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Review Article

MT1-MMP-dependent cell migration: proteolytic and non-proteolytic mechanisms

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Membrane-type 1 matrix metalloproteinase (MT1-MMP) is a type I transmembrane proteinase that belongs to the matrix metalloproteinase (MMP) family. It is a potent modifier of cellular microenvironment and promotes cell migration and invasion of a wide variety of cell types both in physiological and pathological conditions. It promotes cell migration by degrading extracellular matrix on the cell surface and creates a migration path, by modifying cell adhesion property by shedding cell adhesion molecules to increase cell motility, and by altering cellular metabolism. Thus, MT1-MMP is a multifunctional cell motility enhancer. In this review, we will discuss the current understanding of the proteolytic and non-proteolytic mechanism of MT1-MMP-dependent cell migration.

Introduction

Cell migration is a fundamental process for multicellular organisms and plays a crucial role in different physiological phenomena including embryonic development, wound healing and immune response, while it is also involved in the progression of various diseases, including cancer and rheumatoid arthritis [1]. Basic concepts of cell migration have been described for the first time by Abercrombie and colleagues [2–4], who have studied the two-dimensional (2D) locomotion of fibroblasts moving on a flat substratum. However, cell migration on 2D surface inadequately reflects cell migration *in vivo*, where cells are constantly exposed to the physical constraint of the extracellular matrix (ECM) [5]. Basic steps of cell migration through the ECM have been purposed through the three-step model of invasion [6]. According to this theory, when cells migrate, they first recognize and attach to the ECM through adhesion molecules such as integrins [6]; secondly, proteinases are recruited to cause local ECM degradation; finally, the cell body moves into the degraded ECM space [6]. The repetition of the three steps allows cells to migrate across the ECM effectively. This mode of migration is known as mesenchymal-type and requires the harmonic coordination of integrin-mediated cell adhesion, cytoskeletal re-organization and proteinase activity [5]. In response to the existence of large enough, pore-sized matrices, cells can also adopt a protease-independent mode of locomotion, known as amoeboid movement [7]. Nevertheless, when cells require to degrade the ECM components and make a path to migrate, they employ matrix metalloproteinases (MMPs), a group of proteinases that play a primary role in ECM degradation [8,9].

MMPs are a group of zinc-dependent metalloproteases which can degrade all the ECM components. There are 23 MMPs in humans, and they can be classified based on substrate specificity or domain structure [10]; alternatively, they can be categorized to soluble MMPs or membrane-type MMPs (MT-MMPs) (Figure 1). The typical domain structure of MMPs consists of a signal peptide, a pro-domain, a catalytic domain, a linker peptide also known as hinge region, and a hemopexin domain [10] (Figure 1). Many of the soluble MMPs are secreted as inactive zymogens and need to be activated extracellularly by other proteinases. MT-MMPs share a common domain structure with other MMPs but they are tethered to the plasma membrane either through a transmembrane domain followed by a short cytoplasmic tail (CT) (MT1-, MT2-, MT3-, and MT5-MMPs) or a glycosylphosphatidylinositol- (GPI) anchor (MT4-, MT6-MMPs) at their C-terminus [11] (Figure 1).

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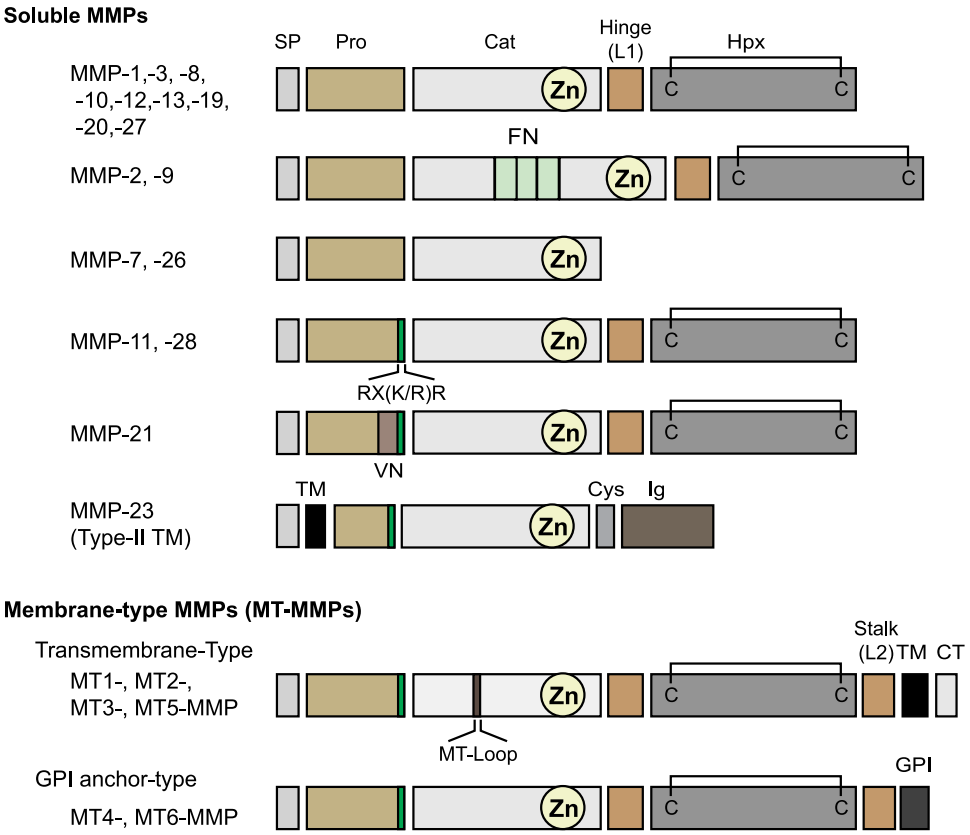

Figure 1. Domain structure of MMP family.

SP, Signal peptide; Pro, pro-domain; Cat, catalytic domain; L1, linker 1; Hpx, hemopexin domain; FN, fibronectin type II repeats; VN, vitronectin-type domain; TM, transmembrane domain; Cys, cysteine-rich domain; Ig, immunoglobulin-like domain; L2, linker 2; CT, cytoplasmic tail; GPI, GPI-anchor signal sequence. RX(K/R)R: PC recognition sequence; MT-Loop: eight-amino acid insertion characteristic to TM-type MT-MMPs. Hpx domain contains one di-sulfide bond (C-C). MT1-MMP is palmitoylated at Cys574 in the CT.

All MT-MMPs are activated intracellularly by proprotein convertases (PCs) such as furin and expressed as an active form on the cell surface. These PCs recognize and cleave a basic amino acid motif of RX(K/R)R at the C-terminus of the pro-domain, which is common to all MT-MMPs and some soluble MMPs (MMP-11, -21, -23 and -28) [11]. Transmembrane-type MT-MMPs are also characterized by an eight-amino acid loop insertion in their catalytic domain, named as MT-Loop [11].

Among these, membrane-type I MMP (MT1-MMP) has been shown to be the sole MMP that promotes cell migration in a collagen-rich environment [12]. MT1-MMP-mediated cell migration/invasion has been implicated in different disease processes, including inflammation [13], atherosclerosis [14], rheumatoid arthritis [15], cancer invasion and metastasis [16]. Therefore, understanding the mechanisms of MT1-MMP-driven cell migration/invasion is crucial to comprehend the pathogenesis of different diseases. Accumulated evidence suggests that MT1-MMP promotes cellular invasion in both proteolytic activity-dependent and independent manner, and this review will discuss the mechanism of these different modes of MT1-MMP-dependent cell migration/invasion.

Properties of MT1-MMP

Substrates of MT1-MMP

ECM components

MT1-MMP degrades a variety of ECM components including fibrillar collagen types I, II, III, vitronectin, fibronectin, laminin-1, -2/4 and -5, fibrin/fibrinogen, aggrecan, and perlecan [11]. Among these ECM macromolecules,

collagens are the most abundant ECM components, forming the structural scaffolding of tissues and organs and thus contributing to their integrity and stability [17]. Collagen type I is ubiquitous and found in the majority of connective tissue [18]. Collagen type II is abundant in cartilage and vitreous humor, whereas collagen type III is observed in cardiovascular and visceral tissue [18]. Collagens are characterized by three long and parallel left-handed polypeptide chains, coiled together to form a right-handed triple helical structure [17]. As a consequence, only collagenolytic enzymes belonging to the MMP family, including MMP-1, MMP-2, MMP-8, MMP-13, and MT1-MMP, can degrade collagen at neutral pH [17]. MT1-MMP-dependent collagen degradation contributes to the physiological remodeling of connective tissues during growth and development. MT1-MMP-deficient mice have severe defects in postnatal skeletal development due to the loss of collagenolytic activity at the cellular level [19,20]. Mice present a progressive cranial dysmorphism, dwarfism, osteopenia, osteoclast-mediated arthritis, fibrosis of the soft tissues and die between 3 and 16 weeks [19,20]. These abnormalities indicate that MT1-MMP-mediated collagenolytic activity has an indispensable role in stromal remodeling after birth.

Soluble MMPs

MT1-MMP was originally discovered as a proMMP-2 activator, expressed on the surface of invasive cancer cells [21]. Since activated MMP-2 degrades type IV collagen, a major component of basement membrane (BM), the activation of proMMP-2 by MT1-MMP is considered to be a crucial step for cancer cells to invade into BM [21]. MT1-MMP forms a homo-dimeric complex through its hemopexin and transmembrane domains, which has been proven to be necessary for the cell surface proMMP-2 activation [22,23]. The current well-accepted activation model is shown in Figure 2. One molecule of the endogenous inhibitor for MMPs, tissue inhibitor of metalloproteinases-2 (TIMP-2), binds and inhibits one of the MT1-MMP molecules of the dimeric complex, interacting through its N-terminal inhibitory domain with the catalytic domain of MT1-MMP (Steps 1–2) [24]. TIMP-2 C-terminal domain has an affinity to proMMP-2 hemopexin domain; thus an (MT1-MMP)2–TIMP-2–proMMP-2 complex is formed on the cell surface (Steps 2–3) [11]. MT1-MMP free from TIMP-2 then cleaves in the middle of proMMP-2 pro-peptide, to generate an intermediate form, triggering the auto-catalytic activation of the intermediate MMP-2 itself (Steps 3–4) [11]. It has also been shown that MT1-MMP activates proMMP-13 on the cell surface [25] and that MMP-13 C-terminal

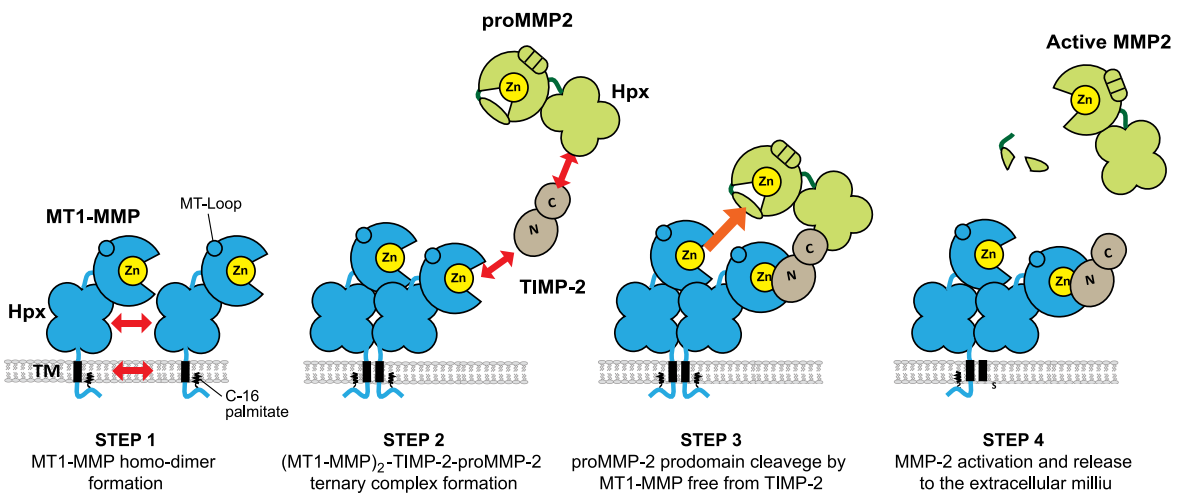

Figure 2. A model of the cell surface activation of proMMP-2 by MT1-MMP.

Step 1: MT1-MMP forms a homo-dimeric complex through its hemopexin and transmembrane domains on the cell surface. Step 2: A molecule of tissue inhibitor of metalloproteinase-2 (TIMP-2) binds and inhibits one of the MT1-MMP molecules in the dimer complex, interacting through its N-terminal inhibitory domain with the catalytic domain of MT1-MMP. TIMP-2 C-terminal domain has affinity to Hpx domain of proMMP-2, and a $(MT1\text{-}MMP)_2$-TIMP-2-proMMP-2 ternary complex is formed. Step 3: MT1-MMP free from TIMP-2 cleaves proMMP-2 in the middle of the pro-domain and triggers the auto-catalytic activation of the intermediate MMP-2. Step 4: MMP-2 is released as an active form into extracellular milieu.

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domain is required for the activation process, while TIMP-2 is dispensable [26], but the detailed mechanism has not been clearly understood.

Cell adhesion molecules and other membrane proteins

It has been shown that MT1-MMP sheds the hyaluronan receptor CD44 [27], promoting cell migration by modifying cell adhesion properties [27]. It has also been reported that the interaction of MT1-MMP with CD44 occurs through the hemopexin domain [28,29]. This interaction occurs before the shedding takes place and mediates localization of MT1-MMP to the lamellipodium membrane structure [29]. CD44 is known to interact with actin cytoskeleton through the interaction of basic amino acids in its cytoplasmic domain and ezrin/radixin/moesin (ERM) proteins [30]. Therefore, the interaction between MT1-MMP and CD44 mediates the association of MT1-MMP with cytoskeletal actin [29]. MT1-MMP has been reported to shed the ectodomain of syndecan-1, a transmembrane heparan sulfate proteoglycan [31], processes the αv integrin subunit (pro-αv) into heavy and light α chains [32,33]. MT1-MMP also sheds the ectodomain of the adhesion molecule ICAM-1 and colocalizes with it at the ruffling membrane structures [34]. MT1-MMP was also shown to cleave low-density lipoprotein receptor-related protein (LRP) in cancer cells, controlling the subsequent fate of MMP-2 and other proteinases [35]. In vascular smooth muscle cells, MT1-MMP-mediated LRP1 cleavage has been reported to be an important proteolytic regulatory mechanism for their dedifferentiation program [36]. Shedding of LRP-1 by MT1-MMP was also found in human chondrocytes, and this process has been shown to alter the normal turnover of ECM and the cartilage homeostasis by influencing LRP-1-dependent endocytosis of MMP-13 and aggrecanases in osteoarthritis [37]. MT1-MMP has been reported to inactivate ADAM-9 by cleaving it, controlling ADAM9-dependent FGFR2 ectodomain shedding, which leads to unpaired FGFR2 signaling in calvarial osteoblasts and thus retarded calvarial osteogenesis [38].

Regulation of MT1-MMP

Gene regulation

MT1-MMP is expressed in many cell types including mesenchymal stem cells, fibroblasts, osteoblasts, osteoclasts, chondrocytes, epithelial cells, endothelial cells, adipocytes, myeloid cells, neuronal cells, T cells, and B cells [11]. Moreover, MT1-MMP has been found to be overexpressed in many cancer cells [39], associated with poor prognosis [40]. In physiological conditions, the transcription of MT1-MMP gene in different cell types should be under strict control. However, very little is still known about the detailed mechanisms which regulate MT1-MMP gene in specific tissues. MT1-MMP gene counts 10 exons and 9 introns with exon–intron boundaries comparable to other MMPs [41]. MT1-MMP promoter differs from other classical MMP, such as MMP-1, -3, -9 and -13, due to the lack of a conserved TATA box in position -25 and an AP-1-binding site in position -80 [41]. MT1-MMP promoter activity has been shown to be strongly influenced by Sp1 in humans [41]. Sp1-binding site partially overlaps with EGR1-binding site, which has been shown to contribute to enhanced transcriptional activity in endothelial cells [42]. Other important binding sites include Nkx-2, AP-4, CARG Box, E-box, Lyf1 and c-Myc, which are all within 2 kb upstream the translation start site [42]. There is the NF-κB-binding site at −2.16 kb, and it has been shown to play a role in some cell types. For instance, the suppression of NF-κB pathway by the histone acetyltransferase Tip 60, reduces MT1-MMP transcription in glioblastoma cells [43]. The zinc-finger transcription factor Snail1 has been reported to support MT1-MMP transcription in fibroblasts [44]. In fact, Snail1-deficient fibroblasts exhibit defects in MT1-MMP-dependent invasion [44]. In dermal fibroblasts, it was shown that platelet-derived growth factor D (PDGF-D) activates PI3K, JNK and ERK1/2 signaling pathways, which induce Snail-mediated MT1-MMP up-regulation [45]. The zinc-finger transcription factor Sp1 is also involved in MT1-MMP transcription [46]. In prostate cancer cell lines, MT1-MMP expression levels vary depending on Sp1 regulation and AKT, JNK and ERK signaling pathways [46]. In melanoma cells, CD81 has been found to induce phosphorylation of Sp1, triggering MT1-MMP transcription [47]. In squamous carcinoma cells, vinculin enhances MT1-MMP production at the transcriptional level, thus increasing tumor cell invasion [48]. The binding site for Sp1, located at −125 bp upstream the translation start site, has been reported to co-operate with hypoxia-inducible factor 2α (HIF-2α) to promote MT1-MMP transcription in von Hippel–Lindau renal carcinoma cells [49,50]. Different stimuli have been reported to control the production of MT1-MMP in various cell types. Fibroblasts, endothelial and epithelial cells up-regulate their MT1-MMP production when cultured in a 3D collagen matrix [42,51,52]. DDR2 has been proven to be the receptor which mediates collagen-induced MT1-MMP expression in non-transformed

human fibroblasts but not in cancer cells such as HT1080 and MDA-MB231 [53]. MT1-MMP has been described to be up-regulated by concanavalin A in fibroblasts [25], MDA-MB231 [54] and HT1080 cells [55], and by phorbol ester in HT1080 cells [56].

ProMT1-MMP activation

MT1-MMP is synthesized as a pre-pro-enzyme followed by the removal of the signal peptide by signal peptidase in the rough endoplasmic reticulum. For activation, further removal of the pro-peptide, by PCs such as furin, is required and it takes place in the trans-Golgi during the secretory process [21]. PCs recognize a ^{108}RRKR motif at the C-terminus of the pro-domain and remove the pro-peptide directly [21]. It has been shown that PCs, except furin, can also recognize the ^{86}KAMRRPR motif within the pro-peptide, to cause an alternative processing [57]. MT1-MMP is thus expressed on the cell surface as an active enzyme.

Endogenous inhibition

Inhibition by endogenous inhibitors is an important regulatory step to modulate its activity on the cell surface. MT1-MMP can be inhibited by TIMP-2, -3 and -4 but not TIMP-1 [58]. TIMP-2 has been characterized as MT1-MMP inhibitor by many investigators, but as discussed above, TIMP-2 participates in MT1-MMP-dependent proMMP-2 activation [21]. TIMP-2 null mice displayed neither excess MT1-MMP activity nor abnormality in ECM architectures [59], suggesting that the physiological role of TIMP-2 may not be MT1-MMP inhibition but rather supporting MT1-MMP-dependent proMMP-2 activation. In contrast with TIMP-2, it was found that TIMP-3 null mice display accelerated ECM destruction [60]; proMMP-2 activation was noticeably enhanced in TIMP-3-null cells [61], suggesting that TIMP-3 may play a role as a guardian of the ECM, by inhibiting MT1-MMP and other enzymes. Recently, TIMP-2 chimeras have been purposed as effective inhibitors of MT1-MMP, both intracellularly and on the cell surface, suppressing gelatinolytic and invasive abilities of cervical carcinoma cells [62]. Besides TIMPs, it has been reported that reversion-inducing cysteine-rich protein with kazal motifs (RECK) inhibits MT1-MMP [63]. Other reported MT1-MMP inhibitors are testican-3, its variant N-Tes [64].

Processing to lower molecular mass species on the cell surface

Proteolytic processing of MT1-MMP has been described as another way to regulate MT1-MMP proteinase activity on the cell surface [65,66]. Active 60 kDa MT1-MMP undergoes processing to a 44–45 kDa species by MMP-2 or MT1-MMP itself [65–67]. This process removes the catalytic domain; thus, it is considered to be a regulatory function to down-regulate MT1-MMP activity; the generation of processed form coincides with the functional activation of MT1-MMP [65–67].

Endocytosis and recycling

Endocytosis is a major mean by which cells regulate the cell surface level of MT1-MMP [68]. MT1-MMP is internalized through the clathrin- and the caveolae-mediated pathways [69,70]. Clathrin-driven MT1-MMP endocytosis requires the LLY^{573} motif in the CT to interact with the adaptor protein-2 (AP-2) of the clathrin adaptor complex [70]. The palmitoylation at Cys^{574}, downstream the LLY^{573} motif, is required for MT1-MMP to be internalized in a clathrin-dependent manner [71]. Interestingly, although endocytosis is mean to decrease cell surface level of MT1-MMP, disturbing clathrin-dependent endocytic pathway was found to significantly decrease its ability to promote cell migration [70,71], suggesting that functional MT1-MMP needs to be constantly replaced by newly secreted molecules. The knockdown of clathrin light chain B (CLTHB) has recently been found to reduce MT1-MMP protein expression and consequent invasion through collagen matrices by endometrial cancer cells [72]. The phosphorylation of Thr^{567} in the cytoplasmic domain of MT1-MMP by protein kinase C (PKC) has also been reported to be required for MT1-MMP internalization [73]. Endophilin A2 has been reported to promote MT1-MMP endocytosis in MDA-MB-231 [74]. Endocytosed MT1-MMP is recycled back to the cell surface although this process is not essential for the proteinase to promote cell migration and invasion [70,75].

Intracellular trafficking and polarised localization on the cell surface

MT1-MMP cell surface exposure is achieved by intracellular trafficking mechanisms regulated by kinesin superfamily motor proteins (KIFs) [76]. MT1-MMP-containing vesicles are trafficked along microtubules in a bidirectional way, and in primary human macrophages, the anterograde movement of the vesicles has been

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shown to be mediated by KIF5B and KIF3A/3B, while the retrograde transport is mediated by dynein [76]. KIF5B has also been reported to mediate MT1-MMP cell surface localization in breast cancer cells [77,78]. KIF1B has been shown to mediate leptin-dependent MT1-MMP cell surface exposure in gastric cancer cells [79]. In accordance with, KIF1B knockdown causes a decrease in the MT1-MMP cell surface amount without affecting the overall MT1-MMP protein level in glioma cells [79,80].

MT1-MMP-dependent cell migration

Proteolytic mechanisms

Direct ECM proteolysis

MT1-MMP promotes cellular invasion by directly degrading pericellular ECM to clear the path for migration [58]. For MT1-MMP to promote cell invasion, it needs to retain its membrane-anchored nature since soluble mutant MT1-MMP is unable to support cell invasion [12]. As discussed above, collagens are the most abundant ECM molecules and among the five collagenase MMPs (MMP-1, -2, -8, -13, MT1-MMP), MT1-MMP is the only enzyme that directly promotes cell migration in a collagenous environment [12,81]. It has been shown that a wide variety of cell types including fibroblasts, endothelial cells, and cancer cells, use MT1-MMP-dependent invasion program within the collagen matrix [82]. Moreover, it has been found that MT1-MMP plays a fundamental role in human mesenchymal stem cells mobilization from the bone marrow [83]. MT1-MMP and MMP-2 productions are up-regulated in human mesenchymal stem cells by inflammatory cytokines such as TGF-β1 and IL-1β, and sustain chemotactic migration through ECM [84]. It has also been reported that cancer cells can adopt a proteinase-independent invasion within the collagen gel [85]. This mode of migration is named amoeboid-type migration: cells change their shape and squeeze through pre-existing matrix pores using actomyosin-based mechanical forces [85]. However, the collagen matrix used in this study used pepsin-extracted collagen that has lost the non-helical telopeptide regions due to the pepsin treatment. These telopeptides contribute to the formation of covalent cross-links that define fibril architecture and structural rigidity of the tissue [82], so collagen lacking telopeptides forms a much weaker gel, and cells can manage to migrate without degrading the matrix [86]. Thus, these experimental conditions were not reflecting the real collagenous environment [82]. It is now clear that amoeboid migration is only possible when the size of the open pores in the ECM is large enough for migrating cells to manage for squeezing their nucleus to migrate through [87]. The microstructure of the ECM seems to dictate cell migration speed, invasion distance and number of cellular protrusions [88]. For instance, aligned fibres help cells to spatially and temporally focus MT1-MMP to the membrane protrusions [88]. Moreover, it has been reported that matrix pore sizes and laminin A expression, which modulates nuclear stiffness, contribute to MT1-MMP localization at confined collagen fibrils to widen the pore size of the matrix to promote cancer cells invasion through the linker of nucleoskeleton and cytoskeleton (LINC) complex protein nesprin-2 and dynein adaptor Lis1 [89]. Taken together, these findings highlight that cancer cells actively adjust to the microenvironment, employing a digest-on-demand response to achieve confined cell migration within 3D ECM. In addition to creating a migrating path, MT1-MMP-dependent cleavage of laminin 5 was shown to enhance cellular motility of epithelial cells [90,91]. MT1-MMP cleaves the γ2 chain at two sites, releasing a fragment containing epidermal growth factor (EGF)-like motifs (DIII fragment). The liberated DIII fragment bound the EGF receptor (EGF-R) and stimulated epithelial cell scattering and migration.

Indirect ECM proteolysis

MT1-MMP also indirectly promotes cell migration and invasion by activating proMMP-2 [21] and proMMP-13 [25]. MT1-MMP-mediated proMMP-2 activation has a high significance in the context of cancer cell invasion into the BM since MT1-MMP cannot cleave type IV collagen [92], a major component of the BM. BM is a thin ECM construct (100–200 nm), which provides support for the epithelium and function as an efficient selective barrier to both cellular and molecular traffic [93]. During cancer progression, tumor cells acquire the ability to breach BM barriers to reach the stromal matrix both at the primary tumor site and at distant organs where metastasis are developed [94]. Since activated MMP-2 can degrade type IV collagen, activation of proMMP-2 by MT1-MMP is a major trigger of protease-dependent BM transmigration, associated with tissue-invasive phenotype [94]. When well-differentiated cancer cells grow in the tissue, they need constant degradation of their own BM in order to increase the mass. It was shown that MT1-MMP-dependent growth of gastric cancer cells *in vivo* requires MT1-MMP-dependent proMMP-2 activation [95], highlighting

the importance of proMMP-2 activation in BM degradation. However, the presence of MMP-2 itself is not sufficient for BM degradation and requires MT-MMPs. In MDA-MB231 cells, it was shown that three MT-MMPs, MT1-, MT2-, and MT3-MMP are necessary for BM invasiveness [96]. MT1-MMP also activates proMMP-13 on the cell surface [25], but it is not clear if proMMP-13 activation would contribute to cellular invasion.

Processing of cell adhesion molecules

MT1-MMP promotes cell migration and invasion by processing cell adhesion molecules. As discussed above, shedding of CD44 ectodomain by MT1-MMP at the leading edge has been shown to promote cell migration on a hyaluronan-based matrix [27]. MT1-MMP-dependent shedding was shown to influence CD44-dependent cell adhesion at the leading edge, and the spatiotemporal shedding of CD44 is considered to play a role [27]. Besides MT1-MMP, ADAM (a disintegrin and a metalloproteinase)-10 and -17 were also shown to shed CD44 and enhance cell migration [97]. Syndecan-1 ectodomain shedding by MT1-MMP was reported to enhance cell motility on collagen matrices in HT1080 human fibrosarcoma cells [31]. α_V integrin processing by MT1-MMP has also been found to enhance motility on fibronectin substrates [98]. Finally, MT1-MMP plays a crucial role in endothelial transmigration shedding the adhesion molecule ICAM-1 [34].

Cellular regulation of the proteolytic mechanisms of cell migration

MT1-MMP localization to the leading edge of the migrating cell

For MT1-MMP to promote cell migration and invasion, its localization to the leading edge is crucial [99]. During cell migration, actin polymerization drives the formation of membrane protrusions to form the leading edge. Cell adhesions are established with the ECM molecules though transmembrane ECM receptors and degrading proteinases like MT1-MMP are recruited to the adhesion sites to achieve localized proteolysis [100]. Membrane protrusions can result in various types of leading edges, characterized by different morphologies and force-generation capabilities, comprising filopodia, lamellipodia, podosomes and invadopodia [100]. MT1-MMP has been reported to localize to all of these motility-associated structures [22,101–103].

Filopodia are thin finger-like actin-rich membrane protrusions, which are used by cells to probe their microenvironment [104]. The small GTPase of the Rho family cdc42 promotes filopodia formation through activation of WASP (Wiskott–Aldrich Syndrome protein) and N-WASP (neural-WASP), which promote actin filament nucleation [104]. MT1-MMP and cdc42 have been found to colocalize at filopodia in oral squamous carcinoma cells, significantly contributing to the formation of new cellular protrusions and thus to cellular invasiveness [105]. Lamellipodia are broad and flat membrane protrusions which are developed by cells moving on a flat substratum [106]. CD44 has been reported to drive MT1-MMP localization to lamellipodia by interacting with its hemopexin domain [29].

Podosomes were described for the first time in 1985 referring to the protrusions of the cell ventral membrane towards the ECM, enriched with actin and Tyr-phosphorylated proteins [107]. Shortly after, invadopodia were described for the membrane structures towards the ECM enriched with ECM-degrading enzymes [108]. Both podosomes and invadopodia are composed by an actin-rich core, surrounded by adhesion and scaffolding proteins [109]. The adaptor proteins Tyr kinase substrate with four SH3 domains (TKS4) and with five SH3 domains (TKS5), the actin regulator cortactin, N-WASP, and MT1-MMP have all been recognized to be components and key players for both podosomes and invadopodia [110]. Podosomes are developed by monocytes, endothelial and smooth muscle cells, while invadopodia are found in cancer cells [109]. MT1-MMP localization at podosomes has been shown to impact on ECM degradation by macrophages [76,111,112]. MT1-MMP has also been found to have a non-proteolytic function in the turnover of podosomes [101]. MT1-MMP localizes to podosomes and remains in the 'islets' even after podosome dissolution, mediating podosome re-emergence in the same site [101]. MT1-MMP is a major functional component of invadopodia, and its traffic and localization to these membrane structures have been extensively reviewed lately [75,103,113]. MT1-MMP is thought to be internalized from the cell surface and continuously re-routed to invadopodia through fine-tuned endo/exocytic fluxes [75]. For instance, it has been described that the Wiskott–Aldrich syndrome protein with Scar homolog (WASH) mediates MT1-MMP traffic from late endosomes to invadopodia in breast cancer cells [114]. Recently, it has been found that coronin 1C (CORO1C) contributes to the invasiveness of triple negative breast cancer cells MDA-MB-231, by promoting MT1-MMP trafficking from endosomal structures to invadopodia [115]. MT1-MMP is also known to localize at focal adhesions (FAs), integrin-containing cell adhesion

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complexes, which mediate the interaction between the cell and the ECM [116]. This localization has been shown to depend on MT-Loop sequence in the catalytic domain of the proteinase [116]. Inefficient localization of MT1-MMP to FAs significantly reduces cell invasion, suggesting that FAs may be a precursor of the leading edge for cellular invasion [116]. However, the molecular mechanisms of the localization of MT1-MMP to these motility-associated structures are still largely unclear.

Dimer formation at the leading edge

MT1-MMP dimerization is a crucial regulatory mechanism for the proteinase to enhance cell migration and invasion [102]. MT1-MMP forms homo-dimeric complexes on the cell surface through its hemopexin [22] and transmembrane domains [23]. The crystal structure of the hemopexin domain uncovered the potential molecular basis of the hemopexin domain-driven dimer [117]. This dimerization is characterized as a symmetrical dimer, where blades II and III of molecule A interact with blades III and II of molecule B [117]. Hemopexin domain-dependent dimerization has been shown to be essential for cleaving collagen matrix on the cell surface [118]. The importance of MT1-MMP dimerization during cell migration has been analyzed using fluorescence resonance energy transfer (FRET), showing that HT1080 cells migrating in a 3D collagen matrix form MT1-MMP dimer constantly at the leading edge but not at the trailing edge [102]. This MT1-MMP dimerization at the leading edge was shown to be driven by cdc42- and Rac1-dependent actin cytoskeleton re-organization [102]. These findings highlight that MT1-MMP dimerization is a vital mean of controlling the polarised proteolytic activity of the proteinase on the cell surface, which is essential for cellular invasion.

MT1-MMP endo/exocytic circuities

As discussed above, endocytosis and recycling of MT1-MMP are crucial for the proteinase to promote cell migration and invasion [75]. Endo/exocytic fluxes ensure a constant flow of active MT1-MMP at the leading edge. Rab GTPases are a family of small GTPases which have emerged to be critical for MT1-MMP endo/exocytic fluxes in both primary human macrophages and cancer cells. In primary macrophages, Rab5a seems to play a role in MT1-MMP endocytosis, while Rab8a in MT1-MMP exocytic vesicle transport from the Golgi to the plasma membrane [112]. On the other hand, Rab14 and Rab22 appear to potentially drive MT1-MMP recycling pathways [112]. An early study has reported that Rab8 is a regulatory component of MT1-MMP exocytic trafficking to the membrane in contact with the collagen matrix in breast cancer cells [119]. It has also been reported that Rab5a promotes Rab4- and Rabenosyn5-dependent endo/exocytic pathways of MT1-MMP and α3 integrins, leading to ECM degradation in MDA-MB-231 cells and tumorigenic derivative of human mammary epithelial MCF10A cells [120]. Rab7 and the vesicle-associated membrane protein 7 (VAMP7) have been shown to be actively involved in MT1-MMP recycling from the late endosome to the plasma membrane, influencing migration and invasion of HT1080 cells [73]. VAMP7 colocalizes with MT1-MMP at proteolytic sites and its depletion has been found to reduce the degradative and invasive capacities of cancer cells [121]. Rab2a has been reported to be critical for MT1-MMP-dependent ECM proteolysis and invasion activity of breast cancer cells [122]. In particular, this Rab GTPase traffics MT1-MMP from the late endosome to the cell membrane, interacting with the component of the late endosomal complex, VPS39 [122]. Recently, Rab5 was found to be essential for inducing flotillin-dependent MT1-MMP endocytosis towards endolysosomal compartment before its delivery to invadosomes in carcinoma and sarcoma cell lines [123]. These findings indicate that these Rab GTPases play a critical role in modulating MT1-MMP endo/exocytic circuities, impacting on ECM degradation and invasion both in macrophages and cancer cells.

Other molecules have been reported to be involved in MT1-MMP endo/exocytic pathways. For instance, neural precursor cell expressed developmentally down-regulated 9 (NEDD9) and ADP-ribosylation factor 6 (ARF6) have been found to regulate MT1-MMP trafficking to late endosomes, affecting cell migration and invasion of breast cancer cells [124]. In particular, NEDD9 is required to decrease the levels of active ARF6, thus promoting MT1-MMP/TIMP2 complex trafficking to late endosomes [124]. ARRF6 has been described to interact with JNK-interacting proteins 3 and 4 (JIP3 and JIP4) opposing dynactin–dynein-dependent movement of MT1-MMP-containing endosomes towards the plasma membrane [78]. The interaction between JIP3/JIP4 and AFRF6 promotes endosomal tubulation by KIF5B that can carry out the anterograde movement of MT1-MMP-containing endosomes [78]. Inhibition of NEDD9 and ARF6 through progesterone–calcitriol treatment has been shown to impair MT1-MMP recycling to invadopodia-like structures, suppressing cell invasiveness and metastasis of endometrial cancer cells [125]. Chloride intracellular channel 3 (CLIC3) have also been

described as a critical regulator of MT1-MMP sorting into the late endosomes and consequently of MT1-MMP-driven invasiveness of breast cancer cells [126].

Non-proteolytic mechanisms

Besides ECM degradation and shedding of adhesion molecules on the cell surface, MT1-MMP can also promote cell migration and invasion in its catalytic activity-independent manner (Figure 3). In macrophages, MT1-MMP enhances cell motility independently of its proteinase activity, and its CT has been shown to be involved [127]. Macrophages constitutively employ glycolysis for ATP production regardless of normoxic and hypoxic conditions. Although glycolysis is not the most efficient mean to generate a large quantity of ATP, it allows macrophages to quickly produce sufficient energy to move around the body and maintain adequate immune surveillance. MT1-MMP CT has been found to maintain hypoxia-inducible factor 1 (HIF-1) activity during normoxic conditions by binding to factor inhibiting HIF-1 (FIH-1) at its cytoplasmic domain, which allows Mint3/APBA3 to inhibit FIH-1 [128]. As a consequence, HIF-1-driven glycolytic pathway is kept active, and a constant and quick supply of ATP is available for macrophages to carry out their activities (Figure 3). MT1-MMP has also been described to modulate inflammatory responses of macrophages in a protease-independent manner [129]. Specifically, its trafficking to the nuclear compartment triggers the activation of phosphoinositide 3-kinase δ (PI3Kδ)/Akt/GSK3β signaling cascade, which regulates the immunoregulatory Mi-2/NuRD nucleosome remodeling complex [129]. MT1-MMP has been found to mediate cell motility and morphology of bone marrow myeloid progenitors in a catalytic-independent fashion [130]. Specifically, MT1-MMP interacts with p130Cas, an adaptor protein of Rac1, through its CT phosphorylated at Tyr^{573} and it contributes to myeloid cell migration and fusion during osteoclastogenesis [130]. MT1-MMP has also been reported to control cell migration and differentiation of hematopoietic stem cells through the HIF signaling pathway [131]. MT1-MMP modulates HIF signaling promoting the transcription of HIF-responsive genes which are responsible for the production of vital niche chemokines and cytokines [131].

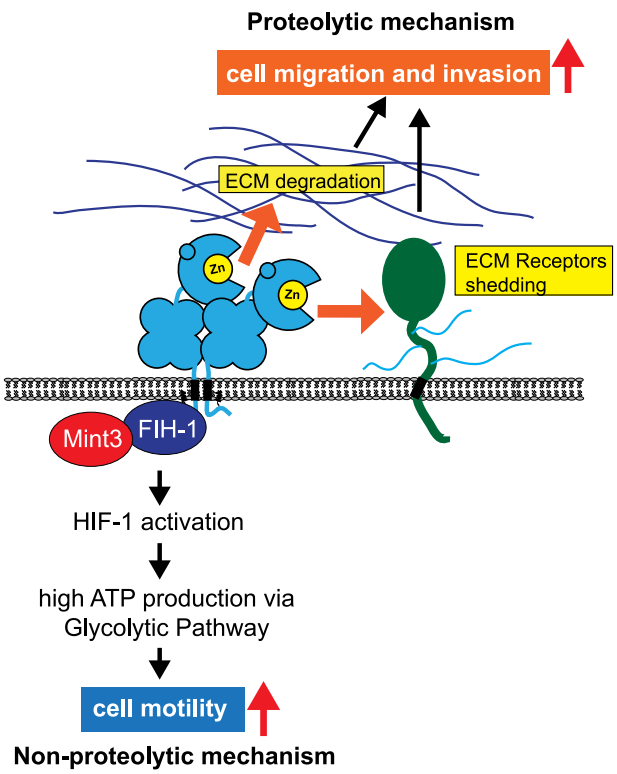

Figure 3. MT1-MMP promotes cell migration and invasion through proteolytic and non-proteolytic mechanisms.
MT1-MMP degrades ECM components and sheds ECM receptors on the cell surface, promoting cell migration and invasion in a proteolytic-dependent manner. MT1-MMP CT binds to FIH-1 which is then inhibited by Mint3. As a consequence, HIF-1 is kept active even under normoxic conditions and sustains a constant and quick supply of ATP for cell motility.

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Cancer cells also exhibit constitutively active glycolysis even under normoxic conditions via a phenomenon called the Warburg effect. High glycolytic rates allow neoplastic cells to produce high levels of ATP which sustains cell growth, proliferation, migration, and invasion [132]. MT1-MMP has involved in the increased glycolytic activity observed in malignant tumor cells [133]. Like in macrophages, MT1-MMP CT binds to FIH-1, mediating FIH-1 to be inhibited by Mint3 [133] (Figure 3). Thus, the HIF-1-driven glycolytic pathway is sustained and allows a high level of ATP production in MDA-MB-231 [133]. The MT1-MMP/Mint3 axis has been reported to involve mTOR regulation in HT1080 [134]. Mint3 is phosphorylated at the N-terminus by mTOR, which causes increased binding of Mint3 to FIH-1 and inhibition of FIH-1 in the presence of MT1-MMP [134]. The cross-talk between mTOR and MT1-MMP is thus vital for HIF-1 activation in normoxic conditions in cancer cells. In HT1080 cells, the cytoplasmic domain was shown to be involved in the interaction with p27RF-Rho, a protein which enhances RhoA activation [135]. Therefore, MT1-MMP can potentially control actin cytoskeleton dynamics to increase cancer cell invasion. The CT has also been found to bind to MTCBP-1 (MT1-MMP CT-binding protein 1) a member of the Cupin superfamily [136]. Binding of MTCBP-1 to MT1-MMP CT significantly reduced MT1-MMP-dependent invasion by HT1080 cells [136]. Recently, it has been found that binding of MTCBP to MT1-MMP CT reduces the interactions of the proteinase with the invadopodial actin scaffolding in pancreatic cancer cells, showing a significantly decreased capability of invading and metastasizing to adjacent tissues [137]. Altogether these data suggest that MT1-MMP is not only a key mediator of cell migration and invasion through the extracellular proteinase activity but also a regulator of these phenomena via its intracellular non-proteolytic pathways in both physiological and pathological settings such as seen in macrophages and cancer cells.

Conclusions

MT1-MMP-mediated cell migration has a crucial role in the development of several diseases, and there is well-established evidence that elevated MT1-MMP expression correlates with poor prognosis in various cancer types [40]. MT1-MMP localization to the mortality-associated membrane structures is crucial for the proteinase to promote cell migration in a proteolytic-dependent manner. This localization relies on the harmonic orchestration of cytoskeleton rearrangements and endo/exocytic fluxes of MT1-MMP. Recent studies have focused on these endo/exocytic circuities and have identified new players such as Rab2a [122], flotillin [123], ARF6 and NEDD9 [78,124]. KIF-driven MT1-MMP intracellular trafficking has also recently attracted the attention in the scientific community [77]. Nevertheless, there are still many questions to be answered. It is not exactly known which KIFs are responsible for MT1-MMP intracellular trafficking in the various cell types and whether they require specific adaptor molecules to carry out the transport. Moreover, the interplay between KIFs, endo/exocytic pathways and cytoskeleton rearrangements and its exact contribution to MT1-MMP-mediated cell migration is still largely unknown. It is now recognized that several features of the ECM barrier can affect MT1-MMP localization on the cell surface. In particular, it has been recently highlighted that this localization follows a digest-on-demand strategy which depends on the interplay between nucleoskeleton and cytoskeleton [89]. Shedding light on these different aspects of MT1-MMP cell surface localization in a variety of cell types would enable the identification of novel targets to develop potential disease therapies in the future.

Perspectives

- Cell migration in tissue is a fundamental phenomenon that is required for many physiological and pathological events. MT1-MMP-dependent migration is a major mean adopted by different cell types and thus investigating its mechanism is extremely important to understand different pathophysiological events.

- MT1-MMP promotes cell migration through proteolytic and non-proteolytic mechanisms. It modifies cellular microenvironment by degrading pericellular matrix; modifying cell–ECM interaction by cleaving cell adhesion molecules; and controlling glycolytic pathways through its CT. Therefore, MT1-MMP is a multifunctional cell motility enhancer.

- MT1-MMP has been extensively investigated to date, but its mechanism of action to express different biological functions is not clearly understood yet. Further investigation of this mechanism may contribute to identifying pathogenesis of different diseases and novel means to control undesired cellular invasion in the future.

Abbreviations

AP-2, adaptor protein-2; ARF6, ADP-ribosylation factor 6; BM, basement membrane; CLIC3, chloride intracellular channel 3; CLTHB, clathrin light chain B; CORO1C, coronin 1C; CT, cytoplasmic tail; ECM, extracellular matrix; EGF, epidermal growth factor; EGF-R, EGF receptor; ERM, ezrin/radixin/moesin; FAs, focal adhesions; FIH-1, factor inhibiting HIF-1; FRET, fluorescence resonance energy transfer; GPI, glycosylphosphatidylinositol; HIF-1, hypoxia-inducible factor 1; KIFs, kinesin superfamily motor proteins; LINC, linker of nucleoskeleton and cytoskeleton; LRP, lipoprotein receptor-related protein; MMP, matrix metalloproteinase; MT1-MMP, membrane-type 1 matrix metalloproteinase; MT-MMPs, membrane-type MMPs; NEDD9, neural precursor cell expressed developmentally down-regulated 9; PCs, proprotein convertases; PDGF-D, platelet-derived growth factor D; PKC, protein kinase C; RECK, reversion-inducing cysteine-rich protein with kazal motifs; TIMP-2, tissue inhibitor of metalloproteinase-2; TKS4, Tyr kinase substrate with four SH3 domains; TKS5, Tyr kinase substrate with five SH3 domains; VAMP7, vesicle-associated membrane protein 7; WASH, Wiskott–Aldrich syndrome protein with Scar homolog; WASP, Wiskott–Aldrich syndrome protein.

Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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