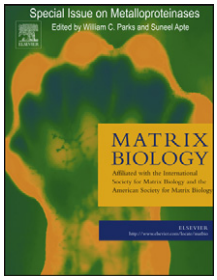

Membrane-type matrix metalloproteinases: Their functions and regulations

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http://dx.doi.org/10.1016/j.matbio.2015.03.004
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Abstract

Membrane-type matrix metalloproteinases (MT-MMPs) form a subgroup of the matrix metalloproteinase (MMP) family, and there are 6 MT-MMPs in humans. MT-MMPs are further sub-classified into type I transmembrane-type (MT1, –MT2-, MT3- and MT5-MMPs) and glycosylphosphatidylinositol (GPI)-anchored type (MT4- and MT6-MMPs). In either case MT-MMPs are tethered to the plasma membrane, and this cell surface expression provides those enzymes with unique functionalities affecting various cellular behaviours. Among the 6 MT-MMPs, MT1-MMP is the most investigated enzyme and many of its roles and regulations have been revealed to date, but the potential roles and regulatory mechanisms of other MT-MMPs are gradually getting clearer as well. Further investigations of MT-MMPs are likely to reveal novel pathophysiological mechanisms and potential therapeutic strategies for different diseases in the future.

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Introduction

Membrane-type matrix metalloproteinases (MT-MMPs) form a subgroup within the matrix metalloproteinase (MMP) family, and there are 6 enzymes in humans. The first MT-MMP to be discovered was MT1-MMP (MMP-14) and it was characterized as a cell surface proMMP-2 activator [1]. Following this, MT2-MMP (MMP-15) [2], MT3-MMP (MMP-16) [3], and MT4-MMP (MMP-17) [4] were discovered in a short period of time, and later MT5-MMP (MMP-24) [5,6], and MT6-MMP (MMP-26) [7,8] were further discovered. Among those 6 MT-MMPs, MT4-MMP and MT6-MMP are tethered to the plasma membrane through a glycosylphosphatidylinositol (GPI) -anchor, while the other MT-MMPs are tethered through transmembrane domain. The function of MT1-MMP has been characterized extensively since its discovery while the functions of other MT-MMPs are still not clearly understood. In this mini-review, the known character, biological functions and regulatory mechanism of each MT-MMPs are discussed.

Characters of Mt-Mmps

Domain structures

MT-MMPs share a common domain structure consisting of a signal peptide, a pro-domain, a catalytic domain, a hinge (linker-1), a hemopexin-like (Hpx) domain, and a stalk region (linker-2) (Fig. 1). Transmembrane-type MT-MMPs including MT1, MT2, MT3, MT5-MMPs have a transmembrane (TM) domain and a short cytoplasmic (CP) domain following a linker-2, and GPI-anchored type MT-MMPs including MT4-MMP and MT6-MMP have a short hydrophobic sequence following a linker-2 that functions as a GPI-anchoring signal peptide (Fig. 1). All MT-MMPs have a basic amino acid motif of RX(K/R)R at the C-terminus of their prodomain, which is recognized and cleaved for activation by proprotein convertases (PCs) such as furin during secretion. Thus all MT-MMPs are expressed as active enzymes on the cell surface. MT6-MMP has an unpaired cysteine, Cys-532, at its stalk region (linker-2), and this mediates disulfide

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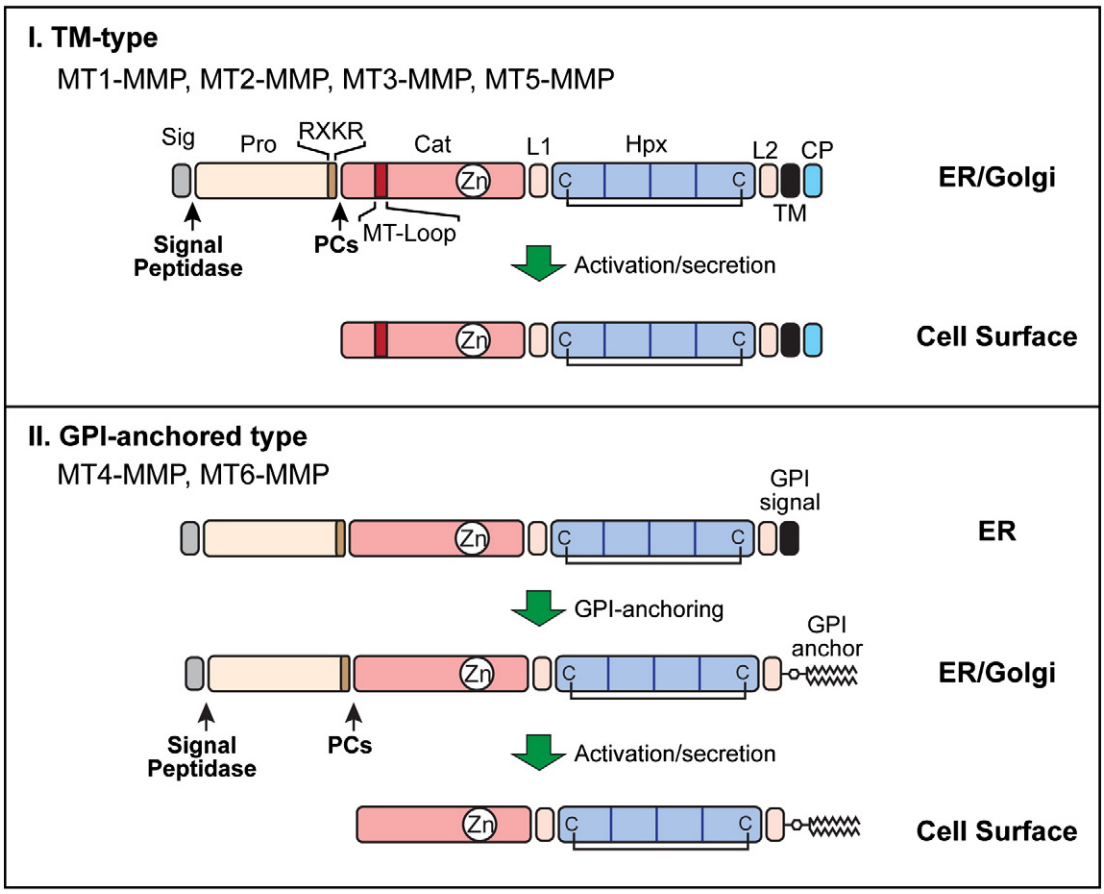

Fig. 1. Domain structure and processing of MT-MMPs. TM-type MT-MMPs including MT1-MMP, MT2-MMP, MT3-MMP and MT5-MMP share the same domain structures. They are synthesized as pre-pro enzymes and processing of the signal peptide and prodomain occurs before they are secreted to the cell surface. They have a basic amino acids motif of RXKR at the C-terminus of the prodomain which is recognized by proprotein convertases (PCs). They also harbour an 8-amino acid loop insertion in the catalytic domain named the MT-Loop. This loop is unique to TM-type MT-MMPs amongst all the MMPs. GPI-anchored MT-MMPs including MT4-MMP and MT6-MMP share the same domain structures. They are synthesized as pre-pro enzymes harbouring hydrophobic amino acids stretch at their C-terminus. This hydrophobic sequence acts as a GPI-anchoring signal peptide. This sequence is cleaved and replaced by a de novo-synthesized GPI-anchor by transamidase in the ER. Processing of signal peptide and propeptide occurs before secretion to the cell surface as for TM-type MT-MMPs. Sig, signal peptide; Pro, prodomain; Cat, catalytic domain; L1, hinge or linker-1; Hpx, hemopexin-like domain; L2, stalk or linker-2; TM, transmembrane domain; CP, cytoplasmic domain; PCs, proprotein convertases; C, cysteine; GPI signal, GPI signal peptide; ER, endoplasmic reticulum.

bond-mediated homo-dimer formation on the cell surface [9]. TM-type MT-MMPs have an insertion of 8–9 amino acids in the catalytic domain, named the MT-Loop (Fig. 1). This is unique to TM-type MT-MMPs and does not exist in any other enzymes of the MMP family.

Substrates

The reported substrates of MT-MMPs are listed in Table 1. Many of these substrates were identified by incubating recombinant soluble MT-MMP proteins with potential substrate in a test tube, whereas others were identified in cell culture systems and by proteomics approaches. While some of the substrates were confirmed to be physiological substrates, some of them may not be. Among the 6 MT-MMPs, MT1-MMP has the widest substrate specificity, especially against extracellular matrix (ECM) components. Collagens are the most abundant ECM component and act as a major structural component and barrier matrix in tissues. MT1-MMP degrades fibrillar collagens including types I, II, and III, but it does not degrade type IV collagen, a major component of basement membranes [10]. MT2-MMP was also reported to degrade collagen I, but its specific activity was shown to be 1/100 of MT1-MMP [11], and thus it is not considered as a major collagenolytic enzyme. MT3-MMP was shown to degrade type III collagen, but it cannot degrade type I collagen [12]. Other

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