Membrane type-matrix metalloproteinases and tumor progression

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Abstract: Matrix metalloproteinases (MMPs) are a family of zinc endopeptidases that process growth factors, growth factor binding proteins, cell surface proteins, degrade extracellular matrix (ECM) components and thereby play a central role in tissue remodeling and tumor progression. Membrane-type matrix metalloproteinases (MT-MMPs) are a recently discovered subgroup of intrinsic plasma membrane proteins. Their functions have been extended from pericellular proteolysis and control of cell migration to cell signaling, control of cell proliferation and regulation of multiple stages of tumor progression including growth and angiogenesis. This review sheds light on the new functions of MT-MMPs and their inhibitors in tumor development and angiogenesis, and presents recent investigations that document their influence on various cell functions.

Keywords: MT-MMP; Protease inhibitors; Cell signaling; Tumor angiogenesis; Cancer

1. Introduction

During cancer progression, some tumor cells become motile and acquire the capacity to invade host tissue leading eventually to metastatic dissemination. Such an invasion process requires specific cell-matrix interactions and proteolytic activities. The degradation of the extracellular matrix (ECM) during tumor invasion and angiogenesis is likely to release active molecules stored in the matrix and/or to generate active fragments of matrix components which promote tumor growth, invasion and angiogenesis [1,2].

Matrix metalloproteinases (MMPs) are a family of zinc endopeptidases capable of digesting the various ECM components. Their specific substrates include an array of other proteinases, MMPs, proteinase inhibitors, growth factors, growth factor binding proteins, chemokines, cytokines, cell surface receptors and cell adhesion molecules [3,4]. Thereby, MMPs control cell migration, proliferation, and apoptosis and regulate tumor expansion, angiogenesis and dissemination.

Regulation of MMP functions occurs at different levels (for recent reviews, see [2,3,5]). MMP transcripts are generally expressed at low levels, but these levels rise rapidly when tissues undergo remodeling, such as during inflammation, wound healing and cancer progression [2,3]. MMPs are synthesized as latent enzymes that can be secreted, anchored to the cell surface or tethered to other proteins on the cell surface or within the ECM. The activation of latent MMPs requires a proteolytic process and the release of N-terminal propeptide domain. Once active, MMPs can be inhibited by tissue inhibitors of metalloproteinases (TIMPs), the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) [6], tissue factor pathway inhibitor (TFPI-2) as well as by a plasma inhibitor (α2-macroglobulin) [7].

Although studies performed in animal models showed great promises for MMP inhibitors (MMPIs) as anticancer agents [8], disappointing clinical trial results led to a reevaluation of MMP inhibition strategies [9,10]. The explanation for these defects was likely related to different tumor sensitivity to MMPIs depending on tumor stage. Most clinical studies have been conducted with late stage tumors, whereas the administration of MMPI in animal models impaired angiogenesis and tumor growth at early stages of tumor development [11]. Another important consideration is that only few MMPs had been discovered when initial MMPI clinical trials were designed (MMP-1, -2 and -3) [5,10]. In the meantime, many metalloproteinases that can be inhibited by broad spectrum MMPIs have been identified with a new structural and functional complexity such as adamalysin-like proteinases with disintegrin-like domain (ADAMs) and ADAMs with thrombospondin motifs (ADAM-TS), membrane type-matrix metalloproteinases (MT-MMPs) and cysteine array matrix metalloproteinase (CA-MMP) [2-4,12-14].

Recently, cell surface localization of proteolytic enzymes has been recognized to be important for cancer and stromal cells to modify their environment [2,15,16]. Intrinsic plasma membrane enzymes such as serine proteases, metalloproteases, cysteine proteases and aspartic proteases have been discovered [16-20]. This article focuses on MT-MMPs and their inhibitors recently implicated in processes related to tumor growth and

angiogenesis. The characteristics and functions of the other MMPs have been described in excellent reviews [4,10,13]. The first human MT-MMP (MT1-MMP/MMP-14) [21] was cloned by a reverse transcriptase-polymerase chain reaction (RT-PCR) based strategy using degenerate oligonucleotides deduced from conserved regions in MMPs on the RNA of placental tissue. Later on, additional studies focused on MT-MMPs led to the discovery of five more members of this family: MT2-, MT3-, MT4-, MT5- and MT6-MMP, also named MMP-15, -16, -17, -24 and -25, respectively [3].

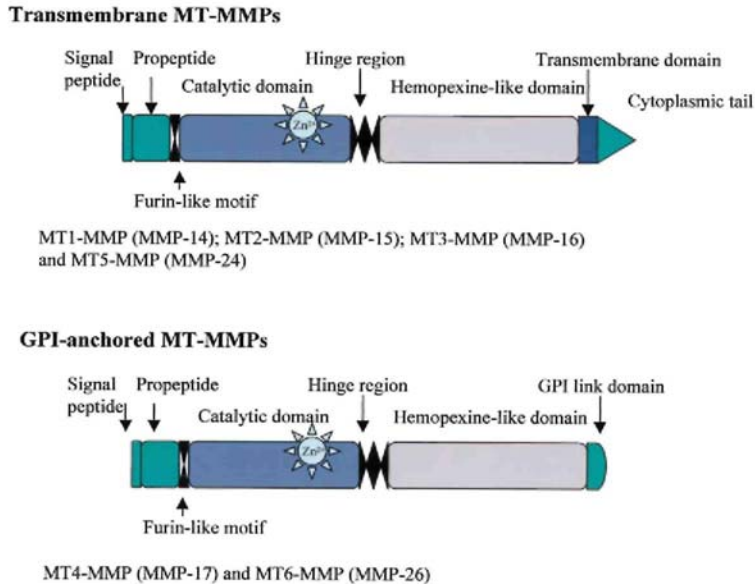## 2. Structure and activation of MT-MMPs

The MT-MMPs contain all protein domains characteristic of MMPs including from the N-terminal to the C-terminal extremities: a signal peptide, a propeptide, a catalytic domain with the zinc binding site, a hinge region and a C-terminal hemopexin domain [2]. We will only describe the specific structural features of MT-MMPs.

All MMPs are produced as zymogens containing a secretory signal sequence and a propeptide whose proteolytic cleavage is required for MMP activation (Fig. 1). The pro-domain of MT-MMPs contains a conserved motif, Tyr^{42}-Gly^{43}-Tyr^{44}-Leu^{45} that acts as an intramolecular chaperone. It appears essential for adequate protease folding and enzymatic activities (proMMP-2 activation, substrate degradation and TIMP-2 binding) [22]. A basic tetrapeptidic sequence Arg^{108}-Arg^{109}-Lys^{110}-Arg^{111} is inserted between the propeptide and the catalytic domain. This furin recognition motif is cleaved by proprotein convertases in the trans Golgi network during the trafficking of MT-MMPs from the endoplasmic reticulum to the plasma membrane [3,23-26]. However, the activation of MT-MMPs by a furin-independent alternative pathway has been reported in some types of cells. This alternative activation pathway depends on an autoproteolytic activation or on the action of non-furin proprotein convertases, or on other proteases located at the plasma membrane [26-29]. In addition, an extracellular activation of proMT1-MMP by plasmin has been reported [30].

The propeptide is followed by the catalytic domain that contains the consensus zinc-binding motif HEBXHXBG-BXH, where X is a variable residue and B is a bulky hydrophobic amino acid. The catalytic domain of MT-MMPs contains a characteristic 8-amino acid insertion between stands β_{II} and β_{III} named MT-loop. The 3D structure of the complex between the catalytic domain of MT1-MMP and TIMP-2 shows that the MT-loop generates a pocket in the MMP catalytic domain fold that interacts with the AB-loop of TIMP-2 [31]. The recently resolved 3D structure of the complex between the MT3-MMP catalytic domain and a synthetic MMP inhibitor (Batimastat) reveals similar features, but shows unique properties such as a modified MT-specific loop and a closed S1 ' pocket which may be important for the substrate specificity and the efficient proMMP-2 activation [32]. Although mutations or deletion of MT-loop of MT1-MMP does not affect its catalytic activity towards synthetic substrates, it impairs the kinetic activation of proMMP-2 [33]. Consistently, divergences in MT-loop structure between MT-MMPs are translated in their ability to activate proMMP-2. For example, MT4-MMP and MT6-MMP which are lacking the MT-loop are either unable to activate or inefficient at activating proMMP-2 [33]. Furthermore, human MT2-MMP is somewhat defective in cell-mediated activation of proMMP-2, whereas mouse MT2-MMP is very efficient in this activity. The replacement of two residues (Pro^{183} and Glu^{185}) in the MT-loop of the human enzyme by the corresponding ones (Ser^{183} and Asp^{185}) of mouse MT2-MMP endowed the human enzyme with efficient activation of proMMP-2 [34].

As all MMPs with the exception of MMP-7 and MMP-26, MT-MMPs contain a C-terminal hemopexin-like domain that confers some degree of substrate specificity [4,35,36]. However, MT-MMPs differ from the other MMPs by the presence of a C-terminal domain rich in hydrophobic residues and involved in their association to the cell membrane (Fig. 1). According to the structure of this C-terminal extension, MT-MMPs can be classified into two sub-groups: (1) type I transmembrane proteins including MT1-, MT2-, MT3- and MT5-MMP characterized by a long hydrophobic sequence followed by a short cytoplasmic tail and (2) glycosylphosphatidylinositol (GPI)-type MT-MMPs (MT4- and MT6-MMP) containing a short hydrophobic signal anchoring to GPL This sequence is not followed by a cytoplasmic tail. The cytoplasmic tail of type I transmembrane MT-MMPs is likely to participate in numerous cellular events such as for instances: cell signaling, sub-cellular localization, MT-MMP trafficking and dimerization [26,37-41].

Fig. 1: *The protein structure of MMPs. Human membrane type matrix metalloproteinases (MT-MMPs) contain the basic common domain of almost MMPs: signal, pro-, catalytic, and hinge domains. MT1-, MT2-, MT3-, and MT5-MMP belong to the transmembrane-anchored type and are characterized by a transmembrane and a cytoplasmic domain. MT4-MMP and MT6-MMP are anchored to the plasma membrane via glycosylphosphatidylinositol, and belong to the GPI group.*

Transmembrane MT-MMPs

MT1-MMP (MMP-14); MT2-MMP (MMP-15); MT3-MMP (MMP-16) and MT5-MMP (MMP-24)

GPI-anchored MT-MMPs

MT4-MMP (MMP-17) and MT6-MMP (MMP-26)

3. Substrates of MT-MMPs

The contribution of MT-MMPs in the degradation of a variety of ECM components results in the release of sequestered biologically active proteins and in the regulation of cell migration, growth, differentiation, and survival by controlling cell adhesion and the cytoskeletal organization [3,4]. Activated MT1-MMP is a potent membrane proteinase with the ability to cleave type I collagen more efficiently than type II or **III** collagens [42]. Consistently, MT1-MMP knockout mice are characterized by a defect in cartilage remodeling and bone development [43,44]. Due to their capacity to cleave type I collagen, both MT1-MMP and MT2-MMP are able to endow uninvasive MDCK cells with the ability to penetrate type I collagen matrix [24]. Although MT3-MMP cannot degrade type I collagen into typical one-and three-quarter fragments, it can cleave the Gly4-Ile5 bond within the triple helical portion of $\alpha 2$(I) chain [45]. The MT3-MMP was shown to digest the fibrillar type **III** collagen into 3/4-and 1/4 fragments with an approximately five-fold higher efficiency than that of MT1-MMP [45]. Through its fibrinolytic activity, MT1-MMP is able to promote endothelial cell migration through a fibrin gel [46]. In MT1-MMP null mice fibroblasts, MT2-MMP and MT3-MMP, but not MT4-MMP, can compensate for MT1-MMP deficiency and favor migration through fibrin matrices [47]. MT1- and MT3-MMP also degrade fibronectin, laminin-1, vitronectin, aggrecan, gelatin, $\alpha 2$-macroglobulin, αl proteinase inhibitor ($\alpha 1$Pi) and syndecan [42,48-52] (Table 1). MT2-MMP cleaves fibronectin, laminin-1, gelatin, tenascin, perlecan and nidogen in identical fragment as MT1-MMP [48,49]. MT4-MMP has a lower activity against extracellular matrix components, but its catalytic domain significantly degrades gelatin, fibrinogen and fibrin [53,54]. The role of MT4-MMP in tissue extracellular matrix degradation seems to be indirectly mediated by its ability to activate aggrecanase-1 (ADAM-TS4) enzyme [55]. The proteolytic activity of MT5- and MT6-MMP has been studied using recombinant catalytic fragments. They are able to degrade several components of the extracellular matrix, their common substrates are gelatin, fibronectin, chondroitine sulfate and dermatan sulfate. MT6-MMP can also cleave type IV collagen, fibrin, fibrinogen, $\alpha 1$ proteinase inhibitor ($\alpha 1$Pi) [56,57]. In addition to these matrix substrates, MT-MMPs are able to cleave other signaling molecules such as cell surface receptors, growth factors, growth factor binding proteins, cytokines/chemokines [3] (Table 1). The importance of such MT-MMP proteolytic regulation in the regulation of cell behavior is described below.

Table 1: *Extracellular and non-extracellular substrates of MT-MMPs (see references in the text)*

MT-MMPs	Extracellular matrix substrates	Non extracellular matrix substrates
MT1-MMP	Gelatin, collagens I, II, III laminin-5, fibronectin,fibrin, proteoglycan	CXCL12 (SDF1), MCP-3, proTNFα, IL-8, CTGF, death receptor-6, secretory leukocyte protease inhibitor, CD44, integrin α_v subunit, tissue Transglutaminase (tTG), gClqr, syndecan-1, β glycan, low density lipoprotein receptor related protein (LRP), proMMP-2
MT2-MMP	Collagen I, fibronectin, gelatin, aggrecan, perlecan, laminin-1, tenascin, perlecan, nidogen	tTG, LRP, proMMP-2
MT3-MMP	Collagen II, III, fibronectin, laminin-1, vitronectin, aggrecan gelatine	tTG, CD44, syndecan, LRP, β glycan, α2-macroglobulin, α1-antiproteinase and pro-MMP-2
MT4-MMP	Fibrinogen, fibrin gelatin	ProTNFα, agrecanase-1 (ADAMTS-4), LRP
MT5-MMP	gelatin, fibronectin, chondroitine sulfate, dermatan sulfate	ProMMP-2
MT6-MMP	gelatin, fibronectin, chondroitine sulfate, dermatan sulfate, collagen type IV, fibrin, fibrinogen	αl-antiproteinase, ProMMP-2

4. MT-MMPs in proMMP and other zymogen proteinase activation

The MT-MMPs control the pericellular activation of proMMPs and other proteases. The major physiological activators of proMMP-2 (gelatinase A) are members of the MT-MMP sub-group. The activation of proMMP-2 by MT1-MMP involves the action of TIMP-2 [58]. The model proposed so far involves stoichiometric binding of TIMP-2 to MT1-MMP catalytic domain on the cell surface, followed by the binding of C-terminal hemopexin-like domain of proMMP-2 to the C-terminus of TIMP-2 [3,59,60]. The formation of such a trimolecular complex of MT1-MMP/TIMP-2/proMMP2 is abolished in unglycosylated MT1-MMP transfected cells due to a defect in TDVIP-2 recruitment at the cell surface [61]. This trimolecular complex facilitates the first cleavage of proMMP-2 prodomain by a neighboring TDVIP-2-free active MT1-MMP, thereby generating a 64 kDa intermediate MMP-2 form. Full activation of the intermediate MMP-2 species is achieved by an intermolecular auto-catalytic process [62,63] or by the action of the plaminogen/plasmin system [64,65]. This activation is completely inhibited at high concentration of TDVIP-2, TIMP-3, TIMP-4, but not TIMP-1 [66,67]. Therefore, proMMP-2 activation occurs in a TIMP-2-dependent two-step cleavage mechanism. The role of TIMP-2 in proMMP-2 activation by MT1-MMP can be substituted by TIMP-3, but not by TIMP-1 [67]. However, TIMP-4, which is considered as a better MT1-MMP inhibitor, is not able to substitute TIMP-2 in proMMP-2 activation [68]. Whereas TIMP-2 may act as a positive regulator of MT1-MMP activity at low concentration, in excess, it blocks proMMP-2 activation [69-71].

MT2-, MT5- and MT6-MMP can also activate proMMP-2, but the use of TDVIP-2 for the activation process is not certain [72,73]. MMP-2 activation by MT1-MMP through a TIMP-2 independent process in endothelial cells can be promoted by αvβ3 integrin [74] or claudin, a tight junction protein [75]. Recently, it has been reported by Zhao et al. [76] that proMMP-2 activation by MT3-MMP involves also a ternary complex formation on the cell surface. ProMMP-2 can assemble trimolecular complexes with the catalytic domain of MT3-MMP and TIMP-2 or TIMP-3. Based on affinity chromatography experiments, it appears that TIMP-3 binds more efficiently to MT3-MMP than to MT1-MMP and enhances the activation of proMMP-2 by MT3-MMP but not by MT1-MMP [76]. Finally, the comparison of the activation of proMMP-2 by cells expressing MT1-, MT2- or MT3-MMP, demonstrated that MT2-MMP and MT3-MMP are less efficient than MT1-MMP [59]. MT6-MMP catalytic domain can activate proMMP-2 and generates a higher ratio of mature/intermediate forms of MMP-2 than MT5-MMP [77]. In the opposite to the other MT-MMP, MT4-MMP is inefficient in the initiation of proMMP-2 activation [33,54].

MT1-MMP contributes also to the activation of procollagenase-3 (MMP-13), directly or indirectly via MMP-2 activation [78]. ProMMP-13 activation by MT1-MMP does not involve the establishment of a trimolecular complex between proMMP-13, MT1-MMP and TIMP-2 [79]. The role of MT-MMPs in proMMP activation was extended by recent studies of Toth et al. [80] reporting that proMMP-9 activation is initiated by MT1-MMP and then mediated by MMP-2 or MMP-3. Such an activation of proMMP-9 by MT1-MMP/MMP-2 axis is regulated

by TIMP-2 concentration [80]. In addition, MT4-MMP can enhance the conversion of ADAMTS-4 p68 inactive form into a ρ53 active species, which can degrade aggrecan. Generation of this active 53 kDa form by ADAMTS is completely inhibited by TIMP-1 [55].

Altogether, these data demonstrate that MT-MMPs participate in a cascade of zymogen activation leading to an amplification of proteolysis, in proximity to the cell surface. This pericellular activation of MMPs acts in a concerted manner with the cascade of protease activation involving the plasminogen/plasmin activator system leading also to proMMP activation [16].

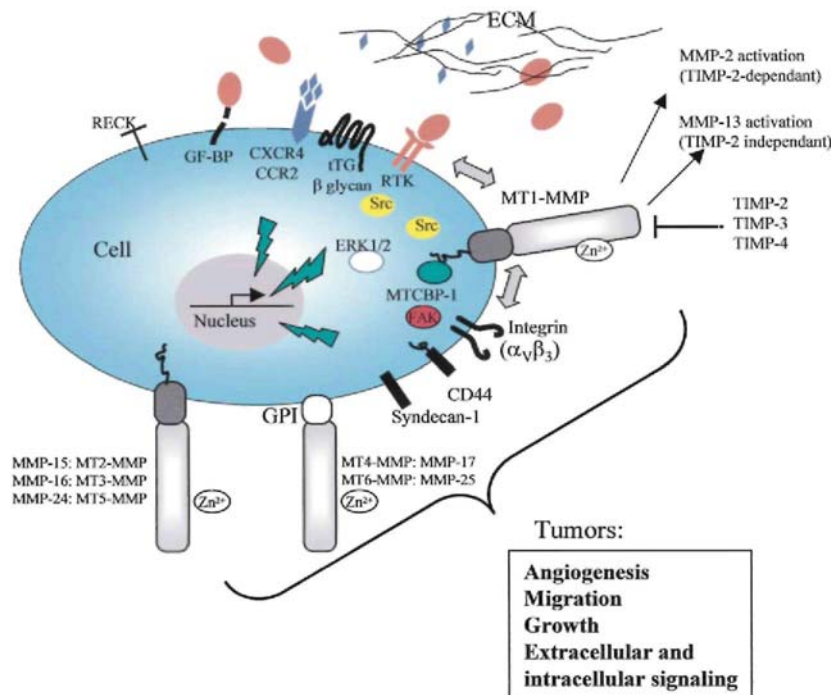## 5. MT-MMP in extracellular signaling

Although MT-MMPs can cleave ECM components, they can also cleave several soluble, cell surface and pericellular proteins, regulating cell behavior in tumor metastasis and angiogenesis. These regulations mechanisms include (1) the alteration of cell-cell interactions, cell-matrix interactions, (2) the release, activation or inactivation of autocrine, or paracrine signaling molecules, (3) the shedding or activation of surface receptors and (4) the activation of intracellular signaling pathways (Fig. 2).

The cell surface-associated MMP-2, MMP-9 and MMP-13 can activate latent transforming growth factor-beta (TGFβ) [4]. MT1-MMP modulates the bioavailability of TGFβ through different mechanisms: (1) by activating MMP-13 and MMP-2 [2], (2) by releasing active TGFβ from cell surface complexes involving αvβ8 integrin [81], (3) by releasing a membrane-anchored proteoglycan, betaglycan that binds TGFβ [82]. A variety of growth factors, growth factor-binding proteins, growth factor receptors are MMP substrates. The degradation of insulin-like growth factor-binding protein (IGF-BP) by several soluble MMPs releases IGFs [83,84]. Cleavage of perlecan releases fibroblast growth factors [85]. The proteolytic process of connective tissue growth factor/VEGF165 complex (CTGF/VEGF165) by MMPs releases an intact VEGF165 recovering its angiogenic activity suppressed by the complex formation with CTGF [86]. Heparin-binding EGF (HB-EGF) shedding is mediated by a specific proteolytic cleavage at a juxtamem-brane site through the action of MMP-3 and MMP-7 [87,88]. Several growth factor receptors are released by MMPs, for example, the release of soluble active fibroblast growth factor receptor 1 (FGFR-1) is mediated by MMP-2 and inhibited by TDVIP-2 [89], whereas the shedding of EGF receptor family including ErbB2 and ErbB4, and hepatocyte growth factor receptor c-Met are blocked by TIMP-1 and TIMP-3, respectively [90-92]. While those last functions are unlikely to be related to a direct implication of MT-MMPs, their role is related to MMP activation.

Recently, the list of non-matrix substrates of MT-MMPs (Table 1) has been completed by cytokines and chemokines. Monocyte chemoattractant protein-3 (MCP-3) is inactivated upon cleavage by MMP-2 [93]. Inactivated MCP-3 molecules can also efficiently be generated by a recombinant MT1-MMP and other soluble MMPs such as MMP-1, MMP-3 and MMP-13 [94]. These data provide a new mechanism by which MMPs could control inflammatory response in cancer and other diseases [95]. Furthermore, the in vivo responsiveness of tumor-infiltrating lymphocytes is suppressed by the MMP-dependent cleavage of IL2 receptor α (IL2Rα) [2]. In addition, the tumor necrosis factor α (pro-TNFα) can be proteolytically activated by MT4-MMP [54] and soluble recombinant MT1-MMP [48]. Stromal cell-derived factor 1 (SDF-1 also known as CXCL12) is an important chemoattractant for breast cancer cell metastasis, for hematopoietic progenitor stem cell migration, and HIV-1 penetration in cells. The activity of SDF-1 and its interaction with its receptor CXCR-4 is attenuated by MMPs under inactivating cleavage by MT1-MMP, MMP-2 and other soluble MMPs such as MMP-1, MMP-3 and MMP-13 [96]. The identification of neutrophil chemokine IL-8, secretory leukocyte protease inhibitor, pro-TNFα, death receptor-6 and CTGF as new substrates of MT1-MMP, emphasizes the importance of this transmembrane protease as a signaling molecule [97].

Finally, cell surface adhesion receptors and proteoglycans are also subject to MT-MMP cleavage and shedding. Over-expression of MT-MMPs by glioma and fibrosarcoma cells led to proteolytic cleavage of cell surface tissue transglutaminase [98]. CD44 (a multifunctional adhesion molecule) [99], syndecan-1 [52] can be directly shed by MT1-MMP and MT3-MMR The αv chain of the αvβ3 integrin, which is reported to play a crucial role in tumor angiogenesis, invasion, and metastasis, is processed by MT1-MMP into a functional form [100]. The multifunctional receptor of complement component 1q (gC1qr) is also susceptible to MT1-MMP proteolysis [101]. Low density lipoprotein receptor (LDLR)-related protein (LRP) is a cell surface-associated endocytic receptors, which is implicated in the internalization and degradation of multiple ligands such as thrombo-spondins (1 and 2), α2-macroglobulin-protease complexes, urokinase- and tissue-type plasminogen activators, MMP-2, MMP-9 and MMP-13 [102,103]. The cleavage of LRP by MT1-MMP in breast cancer (MCF7) and fibrosarcoma (HT1080) cells may thus lead to the control of the bioavailability and fate of many ligands and soluble MMPs in cancer progression [103].

Fig. 2: *Functions of MT-MMPs in cancer progression. The membrane type-matrix metalloproteinases (MT-MMPs) promote cancer progression through different mechanisms: (1) by activating soluble proMMPs, (2) by shedding transmembrane precursors of growth factors, and growth factor binding proteins (GF-BP)), (3) by degrading the extracellular matrix (ECM), facilitating cell migration and the release of growth factors and/or cytokines, (4) by interacting and/or activating receptors and cell surface molecules, (5) by inducing signal transduction and thereby regulating gene expression, (6) by interacting with intracellular molecules such as MTCBP-1. TIMPs and RECK inhibit the activity of MT-MMPs. RTK, receptor tyrosin Kinase; CCR2 and CXCR4, chemokines receptors for MCP-3 and SDF-1, respectively; ERK, extracellular regulated kinase; FAK, focal adhesion kinase; MTCBP-1, MT1-MMP cytoplasmic tail binding protein-1 ; tTG, tissue transglutaminase; GF-BP, growth factor binding proteins; RECK, Reversion inducing cystein-rich protein with Kasal motifs.*

6. MT-MMP can induce intracellular signal transduction

The localization of MT1-MMP at the cell surface into caveoli, specialized membrane domains rich in receptors and signaling intermediates can integrate extracellular signals [104]. MT1-MMP has also been localized at the cell surface in clathrin-coated pits. MT1-MMP can be internalized into intracellular vesicles by a combination of both clathrin-mediated and -independent pathways, most probably involving caveolae [105,106]. MT1-MMP can induce signal transduction and regulate gene expression. The first identified signaling pathway is the activation of extracellular signal-regulated protein kinase (ERK) cascade in cells transfected with MT1-MMP during cell migration [41]. More recently, Takino et al. [107] demonstrate that MT1-MMP-mediated MEK/ERK activation leads to tumor cell invasion in type-1 collagen gel. By using cDNAs encoding dominant negative inhibitors targeted to different signaling pathways, Rac 1 activation by MT1-MMP has also been involved in cell migration [108]. Processing of integrin α_v subunit by MT1-MMP leads to tyrosine phosphorylation of focal adhesion kinase and cell migration [100]. More recently, activation of Src-tyrosine kinase pathway by MT1-MMP has been involved in VEGF up-regulation during tumoral angiogenesis [40]. MT1-MMP is able to specifically cleave the ectodomain of hyaluronate receptor (CD44) [99,109]. The cytoplasmic portion of the processed CD44 is successively cleaved off, followed by a transfer of the fragment into the nucleus to act as a transcription factor [110]. Similarly, the shedding of LDL-related protein (LRP) ectodomain by MT1-MMP may be an initial requirement for the cleavage and the release of its cytoplasmic fragment, which is then translocated to nucleus for transcriptional activation [103]. The role of MMP-2, MMP-9 and MT1-MMP in epidermal growth factor receptor (EGFR) activation has also recently emerged as a new mechanism of growth factor activation. These MMPs contribute to gonadotropin-releasing hormone GnRH-induced EGFR activation and cell signaling via the activation of Src, Ras and extracellular signal-regulated kinase (ERK) pathways [111]. Interestingly, EGFR transactivation is inhibited by TIMPs and synthetic MMP inhibitors in many systems [111-114]. Catalytic activity of MT1-MMP is required for sphingosin 1-phosphate (S1P)-mediated signaling events through G_i protein linked signaling pathway in MT1-MMP-dependent morphologic differentiation and endothelial cell migration [115,116].

The cytoplasmic domain of MT1-MMP is distinct from those of MT2-, MT3-, and MT5-MMP, and is well characterized. In addition to playing an important role in MT1-MMP localization [117] and proMMP-2 activation through homophylic complex formation at the cell surface [26,37], the cytoplasmic domain of MT1-MMP participates in the cell signaling described above. Indeed, the cytoplasmic domain of MT1-MMP is important in ERK activation cascade [41], S1P-dependent G_i protein signaling [118] and VEGF upregulation through Src tyrosine kinase pathways [40]. The multifunctional gC1qR proteins can bind to the cytoplasmic tail of MT1-MMP in a similar manner to the cytoplasmic portion of adrenergic receptor [119]. More recently, Uekita et al. [38] have identified a new 19 kDa MT1-MMP cytoplasmic tail binding protein-1 (MTCBP-1), by yeast two-hybrid screening system. This protein homologue to members of cupin superfamily is localized between three subcellular compartments (membrane, cytoplasm and nucleus) that can regulate gene expression and may suppress the invasion and migration-promoting activity of MT1-MMP [38].

7. MT-MMP in cancer progression

Over the last few years, numerous studies have reported the expression of MT-MMPs, soluble MMPs activated through a MT-MMP-dependent process and their tissue inhibitors in various tumor types [59,120,121]. Clinical studies revealed that the expression of MT1-MMP and MMP-2 is associated with poor prognosis in patients with advanced neuroblastoma [122], small cell lung cancer (SCLC) [123], tongue squamous cell carcinoma [124], head and neck carcinoma [125], bladder cancer [126], and ovarian cancer [127]. Low expression levels of MT1-MMP are considered as favorable survival markers in advanced colorectal carcinoma [128]. MT1-MMP has been detected in tumor cells and adjacent stromal cells in a variety of human tumors, including breast, cervical, colon, bladder, gastric, pancreatic, liver, gastric, ovarian, prostate and thyroid cancer (for review, see [3]). Studies based on in situ hybridation analysis in lung [129] and breast carcinomas [130,131] revealed that MT1-MMP mRNA are expressed by stromal cells surrounding tumor cells. Other studies have shown the expression of MT1 -MMP in cancer cells rather than stromal cells of human thyroid, brain, head and neck cancer [3]. This suggests that MT1-MMP expression profile is likely to vary from one tumor type to another. In addition, production of MT1-MMP by carcinoma cancer cells has been associated with epithelial to mesenchymal transition (EMT) of cancer cells [132].

Although MT2-MMP expression in tumors has been found in cervical, breast, head and neck cancer, glioblastoma and astrocytic cancers [129,133-135], its expression has not been linked to disease progression [121]. Velasco-Loyden et al. [82] have recently reported in an experimental model that MT1-MMP is negatively regulated by MT2-MMP. Such a negative regulation of MT1-MMP may explain the lack of correlation between MT2-MMP expression and the aggressiveness of cancers, however, further investigation are needed [82].

MT3-MMP has been detected in breast and renal carcinomas, astrocytic tumors and melanoma [134,136-138]. MT5-MMP and MT6-MMP are mostly overexpressed in aggressive human brain tumors [56,139].

There is clear evidence that MT1-MMP and MMP-2 are involved at different stages of tumor progression from initial tumor development, growth and angiogenesis to invasion, metastasis and growth at secondary sites [3,35,60]. Many of these insights came from experiments with genetically modified animals or cells. For instances, targeted overexpression of MT1-MMP in the mammary gland leads to the formation of a mammary carcinoma [140], whilst the absence of MMP-2 or overexpression of TIMP-2 can significantly attenuate various tumorigenic processes such as primary tumor growth and angiogenesis [141,142]. Other studies in experimental cancer models demonstrated that human breast, melanoma and glioma cells transfected with MT1-MMP enhanced MMP-2 activation, invasion and in vivo tumor growth [65,141,143-146]. It should be pointed out that MT1-MMP overexpression in human breast cancer can to induce tumor growth, whereas the overexpression of MMP-2 alone in the absence of MT1-MMP does not promote tumor development in nude mice [143,147]. These observations suggest that MT1-MMP may contribute to neoplastic progression independently to its capacity to activate proMMP-2. A new mechanism by which MT1-MMP can induce tumor cell growth has been recently proposed by Hotary et al. [145]. MT1-MMP is viewed as a tumor-derived growth factor that regulates proliferation by controlling cell geometry within the three-dimensional extracellular matrix. This study demonstrates that pericellular proteolysis by MT1-MMP confers a three-dimensional collagen matrix specific growth advantage. When MT1-MMP transfected cells are grown in gels composed of a mutant collagen that cannot be degraded, proliferation is blocked [145]. The role of MT-MMPs as well as other MMPs in cancer metastasis and invasion could not be restricted to the ECM component degradation. In this context, the capacity of MT1-, MT3-, MT5-MMP, active MMP-2 and MMP-9 to inactivate the human metastasis suppressor gene *KiSS-1* produced by cancer cells provides a new mechanism of control [148].

To date, MT1-MMP is mainly believed to be important for tumor invasion and metastasis. Its overexpression strongly promotes cellular invasion in vitro [21,24,60,65,99,143,149] and experimental metastasis [150-152]. Cell invasion is a multistep process involving ECM degradation and cell mobility. While ECM degradation can be orchestred collectively by MMPs, cell migration is likely predominantly associated with MT1-MMP activity. Through its activity towards cell surface adhesion molecules (CD44, tTG and αv integrin) [98,99,153] or specific ECM protein such as laminin-5 [149,154], MT1-MMP can strongly modulate cell adhesion and cytoskeletal organization leading to cell mobility. The importance of endogenous MT1-MMP in cancer invasion was evidenced by downregulation of MT1-MMP in aggressive cancer cells using RNA silencing technology [155]. The specific silencing of MT1-MMP is sufficient to inhibit the invasion of highly invasive fibrosarcoma H1080 cells known to produce high levels of different MMPs.

8. MT-MMP in tumor angiogenesis and vascularisation

Recent investigations have highlighted the important role played by MT-MMPs in the formation of new blood vessels in both physiological and pathological conditions. The activities of MT1-MMP, MT2-MMP MT3-MMP and MT5-MMP are essential for microendothelial cell differentiation into tubes in a fibrin gel [156]. TIMP-2 and TIMP-4, but not TIMP-1, are able to inhibit angiogenesis in vitro [156]. In the absence of uPA/plasminogen system, MT1-MMP fibrinolytic activity supports the tubule formation of endothelial cells in a fibrin gel [46]. In 3D-collagen gel, expressions of MT1-MMP and MT3-MMP are required for MDCK and endothelial cell organisation into a tubular network [50,157,158]. Although embryonic vasculogenesis and angiogenesis are normal in MT1-MMP-deficient mice, the formation of secondary ossification centers during bone formation is severely impaired due to defect of angiogenesis [159]. Angiogenesis is severely impaired in an ex vivo assay using cornea issued from MT1-MMP-deficient mice, compared to wild-type mice [159].

Laminin-5 is a major component of basement membrane, which regulates the functions of epithelial cells. Several cancer breast epithelial cell lines constitutively express MT1-MMP and generate a unique fragment derived from the cryptic site of the γ2-chain of laminin-5, directly affecting the cellular signal and promoting cell migration [149,154]. The generation of a fragment from laminin-5 γ2-chain by MT1-MMP in human uveal melanoma cells plays critical roles in the vasculogenic mimicry [160]. In addition, MT1-MMP may modulate the ability of cancer cells to induce angiogenesis. Tumor cells expressing MT1-MMP grow rapidly and form highly vascularized tumors [65,145]. The pro-angiogenic activity of MT1-MMP is further supported by the effects of MT1-MMP overexpression on tumorigenicity, growth and vascularization of human melanoma [65,161], breast adenocarcinoma [143] or glioma [144] cells transfected with MT1-MMP cDNA. Recent studies provided evidence that this MT1-MMP pro-angiogenic effect is mediated at least by an up-regulation of VEGF at both mRNA and protein levels by activation of signaling pathway involving Src type tyrosine kinases [40,143]. However, the expression of other angiogenic factors such as VEGF-B, -C, -D, P1GF, angiopoietin or their receptors VEGF-R1, -R2, neuropilin, Tie-1 and Tie-2 is not affected by MT1-MMP overexpression [40]. Such a link between the expression of VEGF and MT1-MMP is further confirmed by immunohistochemical and RT-PCR analysis of human glioma tissue samples [162]. Correlation between MT1-MMP and VEGF-A has also been observed in early physiological cartilage formation [163].

The control of VEGF bioactivity by MMPs has also been reported. In this context, MMP-9 controls the bioavailability of VEGF by releasing it from ECM [164]. MMP-1, -3, -7 and -13 selectively degrade connective tissue growth factor (CTGF) bound to the $VEGF_{165}$ and thereby reactive angiogenic activity of $VEGF_{165}$ [86]. MMP-9 and MMP-2 have been shown to contribute to the release of VEGF in the conditioned media of cultured SKOV3 and OVCAR3 cells, and in peritoneal ascites of nude mice bearing human ovarian carcinoma xenografts (HOC22 and HOC8) [165]. However, the mechanisms underlying this process require further investigation. The effects of synthetic MMP inhibitors on the expression of VEGF in MCF7 overexpressing MT1-MMP and in an in vivo T-cell lymphoma model, support the role of MT1-MMP in promoting tumor angiogenesis during cancer progression [40,166].

9. Physiological MMP inhibitors in tumor angiogenesis

The TIMPs are physiological inhibitors, which can control and regulate MMP functions. TIMP-1, -2 and -3 knockout mouse have been generated and are viable and fertile without obvious severe phenotype or angiogenesis defect (for review, see [7,9]). Several studies have demonstrated that overexpression of TIMPs confer less metastatic, angiogenic and tumorigenic phenotypes in different in vivo and in vitro models. Tumors arising from TIMP-2 overexpressing melanoma cells show reduced tumor growth and angiogenesis [167]. The injection of adenoviral TIMP-2 into preexisting tumors (lung, colon and breast cancer models) reduced tumor angiogenesis [168]. TIMP-2 can suppress MT1-MMP expressing tumor cell growth within three-dimensional

collagen or fibrin matrix [145]. Interestingly, the in vivo anti-angiogenic effect of TIMP-2 in murine mammary carcinoma cells is correlated with a strong reduction of VEGF expression [142]. TIMP-1 has no effect on the VEGF levels in both MT1 -MMP transfected cells, however, TIMP-1 can up-regulate VEGF in MCF7 [169]. Overexpression of TIMP-3 in neuroblastoma and melanoma by retroviral delivery decreases tumor angiogenesis in severe combined immunodeficient (SCID) mice by inhibition of functional capillary morphogenesis [170,171]. Human tissue factor pathway inhibitor-2 (TFPI-2) that inhibits the plasmin and trypsin-mediated activation of proMMPs has been reported to inhibit in vivo growth and metastasis of highly metastatic fibrosarcoma cells (HT1080) through a downregulation of VEGF expression in cells overexpressing TFPI-2 cells [172].

Two recent studies have demonstrated a new specific anti-angiogenic property of TIMP-2 and TDVIP-3 independently of their MMP-inhibitory activities. The first study shows that TIMP-3 inhibits angiogenesis in chick chorioallantoic membrane (CAM) assay through binding to VEGFR-2 and blocking the binding and activation of VEGFR-2 by VEGF [173]. The second report demonstrates that TIMP-2 suppresses in vitro human microvascular endothelial cells (hMVEC) proliferation, and mediates inhibition of angiogenesis in vivo through $\alpha 3\beta l$ binding and initiation of a signaling cascade that results in enhanced protein tyrosine phosphatase (PTP) activity associated with angiogenic factor receptors [174].

The RECK (Reversion inducing cystein-rich protein with Kasal motifs) is considered as a cell-associated endogenous inhibitor of MT1-MMP, MMP-2 and MMP-9 [175]. RECK is expressed in a variety of human tissues, but its expression is downregulated in many cancer cell lines and cancer tissues such as hepatocellular carcinoma [176] and pancreatic cancer [177]. RECK-/- mouse have disrupted vascular development, neural tube and mesenchymal tissues integrity and die at embryonic day 10.5 [178]. The RECK-/-MMP-2-/-double knockout mice are partially rescued by delay of death at embryonic day 11.5 and marked recovery of tissue integrity compared to RECK-/-. In a tumor model, when transfected fibrosarcoma HT1080 cells with RECK cDNA were subcutaneously injected into nude mice, tumor angiogenesis is inhibited [178]. In addition to TIMPs, RECK may play an important regulatory control of MMP activity, thereby controlling tumor cell invasion, metastasis and tumor angiogenesis [6].

10. Conclusions

Pericellular proteolysis appears more and more as a crucial event controling the local environment surrounding normal and tumor cells. MT-MMPs are a key subfamily of cell-membrane associated enzymes contributing to the remodeling of extracellular matrix.

MT1-MMP, the first identified member of this sub-family appears as the main activator of proMMP-2 and as a key actor in several cellular events associated with tumor progression. In addition to its capacity to cleave matrix components, MT1-MMP interacts with membrane-associated and intracytoplasmic molecules, controling thereby several cell functions. The role of MT1-MMP in signal transduction needs to be further investigated.

The multifunctionality of all MT-MMPs as well as their in vivo sub-states remain to be explored. One of the important future prospects is to address the differences between the six MT-MMPs identified and to establish their putative redundancy. The generation of animals with single or combined gene deletion, as well as conditional knock-out mice for MT1-MMP will be essential for a better understanding of their functions. Do all MT-MMPs, promote tumor progression? Do some MT-MMPs negatively regulate the evolution of cancer? Are some or all MT-MMPs appropriate targets to develop anti-cancer agents? These questions have to be addressed in order for rational therapy to be developed.

Acknowledgements

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