Cancer Cell Research 20 (2018) 496-506

Available at http:// www.cancercellresearch.org ISSN 2161-2609

Membrane-type 1 matrix metalloproteinase (MT1-MMP): expression, targets, inhibitors and biological functions

Zao Dai, Tian Yang, Min Ke, Shan Lu, Ping Liu*

College of Life Sciences, Nanjing Normal University, Nanjing, Jiangsu 210023, China

Abstract: **Transmembrane type 1 matrix metalloproteinase (MT1-MMP) is a multifunctional proteinase capable of targeting the extracellular matrix, growth factors, cytokines and cell surface-associated adhesion and signaling receptors. With the diversity functions, MT1-MMP plays critical roles involving in many cellular processes, such as tissue and organ development, cancer cell migration, invasion and metastasis, proper wound healing and tissue repair after inflammation, transition of cells from normalcy to malignancy, et al. This review will focus on the expression, targets and bio-functions of MT1-MMP; and will also discuss a little of future research direction about MT1-MMP.**

Keywords: MT1-MMP, EMC, Expression, Inhibitor, Bio-function

Received 26 July 2018, Revised 29 August 2018, Accepted 30 August 2018

*Corresponding Author: Ping Liu, liuping0805@sohu.com

1. Introduction

Cells and their surrounding materials, extracellular matrix (ECM), together form the various organs. ECM is essential for maintaining tissue architecture and providing cells scaffold, cell survival signals and cell growth factor pool, thereby controlling the correct local cellular environment[1,2]. Cells are directly attached to and interacted with ECM through their macromolecules on the cell surface such as phospolipids, polysucroses, and protein receptors. Any changes in the immediate ECM microenvironment, such as degradation of components of ECM, will critically affect cellular behavior and tissue functioning. Therefore, the functions of tissue and organ are pivotal and fine regulated by the ECM turnover[1,3].

MMPs are a broad family of membrane proteins and zinc-binding endopeptidases which are responsible for the degradation of ECM and then play a key role in many cell behaviors including cell differentiation in organ development, tumor growth, cell invasion, and cancer cell metastasis[4-6]. In the family of MMPs, MT1-MMP (MMP14), the first identified MMP, is one of the most important matrix metalloproteinases in regulating many cellular processes, especially in cancer cell invasion, migration, atherosclerosis, inflammation, rheumatoid arthritis and cell transition from normalcy to malignancy via the degradation of ECM[5,6]. In this review, we will be focus on the expression, substrates and bio-functions of MT1-MMP to introduce a comprehensive and basic image of MT1-MMP to you.

2. Expression and Knockout of MT1-MMP in vivo

2.1. Expression of MT1-MMP in vivo

MT1-MMP is differentially expressed in many tissues. From the mRNA transcript level, in general, MT1-MMP can be found in lung, kidney, reactive astrocytes, melanoma, head and neck carcinomas[7,8]; and be also observed in many types of tumors, such as lung[7,9], gastric[10], colon[11], liver[12], breast[9,13], bladder[14], head and neck[15], tyroid[16], ovarian[17] and cervical carcinomas[18], and brain tumors[19]. Transcripts were also detected in both tumor cells and surrounding stroma cells[9,11,17,20].

In the developing mouse embryo, MT1-MMP is mainly expressed in cells of mesenchymal origin including fibroblasts, muscular cells, and osteoblasts, and the expression decreases with maturation after birth[21,22]. Expression can be re-induced, however, when the cells require remodeling ECM again. For example, the expression of MT1-MMP is induced in fibroblasts when tissue is damaged and continues throughout the healing process together with the expression of MMP-2[23]. Since MT1-MMP has collagenase activity and MMP-2 degrades gelatin, these two enzymes cooperate as a system for type I collagen turnover[24]. MMP-2 is frequently co-expressed with MT1-MMP in mesenchymal cells[21,22]. MT1-MMP/MMP-2 system would be important for tumor cells to invade the basement membrane by degrading type IV collagen and then the stroma by degrading type I collagen. MT1-MMP is also expressed in endothelial cells forming new vessels during angiogenesis[25-28].

2.2. Knockout of MT1-MMP in vivo

Knockout of MT1-MMP has the most significant phenotype among MMP gene knockout mice; and the deficiency of MT1-MMP in mice also emphasizes the importance of the degradation of ECM by MT1-MMP during development[29,30]. The deficiency animal showed inadequate collagen turnover, resulting in dwarfism, osteopenia, arthritis, and connective tissue disease. The angiogenic response was also delayed in the mice and the activation of proMMP-2 in fibroblasts was disturbed. At the cellular level, MT1-MMP

deficiency resulted in the loss of a collagenolytic activity. Skin fibroblasts from MT1-MMP deficient mice completely lost the ability to degrade collagen fibrils in vitro whereas wild-type and heterozygous cells readily degrade the underlying matrix (Figure 1A). As a consequence, MT1-MMP deficient mice developed severe and progressive fibrosis in many tissues. Moreover fibroblasts, which populate these fibrotic tissues, accumulate large cytoplasmic inclusions of coarse cross-striated collagen fibrils indicative of mobilization of the phagocytic pathway (Figure 1B).

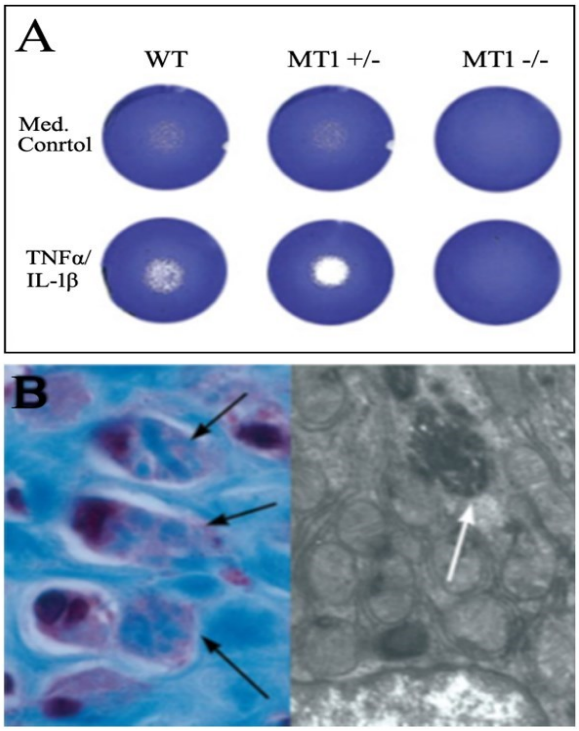

Figure 1. MT1-matrix metalloproteinase (MMP) deficiency results in loss of collagenolytic activity. A: Fibroblasts from MT1-MMP deficient mice display total inability to degrade reconstituted fibrillar collagen in vitro. B: Fibroblastic cells in the periosteum of an MT1-MMP deficient mouse contain copious quantities of intercellular collagen (black arrows in trichrome stain) which can be visualized as coarse fibrillar material in transmission electron microscopy (white arrow in TEM micrograph). (Reprinted from CELL, 99, 1999 p. 81-92, with permission from Elsevier.)

From the organ and organism level, MT1-MMP deficiency results in severe impairment of growth, skeletal dysmorphisms, scarring of joints and periskeletal tissues, reduced bone formation, and greatly enhanced bone resorptive activity, ultimately leading to a "vanishing bone" condition. For example, excessive and prolonged osteoclastic activity in the cranial sutures leads to the almost complete disappearance of cranial bones in aged mice. Furthermore, several assumptions or predictions made about the function of MT1-MMP in skeletal physiology were dispelled. For example, a critical role of MT1-MMP in osteoclastic function could not be reconciled with the unabated osteoclastic activity observed in the bones of MT1-MMP deficient mice. In addition, the loss of a catabolic function (collagen degrading activity) proved to profoundly perturb both anabolic functions (bone formation, bone growth) and catabolic activity (osteoclastic resorption of bone)[31].

Aging in MT1-MMP deficient mice is associated with readily identifiable features such as generalized fibrosis, loss of hair, joint contractures, and increasingly reduced mobility[31].

3. Targets of MT1-MMP

It's reported that MT1-MMP is presented to the cell surface in active form either for zymogen activation or for proteinase in plasma membrane trafficking[32]. Stringent control of proteolysis is essential for maintenance of tissue integrity and homeostasis, and multiple mechanisms have evolved for both systemic and highly localized control of proteolytic activity[33]. As a proteinase, the substrates are very important and play critical roles in the interaction between enzyme and substrate and in the executions of enzyme activity. As we known, captivating proteinase MT1-MMP was originally discovered based on its ability to catalyze cell surface-associated processing of a soluble substrate, proMMP-2[7,34]. In recent years, however, a wealth and increasing of additional protein and polypeptide MT1-MMP substrates have been described, providing abundant examples to illustrate the diverse functional consequences of pericellular proteolytic processing of matrix, soluble, and cell surface-associated substrates (Figure 2). All of these substrates of MT1-MMP play important roles in many cellular processes, such as cell growth, invasion, metastasis, cell adhesion, and cell apoptosis. The proteolysis of these substrates by MT1-MMP may be a kind of functional regulation during cellular processes. Here we briefly described as below.

3.1. Extracellular matrix substrates

Collagens I, II and III, gelatin, laminins 1and 5, fibronectin, vitronectin, aggrecan, fibrin, tenascin, nidogen, fibrinogen and lumincan are all components of ECM and associated with cell growth, cell attach and cell connection/adhesion. MT1-MMP can degrade them and promote cell migration, invasion, and cancer cell metastasis[24,25,35,36].

3.2. Soluble protein substrates

Centrosomal protein pericentrin is associated the formation of mitotic spindle. Its degradation catalyzed by MT1-MMP can led to mitotic spindle aberrations. Ectopic expression of MT1-MMP in normal mammary

epithelium resulted in enhanced extracellular invasive activity, pericentrin cleavage, and tumor growth in a xenograft model[37,38].

Active MMP-2, -8, -13 are all collagenases and involved in specially collagens degradation. Activation of pro-MMP-2, pro-MMP-8 and pro-MMP-13 via degradation by MT1-MMP is a key turnover for regulation of functions of MMP-2, -8, -13[39-41]. Processing of latent growth factors such as transforming growth factor beta (TGF-beta) by MT1-MMP has also been reported in epithelial cells, neuronal cells and osteoblasts[42,43]. These data suggest that MT1-MMP may indirectly impact cellular functions by altering the pericellular concentration of active growth factors that regulate matrix deposition.

Secreted mannose-binding lectin (MBL) plays an essential role in innate immunity by recognizing microorganisms and mediating their destruction by complement activation of phagocytosis[44]. Several point mutations of the MBL gene predispose patients to infections and diseases. It was shown that mutants of MBL were susceptible to MT1-MMP-catalyzed cleavage at Gly39-Leu40→Asn80-Met81 sites, homologous to those cleaved in denatured human MBL, suggesting that MT1-MMP may be involved in altering the host response through clearing MBL[45].

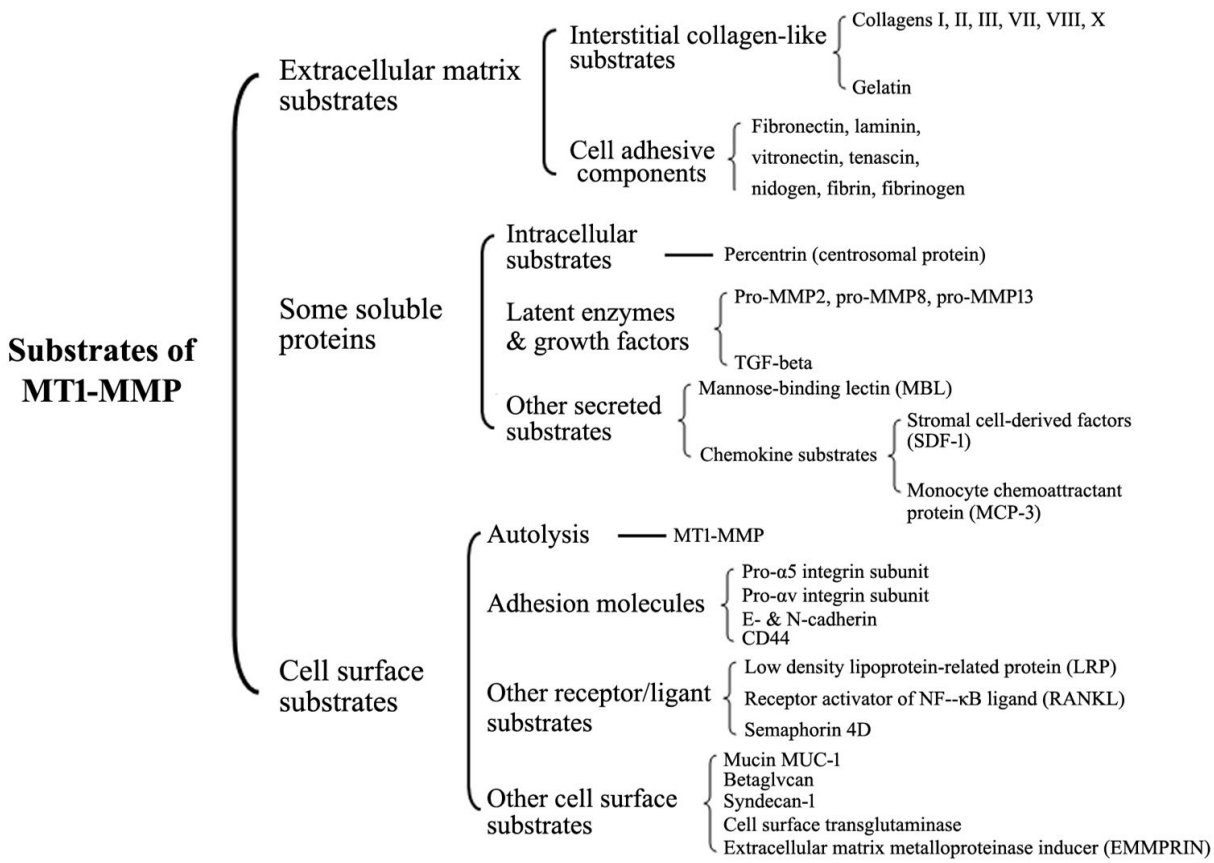

Figure 2. Summary of substrates of MT1-MMP. There are three groups of substrates: extracellular matrix substrates, soluble substrates, and cell surface substrates.

Chemokine substrates of MT1-MMP include stromal cell derived factor (SDF-1)[46] and monocyte chemoattractant protein (MCP)-3[47]. SDF-1 cleavage resulted in loss of receptor binding to CXCR-4, functionally manifested as a loss of CD34 (+) hematopoietic stem cell chemoattractant activity[46]. MMP-cleaved MCP-3 retained CC chemokine receptor binding activity but was unable to stimulate a chemoattractant response following receptor engagement[47]. These data provide a functional link between MT1-MMP activity and modulation of inflammatory and immune responses.

3.3. Cell surface substrates

Autolysis of MT1-MMP is the result of cleavage at G284-G285 in the linker region of MT1-MMP, followed by an additional cleavage at A255-I256 near the conserved methionine turn, rendering the resulting autolysis product catalytically inactive[48]. Although lacking the catalytic domain, the 44 kDa transmembrane hemopexin domain-containing autolysis product is retained on the cell surface[49] and inhibits collagenolytic activity, cellular invasion of collagen gels, and tumor formation[50].

MT1-MMP has been demonstrated to exhibit integrin convertase activity and participate in an alternative processing of the pro-αv integrin subunit, generating a disulfide-bonded heavy chain and light chains[51]. This cleavage facilitated αvβ3-dependent adhesion, contributing to migration of MCF-7 breast cancer cells on vitronectin[52]. Other integrin precursors, including pro-α5, were also cleaved by MT1-MMP while pro-α2 was resistant to MT1-MMP processing[53].

Soluble E-cadherin ectodomain has been detected in serum, urine and ascites fluids of cancer patients and is frequently associated with development of metastases and poor outcome[54-56]; and several metalloproteinases have been identified as cadherin sheddases[57-59]. In a kidney ischemia model, increased MT1-MMP expression correlated with processing of both E- and N-cadherin[60].

Other adhesion receptors such as CD44, a hyaluronan receptor, are also processed by MT1-MMP, generating shed ectodomain fragments of various sizes. In MIA PaCa-2 pancreatic cancer cells, MT1-MMP catalyzed shedding of a 70 kDa CD44 ectodomain fragment, resulting in enhanced motility; while a mutant CD44 lacking the MT1-MMP cleavage site was not processed and did not enhance migration[61].

In vitro analyses showed proteolytic processing of the high molecular weight alpha subunit of lipoprotein receptor-related protein (LRP) by recombinant MT1-MMP catalytic domain and a concomitant decrease in cell surface LRP levels in cells co-expressing LRP and MT1-MMP[62].

Receptor activator of NF-kB ligand (RANKL) is a transmembrane glycoprotein that is an important regulator of osteoclast maturation and function[63]. A recent report demonstrated shedding of RANKL by both ADAM-10 and MT1-MMP, generating two distinct products[64]. Downregulation of MT1-MMP expression in osteoblasts resulted in enhanced membrane-associated RANKL and promoted osteoclastogenesis.

Semaphorin 4D is a membrane bound ligand for the plexin-B1 receptor and participates in axonal guidance in the developing nervous system as well as blood vessel development[65]. It is recently demonstrated that MT1-MMP-catalyzed proteolytic processing of semaphorin 4D from the tumor cell surface is necessary for stimulation of endothelial cells[66].

Other cell surface substrates of MT1-MMP also include cell surface transglutaminase[67], syndecan-1[68], Mucin MUC-1[69], beta-glycan[70], and extracellular matrix metalloproteinase inducer (EMMPRIN)[71].

4. Inhibitors: natural and synthesis

Although MMPs and MT-MMPs play critical roles in many cellular processes described above; their activities are always regulated and balanced by series of endogenous inhibitors, such as tissue inhibitors of MMPs (TIMPs)[72]. In general, Inhibitors of MMPs are classified into endogenous inhibitors and exogenous inhibitors (synthetic inhibitors). Up to now, endogenous inhibitors include TIMPs, α2-macroglobulin (α2M)[73], and a membrane-anchored glycoprotein called RECK (reversion-inducing cysteine-rich protein with Kazal motifs)[74]; and exogenous inhibitors (synthetic inhibitors) contain Batimastat (BB94)[75,76], GM6001, Captopril[77], COL-3[78], Neovastat[79], KB-R7785[80], and BMS-275291[81], et al.

There are four vertebrate TIMPs. TIMP-1, -2, and -4 are all diffusible secreted proteins while TIMP-3 is matrix-associated[82]. The TIMPs are the principal tissue inhibitors of MMPs, and as such their primary role is to limit proteolysis during ECM remodeling[83]. The TIMPs can inhibit most MMPs without major selectivity (with the exception that TIMP-1 is a very poor inhibitor of MT1-, MT2-, MT3-, MT5-MMP and MMP-19)[84]. However, TIMPs do differ in other properties such as tissue distribution, transcriptional regulation and specific association with latent MMPs. These differences suggest that they each have separate and specific physiologic roles[83]. RECK is a recently discovered endogenous cell surface glycoprotein that inhibits the secretion and catalytic activity of MMP-9[74] and the catalytic activities of MMP2 and MT1-MMP[74,85].

In synthetic MMP inhibitors, GM6001, BB94 (Batimastat) and BMS-275291 display antiangiogenic properties in vitro and in vivo[75,76,81]. A specific example of this is KB-R7785, a hydroxamate-type metalloproteinase inhibitor that has been shown to inhibit tumor growth and angiogenesis in vivo in the transparent chamber model of tumor progression[80].

In the above inhibitors of MMPs, inhibitors of MT1-MMP include TIMP-2, TIMP-3, TIMP-4, endostatin (a membrane-anchored glycoprotein called RECK) (endogenous inhibitors); and BB94, GM6001, BMS-275291 (synthetic inhibitors)[86,87]. Inhibitor TIMP-2 is different from other inhibitors in inhibiting MT1-MMP activity. When at low concentration, TIMP-2 promotes the formation of a complex with proMMP2 and MT1-MMP on the cell surface, leading to activation of MMP2. Hence, low concentrations of TIMP-2 promote processing of MMP2 to its proteolytically active form, but high concentrations of TIMP-2 inhibit MMP2 activation. The balance between levels of activated MMP and free inhibitors appears to be critical for MMP activity[88,89]. The regulation of MMP2 activation and cell surface presentation is illustrated in Figure 3.

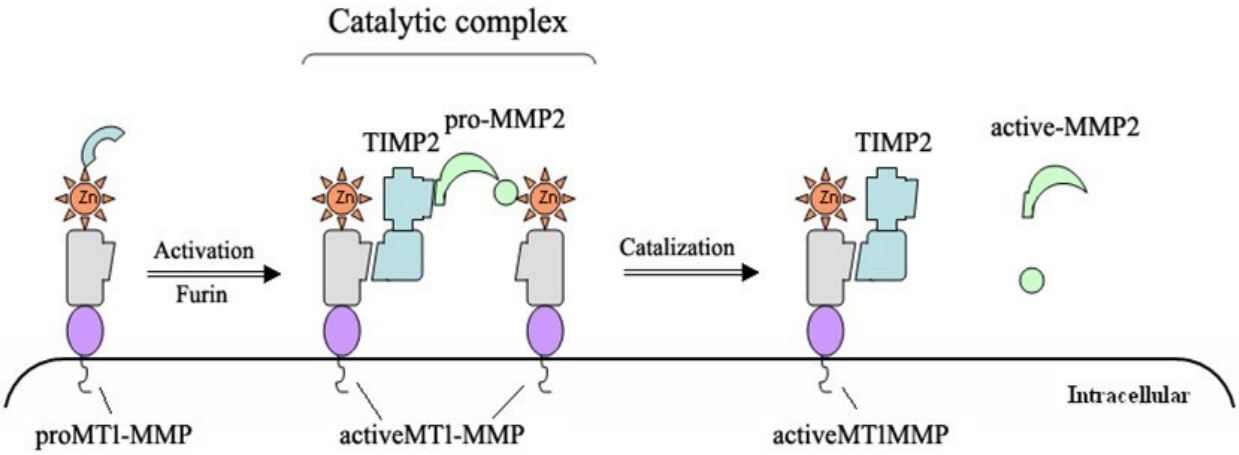

Figure 3. Schematic of the activation process of proMT1-MMP and proMMP2 on cellular membrane. proMT1-MMP is activated either intracellularly by furin-like proteinase or extracellularly by proteases such as plasmin. Activated MT1-MMP binds to TIMP-2, thereby generating the MT1-MMP-TIMP-2 complex that serves as a receptor for proMMP-2 on the cell surface. A second MT1-MMP molecule cleaves and activates the bound proMMP-2.

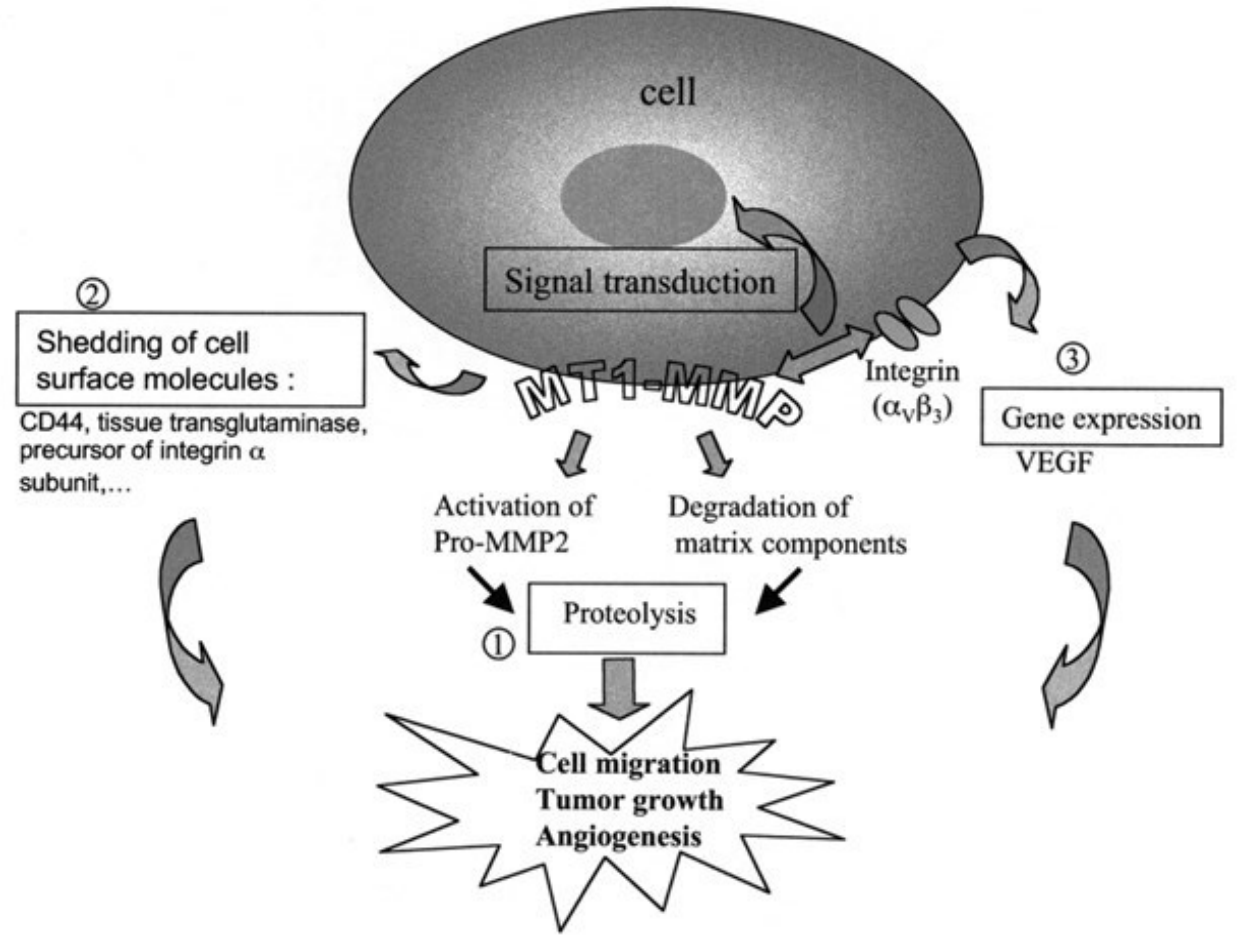

Figure 4. Functions of MT1-MMP in cancer progression. MT1-MMP regulates cell migration, tumor growth and angiogenesis by different mechanisms: (1) MT1-MMP participates in pericellular proteolysis by acting directly against ECM components or indirectly by activating pro-MMP2. (2) MT1-MMP cleaves cell surface molecules, leading to their activation, inhibition or shedding. (3) MT1-MMP participates in signal transduction directly or by interacting with integrins.

In general, endogenous inhibitors inhibit the activities of MMPs via binding to the catalytic domains[90] and/or binding to the COOH-terminal hemopexin-like domains[90] of MMP proteins; whereas the synthetic inhibitors inhibit the activities of MMPs via inhibiting the angiogenesis of tumor[80,91]. Of course, the actually detailed molecular mechanism of the inhibition of MMP activity by inhibitors is still unclear and needs to furthermore figure out.

5. Biological functions and molecular mechanism of MT1-MMP

Active MT1-MMP presents more and more has a complex multifunctional molecule influencing different cell functions (Figure 4). For instance, the expression of MT1 has been described in processes involving cell migration[36]; and over expression of MT1-MMP increases the number of experimental metastasis[92], cell invasion[7] and tumor angiogenesis[93].

5.1. MT1-MMP promotes cell invasion

When a cell migrates and invasion in tissue, the ECM and many cell surface molecules are the physical barriers and need to be degraded to clear a pathway[94]. The white wing here is the MT1-MMP which can degrade many components of ECM and adhesive molecules of cell surface and make a path for cell migration and invasion (Figure 4). For examples, MT1-MMP can shed CD44 and syndecan-1, degrade collagens (such as collagen I, II, III) and other matrix components (such as gelatin, fibronectin, laminins et al), release EGF-like repeats from laminin 5, activate proMMP-2 and proMMP-13, up-regulate ERK, and up-regulate VEGF-A expression through Src. All of these activities of MT1-MMP result in increased cell migration and invasion in tissue.

5.2. MT1-MMP stimulates cell motility

It was found that shedding of CD44 from the cell surface by MT1-MMP enhances cell migration on a hyaluronan-based 2-D matrix[61]. The exact mechanism behind the MT1-MMP/CD44-mediated promotion of cell migration is not clear. MT1-MMP may regulate the adhesion properties of lamellipodia through CD44 shedding or it may modulate signals mediated by CD44. A similar observation was made with syndecan-1[68]. MT1-MMP sheds syndecan-1 and this shedding is required for efficient cell migration on collagen. Expression of MT1-MMP can also activate extracellular signal-regulated protein kinase (ERK) and ERK activation is shown to be essential for MT1-MMP-dependent cell migration[95]. It is not clear how MT1-MMP activates ERK, but this may be a part of the mechanism(s) of CD44- and/or syndecan 1-shedding mediated cell migration.

Another observation of MT1-MMP-mediated stimulation of cell motility is through the cleavage of laminin 5[36], a major component of basement membrane. It has been shown that MT1-MMP cleaves the γ2 chain of laminin 5, releasing EGF-like domains, which ligate with the EGF receptor and stimulate epithelial cell motility[96].

5.3. MT1-MMP promotes angiogenesis

Angiogenesis itself is a process of cellular invasion by endothelial cells. Endothelial cells need to detach from neighboring cells, invade into stromal tissue, proliferate, and generate a tube structure. During this process, MT1-MMP activating MMP2, shedding CD44 is a key player[93].

MT1-MMP also promotes angiogenesis by means other than stimulation of endothelial cell invasion. Expression of MT1-MMP in tumors stimulates angiogenesis in vivo by stimulating VEGF synthesis from the tumor cells[97,98].

6. Important research directions about MT1-MMP in the future

Although mounts of papers on MT1-MMP are publicized, the fine and detailed mechanisms of MT1-MMP on controlling cell growth, transformation, invasion, and metastasis, and on the relationship between MT1-MMP and other pathways or systems which directly control cell cycle, cell moving, and angiogenesis in tumor are still unclear or unknown. So, in the future, some of the fields below should be emphasized.

6.1. MT1-MMP and growth factors and cytokines

More recently, a new view has become apparent on how MT1-MMP and other MMPs modulate growth factors and cytokines and generated new biologically active fragments from matrix and circulating proteins. Inhibitors of MT1-MMP and other MMPs also appear to have additional unexpected effects by themselves, of which much has still to be learned. The new insights in the modulation of cytokines by proteases contribute to the understanding of inadequate cytokine-mediated response in disease, as well as in improving the use of growth factors and cytokines in treating disease. Therefore, this will be a further research field in the future discovering directions about MT1-MMP and its inhibitors.

6.2. MT1-MMP and other pathways and systems

Although it is clear that MT1-MMP can affect cell growth, invasion and migration, the current data are almost the point-to-point effects that are MT1-MMP directly relating one other protein or gene. How the mechanisms between MT1-MMP and other pathway or system controlling one whole cellular process are still unclear, such as MT1-MMP and the system controlling cell cycle, MT1-MMP and the system controlling gene

expression. So, we think these fields should be important new directions for our MT-MMP researchers.

6.3. Others

Although mainly studied from the angle of tumor growth and treatment, the role of MT1-MMP and other MMPs in angiogenesis extends to many other aspects of human life, starting with implantation of the embryo and placentation and growth of the fetus to proper wound healing and tissue repair after inflammation. All the molecular mechanisms need to be unveiled by researchers. Furthermore, how the cooperation MT1-MMP with other MT-MMPs and MMPs also need to be detailed in the future.

Acknowledgments

This work was mainly supported by grants from the National Natural Science Foundation of China (NNSFC) (grant no. 81272850 and 81472415).

References

[1] Genís L, Gálvez BG, Gonzalo P, et al. MT1-MMP: universal or particular player in angiogenesis?[J]. Cancer Metastasis Rev, 2006, 25:77-86.

[2] Itoh Y. MT1-MMP: a key regulator of cell migration in tissue[J]. IUBMB Life, 2006, 58:589-596.

[3] Itoh Y, Seiki M. MT1-MMP: a potent modifier of pericellular microenvironment[J]. J Cell Physiol, 2006, 206:1-8.

[4] Barbolina MV, Stack MS. Membrane type 1-matrix metalloproteinase: substrate diversity in pericellular proteolysis[J]. Semin Cell Dev Biol, 2008, 19:24-33.

[5] Amar S, Smith L, Fields GB. Matrix metalloproteinase collagenolysis in health and disease[J]. Biochim Biophys Acta, 2017, 1864:1940-1951.

[6] Castro-Castro A, Marchesin V, Monteiro P, et al. Cellular and Molecular Mechanisms of MT1-MMP-Dependent Cancer Cell Invasion[J]. Annu Rev Cell Dev Biol, 2016, 32:555-576.

[7] Sato H, Takino T, Okada Y, et al. A matrix metalloproteinase expressed on the surface of invasive tumor cells[J]. Nature, 1994, 370:61-65.

[8] Okada A, Bellocq JP, Rouyer N, et al. Membrane-type matrix metalloproteinase (MT-MMP) gene is expressed in stromal cells of human colon, breast, and head and neck carcinomas[J]. Proc Natl Acad Sci USA, 1995, 92:2730-2734.

[9] Polette M, Nawrocki B, Gilles C, et al. MT-MMP expression and localization in human lung and breast cancers[J]. Virchows Arch, 1996, 428:29-35.

[10] Mori M, Mimori K, Shiraishi T, et al. Analysis of MT1-MMP and MMP2 expression in human gastric cancers[J]. Int J Cancer, 1997, 74:316-321.

[11] Ohtani H, Motohashi H, Sato H, et al. Dual over-expression pattern of membrane-type metalloproteinase-1 in cancer and stromal cells in human gastrointestinal carcinoma revealed by in situ hybridization and immunoelectron microscopy[J]. Int J Cancer, 1996, 68:565-570.

[12] Imamura T, Ohshio G, Mise M, et al. Expression of membrane-type matrix metalloproteinase-1 in human pancreatic adenocarcinomas[J]. J Cancer Res Clin Oncol, 1998, 124:65-72.

[13] Ueno H, Nakamura H, Inoue M, et al. Expression and tissue localization of membrane-types 1, 2, and 3 matrix metalloproteinases in human invasive breast carcinomas[J]. Cancer Res, 1997, 57:2055-2060.

[14] Kanayama H, Yokota K, Kurokawa Y, et al. Prognostic values of matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 expression in bladder cancer[J]. Cancer, 1998, 82:1359-1366.

[15] Yoshizaki T, Sato H, Maruyama Y, et al. Increased expression of membrane type 1-matrix metalloproteinase in head and neck carcinoma[J]. Cancer, 1997, 79:139-144.

[16] Nakamura H, Ueno H, Yamashita K, et al. Enhanced production and activation of progelatinase A mediated by membrane-type 1 matrix metalloproteinase in human papillary thyroid carcinomas[J]. Cancer Res, 1999, 59:467-473.

[17] Afzal S, Lalani EN, Poulsom R, et al. MT1-MMP and MMP-2 mRNA expression in human ovarian tumors: possible implications for the role of desmoplastic fibroblasts[J]. Hum Pathol, 1998, 29:155-165.

[18] Gilles C, Polette M, Piette J, et al. High level of MT-MMP expression is associated with invasiveness of cervical cancer cells[J]. Int J Cancer, 1996, 65:209-213.

[19] Yamamoto M, Mohanam S, Sawaya R, et al. Differential expression of membrane-type matrix metalloproteinase and its correlation with gelatinase A activation in human malignant brain tumors in vivo and in vitro[J]. Cancer Res, 1996, 56:384-392.

[20] Heppner KJ, Matrisian LM, Jensen RA, et al. Expression of most matrix metalloproteinase family members in breast cancer represents a tumor-induced host response[J]. Am J Pathol, 1996, 149:273-282.

[21] Kinoh H, Sato H, Tsunezuka Y, et al. MT-MMP,

the cell surface activator of proMMP-2 (pro-gelatinase A), is expressed with its substrate in mouse tissue during embryogenesis. J Cell Sci, 1996, 109:953-959.
[22] Apte SS, Fukai N, Beier DR, et al. The matrix metalloproteinase-14 (MMP-14) gene is structurally distinct from other MMP genes and is co-expressed with the TIMP-2 gene during mouse embryogenesis[J]. J Biol Chem, 1997, 272:25511-25517.
[23] Okada A, Tomasetto C, Lutz Y, et al. Expression of matrix metalloproteinases during rat skin wound healing: evidence that membrane type-1 matrix metalloproteinase is a stromal activator of pro-gelatinase A[J]. J Cell Biol, 1997, 137:67-77.
[24] Sato H, Takino T. Coordinate action of membrane-type matrix metalloproteinase-1 (MT1-MMP) and MMP-2 enhances pericellular proteolysis and invasion[J]. Cancer Sci, 2010, 101:843-847.
[25] Hiraoka N, Allen E, Apel IJ, et al. Matrix metalloproteinases regulate neovascularization by acting as pericellular fibrinolysins[J]. Cell, 1998, 95:365-377.
[26] Turunen SP, Tatti-Bugaeva O, Lehti K. Membrane-type matrix metalloproteases as diverse effectors of cancer progression[J]. Biochim Biophys Acta, 2017, 1864 (11 Pt A):1974-1988.
[27] Galvez BG, Matias-Roman S, Albar JP, et al. Membrane type 1-matrix metalloproteinase is activated during migration of human endothelial cells and modulates endothelial motility and matrix remodeling[J]. J Biol Chem, 2001, 276:37491-37500.
[28] Haas TL, Davis SJ, Madri JA. Three-dimensional type I collagen lattices induce coordinate expression of matrix metalloproteinases MT1-MMP and MMP-2 in microvascular endothelial cells[J]. J Biol Chem, 1998, 273:3604-3610.
[29] Holmbeck K, Bianco P, Caterina J, et al. MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover[J]. Cell, 1999, 99:81-92.
[30] Gaublomme D, Buyens T, De Groef L, et al. Matrix metalloproteinase 2 and membrane type 1 matrix metalloproteinase co-regulate axonal outgrowth of mouse retinal ganglion cells[J]. J Neurochem, 2014, 129:966-979.
[31] Kenn H, Paolo B, Susan Y, et al. MT1-MMP: A Tethered Collagenase[J]. J C Physiol, 2004, 200:11-19.
[32] Wu YI, Munshi HG, Snipas SJ, et al. Activation-coupled membrane type 1 matrix metalloproteinase membrane trafficking[J]. Biochem J, 2007, 407:171-177.
[33] Ellerbroek SM, Stack MS. Regulatory mechanisms for proteinase activity. In: Smith HJ, Simons C, editors. Proteinase and peptidase inhibition[J]. London: Taylor and Francis, Inc, 2002, 21-34.
[34] Sato H, Takino T, Kinoshita T, et al. Cell surface binding and activation of gelatinase A induced by expression of membrane-type-1-matrix metalloproteinase (MT1-MMP) [J]. FEBS Lett, 1996, 385:238-240.
[35] d'Ortho MP, Will H, Atkinson S, B et al. Membrane-type matrix metalloproteinases 1 and 2 exhibit broad-spectrum proteolytic capacities comparable to many matrix metalloproteinases[J]. Eur J Biochem, 1997, 250:751-757.
[36] Koshikawa N, Giannelli G, Cirulli V, et al. Role of cell surface metalloprotease MT1-MMP in epithelial cell migration over laminin-5[J]. J Cell Biol, 2000, 148:615-624.
[37] Golubkov VS, Boyd S, Savinov AY, et al. Membrane type-1 matrix metalloproteinase (MT1- MMP) exhibits an important intracellular cleavage function and causes chromosome instability[J]. J Biol Chem, 2005, 280:25079-25086.
[38] Golubkov VS, Chekanov AV, Savinov AY, et al. Membrane type-1 matrix metalloproteinase confers aneuploidy and tumorigenicity on mammary epithelial cells[J]. Cancer Res, 2006, 66:10460-10465.
[39] Knauper V, Bailey L, Worley JR, et al. Cellular activation of proMMP-13 by MT1-MMP depends on the Cterminal domain of MMP-13[J]. FEBS Lett, 2002, 532:127-130.
[40] Holopainen JM1, Moilanen JA, Sorsa T, et al. Activation of matrix metalloproteinase-8 by membrane type 1-MMP and their expression in human tears after photorefractive keratectomy[J]. Invest Ophthalmol Visual Sci, 2003, 44:2550-2556.
[41] Seftor RE, Seftor EA, Koshikawa N, et al. Cooperative interactions of laminin 5 gamma2 chain, matrix metalloproteinase-2, and membrane type-1-matrix/metalloproteinase are required for mimicry of embryonic vasculogenesis by aggressive melanoma[J]. Cancer Res, 2001, 61:6322-6327.
[42] Mu D, Cambier S, Fjellbirkeland L, et al. The integrin alpha (v)beta8 mediates epithelial homeostasis through MT1-MMP-dependent activation of TGF-beta1[J]. J Cell Biol, 2002, 157:493-507.
[43] Karsdal MA, Larsen L, Engsig MT, et al. Matrix metalloproteinase-dependent activation of latent transforming growth factor-beta

controls the conversion of osteoblasts into osteocytes by blocking osteoblast apoptosis[J]. J Biol Chem, 2002, 277:44061-44067.
[44] Turner MW. Mannose-binding lectin: the pluripotent molecule of the innate immune system[J]. Immunol Today, 1996, 17:532-540.
[45] Butler GS, Sim D, Tam E, et al. Mannose-binding lectin (MBL) mutants are susceptible to matrix metalloproteinase proteolysis: potential role in human MBL deficiency[J]. J Biol Chem, 2002, 277:17511-17519.
[46] Nishida C, Kusubata K, Tashiro Y, et al. MT1-MMP plays a critical role in hematopoiesis by regulating HIF-mediated chemokine/cytokine gene transcription within niche cells[J]. Blood, 2012, 119: 5405-5416.
[47] McQuibban GA, Gong JH, Wong JP, et al. Matrix metalloproteinase processing of monocyte chemoattractant proteins generates CC chemokine receptor antagonists with anti-inflammatory properties in vivo[J]. Blood, 2002, 100:1160-1167.
[48] Toth M, Hernandez-Barrantes S, Osenkowski P, et al. Complex pattern of membrane type 1 matrix metalloproteinase shedding. Regulation by autocatalytic cells surface inactivation of active enzyme[J]. J Biol Chem, 2002, 277:26340-26350.
[49] Ellerbroek SM, Wu YI, Overall CM, et al. Functional interplay between type I collagen and cell surface matrix metalloproteinase activity[J]. J Biol Chem, 2001, 276:24833-24842.
[50] Nonaka T, Nishibashi K, Itoh Y, et al. Competitive disruption of the tumor-promoting function of membrane type 1 matrix metalloproteinase/matrix metalloproteinase-14 in vivo[J]. Mol Cancer Ther, 2005, 4:1157-1166.
[51] Ratnikov BI, Rozanov DV, Postnova TI, et al. An alternative processing of integrin alpha (v) subunit in tumor cells by membrane type-1 matrix metalloproteinase[J]. J Biol Chem, 2002, 277:7377-7385.
[52] Deryugina EI, Ratnikov BI, Postnova TI, et al. Processing of integrin alpha (v) subunit by membrane type 1 matrix metalloproteinase stimulates migration of breast carcinoma cells on vitronectin and enhances tyrosine phosphorylation of focal adhesion kinase[J]. J Biol Chem, 2002, 277:9749-9756.
[53] Baciu PC, Suleiman EA, Deryugina EI, et al. Membrane type-1 matrix metalloproteinase (MT1-MMP) processing of pro-alphav integrin regulates cross-talk between alphavbeta3 and alpha2beta1 integrins in breast carcinoma cells[J]. Exp Cell Res, 2003, 291:167-175.
[54] Billion K, Ibrahim H, Mauch C, et al. Increased soluble E-cadherin in melanoma patients[J]. Skin Pharmacol Physiol, 2006, 19:65-70.
[55] Syrigos KN, Harrington KJ, Karayiannakis AJ, et al. Circulating soluble E-cadherin levels are of prognostic significance in patients with multiple myeloma[J]. Anticancer Res, 2004, 24:2027-2031.
[56] Wilmanns C, Grossmann J, Steinhauer S, et al. Soluble serum E-cadherin as a marker of tumour progression in colorectal cancer patients[J]. Clin Exp Metastasis, 2004, 21:75-78.
[57] Maretzky T, Reiss K, Ludwig A, et al. ADAM10 mediates E-cadherin shedding and regulates epithelial cell–cell adhesion, migration, and beta-catenin translocation[J]. Proc Natl Acad Sci USA, 2005, 102:9182-9187.
[58] Monea S, Jordan BA, Srivastava S, et al. Membrane localization of membrane type 5 matrix metalloproteinase by AMPA receptor binding protein and cleavage of cadherins[J]. J Neurosci, 2006, 26:2300-2312.
[59] Symowicz J, Adley BP, Gleason KJ, et al. Engagement of collagen-binding integrins promotes matrix metalloproteinase-9-dependent E-cadherin ectodomain shedding in ovarian carcinoma cells[J]. Cancer Res, 2007, 67:2030-2039.
[60] Covington MD, Burghardt RC, Parrish AR. Ischemia-induced cleavage of cadherins in NRK cells requires MT1-MMP (MMP-14) [J]. Am J Physiol Renal Physiol, 2006, 290: 43-51.
[61] Kajita M, Itoh Y, Chiba T, et al. Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration[J]. J Cell Biol, 2001, 153:893-904.
[62] Rozanov DV, Hahn-Dantona E, Strickland DK, et al. The lowdensity lipoprotein receptor-related protein LRP is regulated by membrane type-1 matrix metalloproteinase (MT1-MMP) proteolysis in malignant cells[J]. J Biol Chem, 2004, 279:4260-4268.
[63] Park JH, Lee NK, Lee SY. Current Understanding of RANK Signaling in Osteoclast Differentiation and Maturation[J]. Mol Cells, 2017, 40:706-713.
[64] Hikita A, Yana I, Wakeyama H, et al. Negative regulation of osteoclastogenesis by ectodomain shedding of receptor activator of NF-kappaB ligand[J]. J Biol Chem, 2006, 281:36846-36855.
[65] Lontos K, Adamik J, Tsagianni A, et al. The Role of Semaphorin 4D in Bone Remodeling and Cancer Metastasis[J]. Front Endocrinol (Lausanne), 2018, 9:322.
[66] Basile JR, Castilho RM, Williams VP, et al. Semaphorin 4D provides a link between axon

guidance processes and tumor-induced angiogenesis[J]. Proc Natl Acad Sci USA, 2006, 103:9017-9022.
[67] Belkin AM, Akimov SS, Zaritskaya LS, et al. Matrix-dependent proteolysis of surface transglutaminase by membrane-type metalloproteinase regulates cancer cell adhesion and locomotion[J]. J Biol Chem, 2001, 276:18415-18422.
[68] Endo K, Takino T, Miyamori H, et al. Cleavage of syndecan-1 by membrane type matrix metalloproteinase-1 stimulates cell migration[J]. J Biol Chem, 2003, 278:40764-40770.
[69] Thathiah A, Carson DD. MT1-MMP mediates MUC1 shedding independent of TACE/ADAM17[J]. Biochem J, 2004, 382:363-373.
[70] Velasco-Loyden G, Arribas J, Lopez-Casillas F. The shedding of betaglycan is regulated by pervanadate and mediated by membrane type matrix metalloprotease-1[J]. J Biol Chem, 2004, 279:7721-7733.
[71] Egawa N, Koshikawa N, Tomari T, et al. Membrane type 1 matrix metalloproteinase (MT1-MMP/MMP-14) cleaves and releases a 22-kDa extracellular matrix metalloproteinase inducer (EMMPRIN) fragment from tumor cells[J]. J Biol Chem, 281:37576-37585.
[72] Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors:biological actions and therapeutic opportunities[J]. J Cell Sci, 2002, 115:3719-3727.
[73] Troeberg L, Tanaka M, Wait R, et al. E. coli expression of TIMP-4 and comparative kinetic studies with TIMP-1 and TIMP-2: insights into the interactions of TIMPs and matrix metalloproteinase 2 (gelatinase A) [J]. Biochemistry, 2002, 41:15025-15035.
[74] Takahashi C, Sheng Z, Horan TP, et al. Regulation of matrix metalloproteinase-9 and inhibition of tumor invasion by the membrane-anchored glycoprotein RECK[J]. Proc Natl Acad Sci USA, 1998, 95:13221-13226.
[75] Anand-Apte B, Pepper MS, Voest E, et al. Inhibition of angiogenesis by tissue inhibitor of metalloproteinase-3[J]. Invest Ophthalmol Vis Sci, 1997, 38:817-823.
[76] Fisher C, Gilbertson-Beadling S, Powers EA, et al. Interstitial collagenase is required for angiogenesis in vitro[J]. Dev Biol, 1994, 162:499-510.
[77] Volpert OV, Ward WF, Lingen MW, et al. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats[J]. J Clin Invest, 1996, 98:671-679.
[78] Seftor RE, Seftor EA, Kirschmann DA, et al. Targeting the tumor microenvironment with chemically modified tetracyclines: inhibition of laminin 5 gamma2 chain promigratory fragments and vasculogenic mimicry[J]. Mol Cancer Ther, 2002, 1:1173-1179.
[79] Gingras D, Boivin D, Deckers C, et al. Neovastat. A novel antiangiogenic drug for cancer therapy[J]. Anticancer Drugs, 2003, 14:91-96.
[80] Lozonschi L, Sunamura M, Kobari M, et al. Controlling tumor angiogenesis and metastasis of C26 murine colon adenocarcinoma by a new matrix metalloproteinase inhibitor, KBR7785, in two tumor models[J]. Cancer Res, 1999, 59:1252-1258.
[81] Naglich JG, Jure-Kunkel M, Gupta E, et al. Inhibition of angiogenesis and metastasis in two murine models by the matrix metalloproteinase inhibitor, BMS-275291[J]. Cancer Res, 2001, 61:8480-8485.
[82] Leco KJ, Khokha R, Pavloff N, et al. Tissue inhibitor of metalloproteinases-3 (TIMP-3) is an extracellular matrix associated protein with a distinctive pattern of expression in mouse cells and tissues[J]. J Biol Chem, 1994, 269:9352-9360.
[83] Alameddine HS, Morgan JE. Matrix Metalloproteinases and Tissue Inhibitor of Metalloproteinases in Inflammation and Fibrosis of Skeletal Muscles[J]. J Neuromuscul Dis, 2016, 3:455-473.
[84] Will H, Atkinson SJ, Butler GS, et al. The soluble catalytic domain of membrane type 1 matrix metalloproteinase cleaves the propeptide of progelatinase A and initiates autoproteolytic activation: regulation by TIMP-2 and TIMP-3[J]. J Biol Chem, 1996, 271:17119-17123.
[85] Oh J, Takahashi R, Kondo S, et al. The membrane-anchored MMP inhibitor RECK is a key regulator of extracellular matrix integrity and angiogenesis[J]. Cell, 2001, 107:789-800.
[86] Kim YM, Jang JW, Lee OH, Y et al. Endostatin inhibits endothelial and tumor cellular invasion by blocking the activation and catalytic activity of matrix metalloproteinase[J]. Cancer Res, 2000, 60:5410-5413.
[87] O'Reilly MS, Boehm T, Shing Y, Fukai N, et al. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth[J]. Cell, 1997, 88:277-285.
[88] Remillard TC, Bratslavsky G, Jensen-Taubman S, et al. Molecular mechanisms of tissue inhibitor of metalloproteinase 2 in the tumor microenvironment[J]. Mol Cell Ther, 2014, 2:17.
[89] Butler GS, Butler MJ, Atkinson SJ, et al. The TIMP2 membrane type 1 metalloproteinase 'receptor' regulates the concentration and

efficient activation of progelatinase A[J]. A kinetic study. J Biol Chem, 1998, 273:871-880.
[90] Gomez DE, Alonso DF, Yoshiji H, et al. Tissue inhibitors of metalloproteinases: Structure, regulation and biological functions[J]. Eur J Cell Biol, 1997, 74:111-122.
[91] Uta B. Hofmann, Johan R. Westphal, Goos NP van Muijen, et al. Matrix metalloproteinases in human melanoma[J]. J Investgate Dermatology, 2000, 115:338-344.
[92] Tsunezuka Y, Kinoh H, Takino T, et al. Expression of membrane-type matrix metalloproteinase 1 (MT1-MMP) in tumor cells enhances pulmonary metastasis in an experimental metastasis assay[J]. Cancer Res, 1996, 56:5678-5683.
[93] Chun TH, Sabeh F, Ota I, et al. MT1-MMP-dependent neovessel formation within the confines of the three-dimensional extracellular matrix[J]. J Cell Biol, 2004, 167:757-767.
[94] Sevenich L, Joyce JA. Pericellular proteolysis in cancer[J]. Genes Dev, 2014, 28:2331-2347.
[95] Takino T, Miyamori H, Watanabe Y, et al. Membrane type 1 matrix metalloproteinase regulates collagen-dependent mitogen-activated protein/extracellular signal-related kinase activation and cell migration[J]. Cancer Res, 2004, 64:1044-1049.
[96] Schenk S, Hintermann E, Bilban M, et al. Binding to EGF receptor of a laminin-5 EGF-like fragment liberated during MMP-dependent mammary gland involution[J]. J Cell Biol, 2003, 161:197-209.
[97] Deryugina EI, Soroceanu L, Strongin AY. Up-regulation of vascular endothelial growth factor by membrane-type 1 matrix metalloproteinase stimulates human glioma xenograft growth and angiogenesis[J]. Cancer Res, 2002, 62:580-588.
[98] Sounni NE, Devy L, Hajitou A, et al. MT1-MMP expression promotes tumor growth and angiogenesis through an up-regulation of vascular endothelial growth factor expression[J]. FASEB J, 2002, 16:555-564.

