregulation of MT1-MMP and co-localisation of the enzyme with β1 integrin at cell–cell junctions [28]. Upregulation of MT1-MMP was shown to be due to a reduction in its endocytic uptake by the cells. Similarly, clustering of α3β1 integrin promotes trafficking of MT1-MMP to aggregated integrin complexes in ovarian cancer cells, leading to increased proMMP-2 activation [29]. MT1-MMP associates with αvβ3 integrin in motility-associated structures on migrating endothelial cells [28]. Interaction of MT1-MMP with αvβ8 activates latent transforming growth factor β1 (TGFβ1), where αvβ8 integrin forms a complex with the TGFβ1 latency associated peptide (LAP) and MT1-MMP [30].

Tetraspanins may also regulate MT1-MMP function on the cell surface. MT1-MMP colocalizes with the tetraspanin CD151 and its associated partner α3β1 integrin at lateral cell junctions in endothelial cells [31]. Another tetraspanin, CD63, a component of late endosomal and lysosomal membranes, interacts with the hemopexin domain of MT1-MMP which enhances internalization and lysosomal degradation of MT1-MMP [32], whereas several tetraspanins are thought to chaperone newly synthesised MT1-MMP to the cell surface, preventing its lysosomal degradation and supporting its function at the cell surface [33].

Collagen internalization also regulates MT1-MMP activity [34]. The endocytic mannose receptor C type 2, Endo180, internalizes collagen and its depletion in HT1080 cells by siRNA results in the accumulation of collagen in the medium and an increase of MT1-MMP activity on the cell surface. This suggests that there is an intricate coordination of collagen clearance in the pericellular environment mediated by both collagen internalization and regulated MT1-MMP activity.

Binding to the ECM

Some metalloproteinases have their localization, activity and substrate specificity modulated by interaction with components of the ECM, such as sulfated GAGs. Heparin solubilizes MMP-2, MMP-7, MMP-9 and MMP-13 from tissues [35], and MMP-1, MMP-3 [36], MMP-2 [37], MMP-9 [38] and MMP-13 [39] bind to heparin in vitro, suggesting that these

metalloproteinases may bind to sulfated GAGs in the ECM. MMP-1, MMP-2 and MMP-9 are known to bind to heparin via their hemopexin domains [40,41], while ADAMTS-1 [42], ADAMTS-4 [43] and ADAMTS-5 [44] bind to the ECM via their ancillary domains. Other ADAMTSs with homologous C-terminal domains are also likely to bind to the ECM.

ECM binding can regulate metalloproteinase activity by dictating or limiting access to substrates or by directly modulating activity. For example, heparin inhibits ADAMTS-4 hydrolysis of aggrecan, and has a greater effect on hydrolysis of the interglobular domain than of the chondroitin sulfate attachment region [45]. This suggests that ECM binding may alter the substrate preference of ADAMTSs. Additionally, ECM binding can affect the interaction of metalloproteinases with TIMP-3, the only TIMP that binds to the ECM. GAGs increase TIMP-3 affinity for MMP-2, –7 [46], ADAMTS-2 [47], ADAMTS-4 and ADAMTS-5 [48], and this is likely to be the case for other sulfated GAG-binding metalloproteinases. Notably, the ability of sulfated GAGs to increase the affinity between TIMP-3 and ADAMTS-4 and ADAMTS-5 is highly dependent on the sulfation pattern of the GAG [49].

Endocytosis

Regulation of metalloproteinases and TIMPs by LRP1

Low-density lipoprotein (LDL) receptor-related protein 1 (LRP1, or CD91) is a member of a family of scavenger receptors related to the LDL receptor [50]. It is a type I transmembrane protein consisting of a 515-kDa α-chain containing the extracellular ligand-binding domains and a non-covalently associated 85-kDa β-chain containing a transmembrane domain and a short cytoplasmic tail. The α- and β-chains are derived from a single polypeptide chain that is cleaved by furin during maturation. LRP1 was first characterized as a receptor for apolipoprotein E-containing lipoprotein particles [51] and for α_2M-proteinase complexes [52]. The α_2M-proteinase complexes were shown to be endocytosed within 1 h by a clathrin-dependent pathway [53]. This endocytic process is a general mechanism to eliminate excess active proteinases from tissues and body fluids, since most extracellular endopeptidases with different catalytic mechanisms can react with and be entrapped by α_2M [54]. It is now known that a number of proteases (both active and precursor forms), their endogenous inhibitors and protease-inhibitor complexes can bind to and be internalized by LRP1. More than 40 ligands have been identified to date, including lipoproteins, thrombospondins, fibronectin, amyloid β, peptide, lactoferrin, rhinovirus, and growth factors such as connective tissue growth factor, TGFβ, midkine and platelet-derived growth factor [55,56], and the list is still growing. The importance of LRP1 in biological processes is demonstrated by the lethality of LRP1 gene deletion at an early stage of murine embryonic development [57]. This indicates that endocytic scavenging of bioactive molecules is essential to maintain tissue homeostasis and that disruption of this process may result in pathological conditions.

LRP1-mediated endocytosis of MMPs was discovered much later than that of other proteases. The Partridge group [58] first reported that rat MMP-13 disappeared from the culture medium of a rat osteoblast cell line and demonstrated that this occurred through a receptor-mediated process. Subsequently, the disappearance was shown to be due to endocytosis of MMP-13 by LRP1 with the assistance of a 170 kDa MMP-13-specific receptor [59]. Other metalloproteinases currently known to be endocytosed by LRP1 are MMP-9 [60], MMP-9-TIMP-1 complexes [61], MMP-2-thrombospondin 2 complexes [62], proMMP-2-TIMP-2 complexes [63], ADAMTS-4 [64] and ADAMTS-5 [65]. In addition, TIMP-1 [66], TIMP-2 [67] and TIMP-3 [68] can be endocytosed by LRP1. The rate of their endocytosis varies depending on their affinities for LRP1 [64].

Ectodomain shedding of LRP1

ADAMTS-4 and ADAMTS-5 are two major aggrecan-degrading proteinases ('aggrecanases') in cartilage and they are considered to play a key role in the development of osteoarthritis (OA). However, mRNA levels for ADAMTS-5 are not significantly elevated in OA compared to normal cartilage (see [69,70] for review) and how ADAMTS-5 activity is regulated has not been clear. Studies by Yamamoto et al. [65] shed new insight into the regulation of ADAMTS-5 in OA, showing that endocytic clearance of ADAMTS-5 by LRP1 is impaired in OA chondrocytes due to a reduction in LRP1 protein levels. No reduction in LRP1 mRNA levels was observed. A reduction in MMP-13 endocytosis in OA chondrocytes was also reported [71]. Reduction in cell surface levels of LRP1 may be due to increased shedding of the receptor ectodomain. Quinn et al. [72] first demonstrated that LRP1 can be shed through the action of a metalloproteinase that cleaves the receptor at the membrane proximal region of the β-chain in human BeWo trophoblast cells. LRP1 shedding is increased in malignant cells [73,74] and under inflammatory conditions such as in rheumatoid arthritis and systemic lupus erythematosus [75]. Proteinases reported to shed LRP1 include β-amyloid precursor protein-cleaving enzyme (BACE) [76], MT1-MMP [74], ADAM10 [77], ADAM12 [74] and ADAM17 [77]. Shed LRP1 retains ligand-binding capacity and can act as a decoy receptor [78]. Recently, Scilabra et al. [68] reported that shed LRP1 competes with cell surface LRP1 for binding to

TIMP-3, and that extracellular LRP1-TIMP-3 complexes retain their ability to inhibit target metalloproteinases. Shed LRP1 also binds to ADAMTS-4, ADAMTS-5 and MMP-13 and prevents them being endocytosed (K. Yamamoto, unpublished result). We thus speculate that an increase in LRP1 shedding alters the trafficking of key ECM-degrading enzymes and their inhibitor TIMP-3 (Fig. 2). In articular cartilage, such changes appear to shift the homeostatic balance of ECM turnover toward catabolism. In fact, the addition of the LRP1-ligand binding antagonist to normal cartilage in culture increases aggrecan degradation [65].

Many LRP1 ligands bind to heparin, and heparin competes with LRP1 for binding to ligands. Sulfated glycans may thus shift the extracellular trafficking of LRP1 ligands (Fig. 2). In this regard, Troeberg et al. [49] reported that endocytic removal of TIMP-3 was inhibited by heparin, heparan sulfate proteoglycans and chondroitin sulfate E, making TIMP-3 available for metalloproteinase inhibition. In addition, the sulfated GAG-TIMP-3 complex has higher affinity for ADAMTS-4 and ADAMTS-5 than TIMP-3 alone, but the sulfation pattern of the GAG is crucial for this activity.

Endocytic regulation of MT-MMPs

Endocytosed MT-MMPs can either be trafficked to lysosomes for degradation or recycled back to the cell surface [79,80]. MT1-MMP can be internalized by two distinct (clathrin- and caveolae-dependent) endocytic pathways. Clathrin-dependent endocytosis is initiated by interaction of the μ2 subunit of adaptor protein 2 with the LLY sequence in the MT1-MMP cytoplasmic tail [81]. Caveolae-dependent endocytosis of MT1-MMP plays an important role in endothelial cell migration on a collagen substratum [82]. The definitive role of these independent pathways is unclear, but it has been hypothesized that they may be responsible for internalizing different subpopulations of MT1-MMP at the cell surface, as they differ in speed and localization of internalization. A recent study revealed that α_2M induces cellular migration of Muller glial cells by endocytic recycling and intracellular distribution of MT1-MMP toward cellular protrusions [83]. Although MT1-MMP does not bind to LRP1 directly, its activity is regulated by LRP1-mediated endocytosis via α_2M. As discussed above, CD63 tetraspanin promotes MT1-MMP internalization and lysosomal degradation [32].

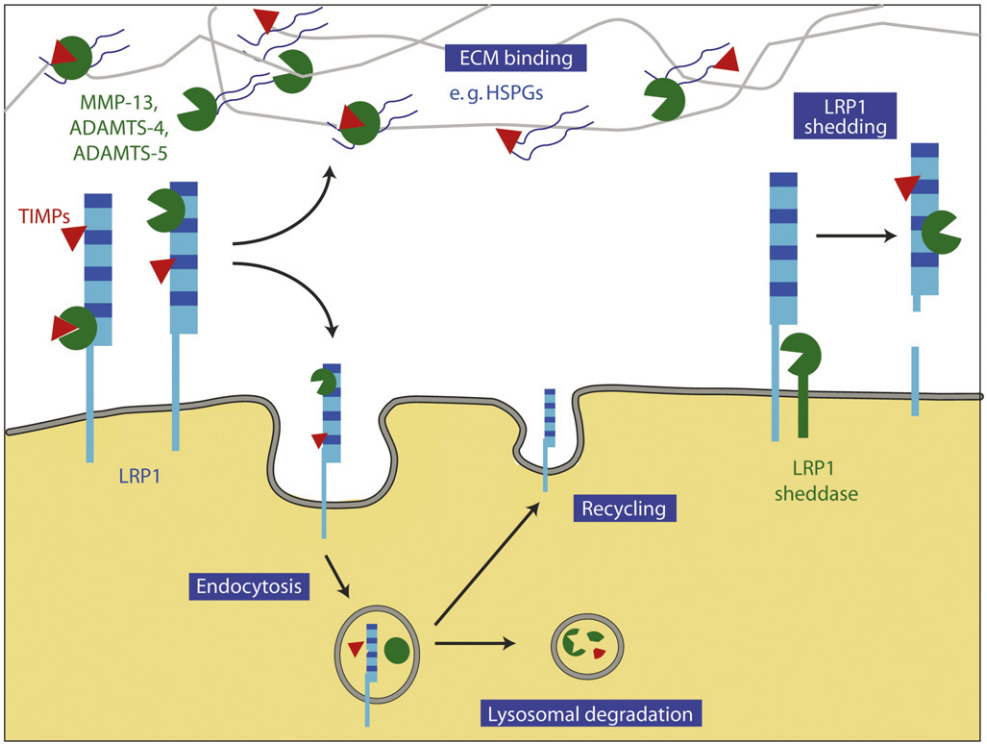

Fig. 2. Trafficking of metalloproteinases and TIMPs between LRP1 endocytic receptor and ECM. Some metalloproteinases (including MMP-13, ADAMTS-4 and ADAMTS-5, shown in green) as well as TIMPs (TIMP-1, TIMP-2, TIMP-3, shown in red) can either bind to the ECM or be endocytosed by the LRP1 receptor. The balance of this trafficking equilibrium determines net ECM turnover, and can be modulated by the pattern of sulfation on HSPGs or by shedding of LRP1.

Conclusions and future directions

A number of studies, including those highlighted in this review, have demonstrated that metalloproteinases interact with a far wider range of molecules on the cell surface and in the extracellular environment than was previously appreciated. In most cases, the functional consequences of such binding on enzyme activity, stability, substrate specificity and affinity for endogenous inhibitors are not known. Such interactions may greatly increase the complexity of metalloproteinase regulation in both health and disease, and warrant further investigation. Most importantly, research is needed to relate the current in vitro observations to the situation in vivo. Such understanding may be of help in designing strategies to inhibit metalloproteinase activity in a targeted manner in pathological conditions.

Similarly, our understanding of allosteric activation of metalloproteinases by their substrates or other binding partners is limited. The demonstration that binding of elastin to an allosteric site on proMMP-2 promotes activation of the enzyme raises the possibility that other matrix molecules or substrates may similarly activate extracellular zymogens. This interplay between metalloproteinases and their substrates is also likely to be amenable to targeted pharmacological intervention.

We are coming to appreciate that endocytic processes, including LRP1-mediated endocytosis, represent important mechanisms for regulating metalloproteinase activity, modulating extracellular levels of the enzymes and their endogenous inhibitors. In addition to endocytic scavenger functions, LRP1 can act as a signalling receptor via interaction of its cytoplasmic domain with various scaffolding and signalling proteins. A recent study by the Gonias group indicates that LRP1 can initiate different signalling pathways in response to binding of particular ligands to its extracellular domain [84]. This raises the possibility that LRP1-mediated uptake of metalloproteinases and their inhibitors is not merely a mechanism for clearing them from the extracellular environment, but that it also serves to deliver information to cells about turnover of their surrounding environment.

Several of the metalloproteinases and their inhibitors studied to date are able to bind to both LRP1 and to sulfated GAGs in the ECM, with their extracellular availability determined by their relative affinity for each. Affinity of proteins for GAGs is dependent on the specific sulfation pattern of the GAG, and factors affecting this sulfation pattern (such as expression of sulfatases and GAG biosynthesis enzymes) thus modulate extracellular trafficking of such metalloproteinases and their inhibitors. Since LRP1 has many potential ligands, the role of competition between ligands for binding and endocytosis could also regulate metalloproteinase and TIMP removal from the extracellular space.

Determining how metalloproteinase activity is regulated in the complex pericellular environment is likely to be technically challenging, but such information will greatly increase our understanding of the physiological interactions of the enzymes, and how their activity becomes disrupted in disease.

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Abbreviations used:
α_2M, α_2-macroglobulin; ADAMTS, adamalysin-like metalloproteinase with thrombospondin motifs; ECM, extracellular matrix; GAG, glycosaminoglycan; LAP, latency associated peptide; LRP1, low-density lipoprotein receptor-related protein 1; OA, osteoarthritis; MMP, matrix metalloproteinase; TGF-β1, transforming growth factor β1; TIMP, tissue inhibitor of metalloproteinases.

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