Activation of MMP-9 by membrane type-1 MMP/MMP-2 axis stimulates tumor metastasis

| 著者 | 李子臣, 高橋貴重, 遠藤義, 佐藤浩志 |
|---|---|
| タイトル | 癌科学 |
| 卷 | 108 |
| 号 | 3 |
| 頁| 347-353 |
| 年 | 2017-03-01 |
| URL | http://hdl.handle.net/2297/47887 |
| doi | 10.1111/cas.13134 |
Activation of MMP-9 by membrane type-1 MMP/MMP-2 axis stimulates tumor metastasis

Zichen Li, Takahisa Takino, Yoshio Endo and Hiroshi Sato

Department of Molecular Virology and Oncology; Central Research Resource Branch, Cancer Research Institute, Kanazawa University, Kanazawa, Japan

Key words
Activation, MMP-2, MMP-9, MT1-MMP, TIMP-1

Correspondence
Hiroshi Sato, Department of Molecular Virology and Oncology, Cancer Research Institute, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan.
Tel: +81-76-264-6710; Fax: +81-76-234-4504; E-mail: vhsato@staff.kanazawa-u.ac.jp

Materials and Methods

Matrix metalloproteinase-2 and MMP-9 are type IV collagenase/gelatinase, and their expression is often associated with tumor aggressiveness and a poor prognosis (reviewed in Ref. 1,2). Membrane type 1 MMP was first identified as an activator of latent MMP-2 (proMMP-2). (3) In addition to proMMP-2, a variety of substrates of MT1-MMP were identified, including ECM proteins, cell adhesion molecules, cytokines, and others. (4-7) ProMMP-2 is activated in a variety of tumor tissues in which MT1-MMP is overexpressed. In contrast, proMMP-9 activation was detected in limited numbers of tumor samples, such as non-small-cell lung carcinoma and colon carcinomas. (8-10) and the active form of MMP-9 was predominantly present in colon carcinoma patients with metastases. (11) ProMMP-9 can be processed in vitro by various proteases including MMP-2, MMP-3, and serine proteases, however, the molecular mechanism of proMMP-9 activation in vivo still remains to be solved. (1)

An artificial receptor for proMMP-9 was created by fusing tissue inhibitor of MMP-1 (TIMP-1) with type II transmembrane mosaic serine protease (MSP-T1). Expression of MSP-T1 in 293T cells induced binding of proMMP-9, which was processed by MMP-2 activated by membrane type 1 MMP (MT1-MMP). HT1080 cells transfected with the MSP-T1 gene produced activated MMP-9 in collagen gel, and addition of proMMP-2 to the culture augmented it, which resulted in intensive collagen digestion. These cells metastasized into chick embryonic liver more than control cells. Treatment of HT1080 cells with concanavalin A in the presence of exogenous proMMP-2 induced activation of not only proMMP-2 but also proMMP-9. Knockdown of MT1-MMP or TIMP-2 expression with siRNA suppressed activation of both proMMP-2 and proMMP-9. Transfection of TIMP-1 siRNA suppressed cell binding and activation of proMMP-9, but not proMMP-2 activation. Knockdown of a disintegrin and metalloproteinase 10 (ADAM10) expression reduced cell binding and processing of proMMP-9. These results suggest that proMMP-9, which binds to a receptor complex containing TIMP-1 and ADAM10, is activated by the MT1-MMP/MMP-2 axis, and MMP-9 thus activated stimulates cellular proteolysis and metastasis.

© 2016 The Authors. Cancer Science published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
of MSP-T2 with that of TIMP-1. The human TIMP-1 cDNA fragment encoding amino acid residues 24–207 was amplified by PCR using 5′ and 3′ primers with extra EcoRI and XhoI site, respectively (GAATTCTGCACC TGTGTCCCA CCCCC and TCTAGATCA ACCATAGAGGTGCCGGATGCC (restriction enzyme site). The cDNA encoding mutant MMP-9 lacking C-terminal hinge and hemopexin-like domains (AMM-9) was amplified by PCR using a primer TCTAGATCA ACCATAGAGGTGCCGGATGCC (restriction site). The cDNA encoding MMP-9 mutants with amino acid substitution at Met41 and Phe88 with Val was amplified by PCR using mutation primers CTCGGGTGGCA GTGCGTGGAGAGTCGA and CAGA CCTGGGCA GTGCC AAACCTTTGAGG (mutated nucleotide), respectively.

RNA interference. RNA interference technology was used to generate specific knockdown of MT1-MMP, TIMP-1, TIMP-2, ADAM10, and MMP-9 mRNA transcription. Small interfering RNA was prepared by FASMAK (Kanagawa, Japan). The siRNA target sequences were as follows: MT1-MMP-I, CCAGAACGTGAA GAAGTGA; TIMP-1-II, GTGCGTGGAGAGTCGA and CAGA CCTGGGCA GTGCC AAACCTTTGAGG (mutated nucleotide), respectively.

Zymography. ProMMP-2, proMMP-9, and proMMP-9 mutant supernatants were prepared from 293T cells transfected with the respective expression plasmids, as previously described. 293T cells cultured in a 24-well microplate were transfected with expression plasmids, cultured in DMEM supplemented with 5% FCS for 24 h, and incubated in 300 μL Opti-MEM (Invitrogen) containing proMMP-2 and proMMP-9. Both MMP-2 and MMP-9 in the supernatant were examined by mixing with a same volume of zymography sample buffer. For the detection of cell-bound MMP-2 and MMP-9, cells were washed twice with PBS, and then dissolved in 200 μL sample buffer by sonication. These samples were incubated at 37°C for 20 min, and subjected to gelatin zymography gel containing gelatin labeled with Alexa Fluor 680 (Molecular Probes, Eugene, OR, USA). Gels were processed and monitored by a LI-COR Odyssey IR imaging system. Cell lysates or proteins precipitated with 10% trichloroacetic acid were analyzed by Western blotting with the indicated antibody. Goat anti-mouse antibody conjugated with Alexa Fluor 680 was used as a secondary antibody. The signal was monitored using a LI-COR Odyssey IR imaging system. Precision Plus Protein Standards were used as molecular weight standards (Bio-Rad, Hercules, CA, USA).

Chick embryo assay. The assay was done as originally described by Endo et al. Briefly, HT1080 cells stably transfected with pEAK control plasmid or MSP-T1 expression plasmid (1.0 × 10⁵ cells per egg) were injected into the chorioallantoic membrane vein of chicken eggs 11 days after fertilization, and incubated for a further 7 days. Ten eggs were used for the injection of each type of cell. The number of HT1080 cells that colonized liver was estimated by quantitative real-time PCR as described previously.

Results

MSP-T1 functions as a receptor for proMMP-9. 293T cells transfected with MSP-T1 and/or MT1-MMP plasmids were incubated with proMMP-2 and proMMP-9, and cell-bound MMP-2 and MMP-9 were examined by gelatin zymography. ProMMP-9 bound to the cells expressing MSP-T1 more efficiently than to control cells (Fig. 1a, Cells). Expression of MT1-MMP alone induced activation of proMMP-2, but not proMMP-9. Coexpression of MSP-T1 with MT1-MMP induced activation of both proMMP-2 and proMMP-9. To confirm that proMMP-9 activation is mediated by transfected cells, transfected cells were incubated with proMMP-2, and then supernatants from transfected cells were incubated with proMMP-9 (Fig. 1a, Sup). ProMMP-9 was not processed in the supernatants from cells expressing MSP-T1, MT1-MMP, and MMP-2. Next, to examine whether proMMP-2 in proMMP-9 was activated through MSP-T1/MT1-MMP, cells coexpressing MSP-T1 and MT1-MMP were incubated with proMMP-9 and 2-fold serially diluted proMMP-2 (Fig. 1b). ProMMP-9 activation was shown to depend on MMP-2 concentration added to the culture. The time-course experiment indicated that proMMP-9 activation by the cells expressing MSP-T1/MT1-MMP/2 was induced at 0.2 h and reached a plateau at 1–2 h after incubation (Fig. 1c). ProMMP-9 binds to TIMP-1 through the carboxy-terminal hemopexin-like domain. ProMMP-9 mutant lacking hemopexin-like domain (AMM-9) was compared with wild-type proMMP-9 for binding and processing by cells expressing MSP-T1 and MT1-MMP in the presence of proMMP-2. Wild-type proMMP-9 bound to the cells expressing MSP-T1 and was activated by the cells expressing MSP-T1 and MT1-MMP in the presence of proMMP-2. However, ΔproMMP-9 failed to bind to MSP-T1-expressing cells and was not activated by the cells expressing MSP-T1 and MT1-MMP. ΔproMMP-9 was shown to be cleaved in vitro by activated MMP-2 at the Glu⁴⁰–Met⁴¹ amide bond to generate an activation intermediate form, which is converted to the fully active form through the autoligase at the Arg⁸⁷–Phe⁸⁸ amide bond. To confirm proMMP-9 cleavage sites by the cells expressing MSP-T1 and MT1-MMP in the presence of proMMP-2, wild-type or mutant proMMP-9 with the amino acid substitution at Met⁴¹ (Fig. 1e, Mut1) or Phe⁸⁸ (Fig. 1e, Mut2) was incubated with the cells expressing MSP-T1 and MT1-MMP in the presence of proMMP-2. Wild-type proMMP-9 was converted to fully active form by these cells, but proMMP-9 mutant with amino acid substitution at Met⁴¹ (Mut1) was not processed. ProMMP-9 mutant with an amino acid substitution at Phe⁸⁸ (Mut2) was cleaved to generate an activation intermediate form. These results indicate that proMMP-9 is processed by the cells expressing MSP-T1, MT1-MMP in the presence of proMMP-2 through the cleavage at the same sites as in vitro activation by active MMP-2. The activation efficiency by these cells was dramatically improved compared with activation by MMP-2 in vitro. Expression of MSP-T1 in HT1080 cells. HT1080 cells were stably transfected with MSP-T1 plasmid, and cultured in collagen gel in the presence or absence of exogenously added proMMP-
2 to examine proMMP-9 activation and degradation of collagen gel (Fig. 2). HT1080 cells migrated out of the collagen gel, but collagen degradation was not obvious in the culture of cells without exogenous proMMP-2. In the presence of exogenously added proMMP-2, collagen gel was degraded intensively by the cells expressing MSP-T1, and moderately by control cells (Fig. 2b). Gelatin zymography analysis showed that endogenous proMMP-2 was activated equally by the cells transfected with control or MSP-T1 plasmid, but proMMP-9 processing was detected only in the cells expressing MSP-T1 in the absence of exogenously added proMMP-2. Addition of proMMP-2 to the culture produced a large amount of active MMP-2, which resulted in significant proMMP-9 processing in control cells and a more dramatic effect in MSP-T1-expressing cells (Fig. 2c). The metastatic ability of HT1080 cells expressing MSP-T1 was analyzed by the chick embryo system. HT1080 cells expressing MSP-T1 metastasized into liver 4-fold more efficiently than control cells (Fig. 2d).

Fig. 1. ProMMP-9 activation by cells expressing artificial receptor for proMMP-9 (MSP-T1), membrane type 1 (MT1)-MMP, and MMP-2. (a) Control plasmid or expression plasmid for MT1-MMP (200 ng) and/or MSP-T1 (300 ng) was transfected into 293T cells in a 24-well microplate. Twenty-four hours after transfection, cells were incubated in Opti-MEM containing proMMP-2 (100 nM) and proMMP-9 (20 nM) for 2 h. Cell-bound MMP-2 and MMP-9 were analyzed by gelatin zymography (Cells). Cells were incubated with proMMP-2 for 2 h, and then the supernatant was incubated with proMMP-9 (20 nM) for a further 2 h. ProMMP-9 processing was monitored by zymography (Sup). Expression of MSP-T1 and MT1-MMP was detected by Western blotting using anti-tissue inhibitor of MMP-1 and anti-MT1-MMP antibodies, respectively (lower panels). (b) 293T cells transfected with expression plasmids for MSP-T1 and MT1-MMP as described above were incubated with proMMP-9 (20 nM) and serially diluted proMMP-2 for 2 h, and then cell-bound MMP-2 and MMP-9 were subjected to gelatin zymography. Gels were processed and monitored by an infrared imaging system with low (top) and high sensitivity (bottom). (c) 293T cells transfected as above were incubated with proMMP-2 (100 nM) for 1 h, and then proMMP-9 (20 nM) was added and incubated for the indicated period. Cell-bound MMP-2 and MMP-9 were detected as above. (d) 293T cells transfected with control, MSP-T1 and/or MT1-MMP plasmid as described above were incubated with proMMP-2 and wild-type proMMP-9 or proMMP-9 mutant lacking hemopexin-like domain (ΔMMP-9) for 2 h, and cell-bound (Cell) or supernatant (Sup) MMP-2 and MMP-9 were detected by gelatin zymography. (e) MT1-MMP plasmid (1 μg) was cotransfected with control or MSP-T1 plasmid (1 μg) into 293T cells cultured in a 35-mm dish. Twenty-four hours after incubation, 50 nM wild-type or mutant proMMP-9 with an amino acid substitution at Met41 (Mut1) or Phe88 (Mut2) was incubated with cells in the presence of proMMP-2 (50 nM) for 3 h. Supernatant was concentrated with trichloroacetic acid, and subjected to Western blotting using an antibody against MMP-9. Expression of MSP-T1 and MT1-MMP was detected by Western blotting as described above (lower panels).
Activation of proMMP-9 by HT1080 cells. HT1080 cells cultured in collagen gel in the presence of exogenous proMMP-2 activated proMMP-2 and slightly activated proMMP-9. To induce more efficient proMMP-2 activation in HT1080 cells, cells were treated with 2-fold serially diluted ConA in the presence of exogenous proMMP-2 (Fig. 3a). ProMMP-2 activation was induced even at low ConA concentration. Treatment with ConA induced cell binding and processing of proMMP-9 in HT1080 cells, but they required higher ConA concentration than proMMP-2 activation.

As shown in Figure 1, activation of proMMP-9 by cells expressing MSP-T1 and MT1-MMP required a considerable concentration of proMMP-2. Thus, requirement of MMP-2 in proMMP-9 activation by ConA-treated HT1080 cells was examined (Fig. 3b). Addition of exogenous proMMP-2 to ConA-treated HT1080 cells induced activation of proMMP-2 and proMMP-9, depending on the proMMP-2 concentration. The time course experiment showed that proMMP-9 was processed to the intermediate activation form in 1 h and to fully active form in 2–3 h (Fig. 3c).

The effect of MMP inhibitors on proMMP-9 activation by ConA-treated HT1080 cells was examined (Fig. 3d). Addition of TIMP-2 or BB94 interfered with activation of both proMMP-2 and proMMP-9 by ConA-treated HT1080 cells. Cells treated with TIMP-1 processed proMMP-2 to the intermediate activation form, and failed to activate proMMP-9. These results suggest that proMMP-2 activation by MT1-MMP is associated with proMMP-9 processing in ConA-treated HT1080 cells.

Analysis of proMMP-9 activation mechanism by siRNA. To confirm the association of MT1-MMP with proMMP-9 processing, MT1-MMP siRNA was transfected into HT1080 cells, and proMMP-9 activation was examined (Fig. 4). Knockdown of MT1-MMP expression suppressed activation of not only proMMP-2 but also proMMP-9 (left panel). MSP-TIMP-1 was shown to act as a receptor for pro-MMP-9, which facilitated proMMP-9 activation by the MT1-MMP/MMP-2 axis. This suggested a possibility that TIMP-1 acts as a part of the proMMP-9 receptor and induces its processing in ConA-treated HT1080 cells. To test it, TIMP-1 expression was downregulated by the transfection of siRNA, and proMMP-9 activation was examined. Knockdown of TIMP-1 did not alter proMMP-2 activation, but suppressed binding of proMMP-9 to the cells and subsequent activation in ConA-treated HT1080 cells (middle panel). Knockdown of TIMP-2 did not alter proMMP-9 binding but interfered with activation of both proMMP-2 and proMMP-9. These results suggest that TIMP-1 serves as a part of the proMMP-9 receptor, which induces subsequent proMMP-9 processing. Expressed at a considerable level in HT1080 cells, ADAM10 is known to be inactivated by TIMP-1. Transfection of ADAM10 siRNA did not affect proMMP-2 activation, but suppressed cell binding and processing of proMMP-9 (right panel).

Contribution of MMP-9 to gelatin degradation by HT1080 cells. In order to examine the contribution of MMP-2 and MMP-9 to ECM degradation by HT1080 cells, MMP-9 expression was knocked down through siRNA transfection, and gelatin degradation by these cells was monitored (Fig. 5). Gelatin was not significantly degraded by ConA-treated HT1080 cells in the absence of exogenous proMMP-2. Addition of proMMP-2 to ConA-treated cells generated active MMP-2 and MMP-9, which resulted in intensive gelatin degradation. Knockdown of
MMP-9 expression in these cells considerably reduced gelatin degradation by ConA-treated cells. These results indicate that not only MMP-2 but also MMP-9 activated by HT1080 cells contributes to gelatin degradation.

**Discussion**

Activation of proMMP-2 by MT1-MMP is a feature of the malignant phenotype of various tumors.\(^4\)\(^\text{–}\)\(^7\) Tumor-specific proMMP-9 activation is restricted to a limited numbers of tissues, and the molecular mechanism of proMMP-9 activation *in vivo* still remains unsolved.\(^8\)\(^\text{–}\)\(^10\) ProMMP-2 and proMMP-9 bind to TIMP-2 and TIMP-1 through the carboxy-terminal domain of each molecule, respectively.\(^1\)\(^,\)\(^2\) Formation of a trimolecular complex consisting of proMMP-2/TIMP-2/MT1-MMP is the initial step for proMMP-2 activation by MT1-MMP.\(^11\)\(^\text{–}\)\(^13\) Previously, MSP-T2 was constructed as an artificial receptor for proMMP-2, which accelerated proMMP-2 activation by MT1-MMP.\(^15\) Assuming a similar scenario in proMMP-9 activation process, in which binding of proMMP-9 to the receptor containing TIMP-1 is the initial step for activation, MSP-T1 was created as an artificial receptor for proMMP-9. Indeed, MSP-T1 served as a receptor for proMMP-9, which was effectively processed by the MT1-MMP/2 axis (Fig. 1). Membrane-bound serine proteases, such as MSP and matriptase, were negative as a cell-surface proMMP-9 activator, when coexpressed with MSP-T1 (data not shown). Toth et al.\(^24\) reported activation of proMMP-9 by membrane fraction from cells expressing MMP-2 and MT1-MMP, however, incubation of proMMP-9 with these cells failed to activate proMMP-9, which was consistent with the present study. Coexpression of MSP-T1 with MT1-MMP induced dramatic proMMP-9 activation in the presence of proMMP-2. ProMMP-9 is activated by these cells through the cleavage at the site identical with those by active MMP-2 *in vitro*.\(^22\) These results suggest a proMMP-9 activation process in which proMMP-9 is anchored to the cell surface through a TIMP-1-containing receptor and is subsequently processed by MMP-2 activated and anchored on the cell surface by MT1-MMP. HT1080 cells in collagen gel did not show detectable proMMP-9 processing, but addition of proMMP-2 induced significant proMMP-9 processing. Treatment of HT1080 cells with ConA caused more efficient proMMP-2 activation than collagen culture, and induced cell binding and

---

**Fig. 3.** Induction of proMMP-2 and proMMP-9 activation in HT1080 cells. (a) HT1080 cells were cultured in DMEM supplemented with 5% FCS for 24 h, and then in Opti-MEM containing proMMP-2 (50 nM) and serially diluted concanavalin (ConA) for 12 h. Cell-bound MMP-2 and MMP-9 were analyzed by gelatin zymography. (b) HT1080 cells cultured as above were incubated in Opti-MEM containing ConA (50 μg/mL) and serially diluted proMMP2 for 12 h, and cell-bound MMP-2 and MMP-9 were analyzed by gelatin zymography. (c) HT1080 cells cultured as above were incubated in Opti-MEM containing ConA (50 ng/mL) and proMMP-2 (50 nM) for the indicated period, and cell-bound MMP-2 and MMP-9 were analyzed by gelatin zymography. (d) HT1080 cells cultured as above were incubated in Opti-MEM containing ConA (50 ng/mL) and proMMP-2 (50 nM) with mock (−), tissue inhibitor of tissue inhibitor of metalloproteinase (TIMP)-1 (10 μg/mL), TIMP-2 (10 μg/mL), or BB94 (1 μM) for 12 h. Cell-bound and supernatant MMP-2 and MMP-9 were analyzed by gelatin zymography.
processing of proMMP-9 in the presence of exogenously added proMMP-2 (Fig. 3). Knockdown of MT1-MMP or TIMP-2 expression, which is essential for proMMP-2 activation, suppressed processing of not only proMMP-2 but also proMMP-9. Knockdown of TIMP-1 expression downregulated cell binding and processing of proMMP-9, but did not affect proMMP-2 activation. These results indicate that TIMP-1 is involved in cell-binding of proMMP-9, which is subsequently processed by MMP-2 activated by MT1-MMP. ADAM10 is known to be inactivated by TIMP-1, suggesting the possibility that ADAM10 acts as a cell-surface binding molecule of TIMP-1. Knockdown of ADAM10 expression by siRNA reduced both binding and processing of proMMP-9. These results may suggest that ADAM10 is one of the receptors for TIMP-1 and that the ADAM10/TIMP-1 complex acts as a receptor for proMMP-9, which is subsequently processed by the MT1-MMP/MMP-2 axis. However, reconstitution of proMMP-9 receptor by coexpressing ADAM10 and TIMP-1 was not successful (data not shown). Actually, ADAM10 and TIMP-1 protein expression was not significantly affected by ConA treatment of HT1080 cells (data not shown). The cell surface event induced by ConA treatment seems to be complicated, and the mechanism by which ADAM10 participates in proMMP-9 processing still remains unsolved. Several TIMP-1 binding molecules such as CD44, CD63, and integrins were reported, which may function as proMMP-9 receptors by forming complexes with TIMP-1. Association of CD44 and MT1-MMP with proMMP-9 activation in osteoclasts and formation of the proMMP-9/CD44/TIMP-1 complex were reported, although the molecular mechanism and physiological significance of them in relation to proMMP-9 processing still remain to be solved.
Expression of MSP-T1 in HT1080 cells stimulated proMMP-9 activation by the MT1-MMP/MMP-2 axis, which in turn enhanced metastatic ability in vivo and collagen degradation in vitro. These results showed for the first time that activation of proMMP-9 stimulates tumor metastasis. Addition of proMMP-2 to ConA-treated HT1080 cells generated active MMP-2, which consequently processed endogenous proMMP-9. Both MMP-2 and MMP-9 cleave various substrates, such as ECM molecules, membrane proteins, cytokines, and growth factors that regulate key signaling pathways in cell growth, migration, invasion, and angiogenesis.\(^1,2\) Membrane-bound MMP-9 thus activated by the MT1-MMP/MMP-2 axis may have advantage over pericellular proteolysis. Participation of MMP-9 thus activated by the MT1-MMP/MMP-2 axis further facilitates pericellular proteolysis for tumor invasion and metastasis. ProMMP-2 is often abundantly expressed by stromal cells located adjacent to malignant epithelial cells, and functions as a mediator of tumor-stroma interaction by being activated by tumor-specific MT1-MMP, which may subsequently activate proMMP-9. In conclusion, proMMP-9, which is anchored though a receptor complex containing TIMP-1, is activated by the MT1-MMP/MMP-2 axis. Thus activated, MMP-9 contributes to pericellular proteolysis for tumor invasion and metastasis in collaboration with MT1-MMP and MMP-2.

Acknowledgments
This work was supported by the grant from the Japan Society for the Promotion of Science (Kakenhi 25460382).

Disclosure Statement
The authors have no conflict of interest.

Abbreviations
ADAM10 a disintegrin and metalloproteinase 10  
ConA concanavalin A  
IR infrared  
MSP mosaic serine protease  
MSP-T2 TIMP-2 fused with type II transmembrane MSP  
MT membrane type  
TIMP tissue inhibitor of metalloproteinase

References

1 Mook OR, Frederik WM, Van Noorden CJ. The role of gelatinases in colorectal cancer progression and metastasis. Biochim Biophys Acta 2004; 1705: 69–89.
2 Bjorklund M, Koivunen E. Gelatinase-mediated migration and invasion of cancer cells. Biochim Biophys Acta 2005; 1755: 37–69.
3 Sato H, Takino T, Okada Y et al. A matrix metalloproteinase expressed on the surface of invasive tumour cells. Nature 1994; 370: 61–5.
4 Seiki M, Yana I. Roles of pericellular proteolysis by membrane type-1 matrix metalloproteinase in cancer invasion and angiogenesis. Cancer Sci 2003; 94: 569–74.
5 Sato H, Takino T, Miyamori H. Roles of membrane-type matrix metalloproteinase-1 in tumor invasion and metastasis. Cancer Sci 2005; 96: 212–7.
6 Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer 2002; 2: 161–74.
7 Overall CM, McQuibban GA, Clark-Lewis I. Discovery of chemokine substrates for matrix metalloproteinases by exosite scanning: a new tool for degradomics. Biol Chem 2002; 383: 1059–66.
8 Zhang ZS, Hiro Y, Cohen AM, Guillemin JG. Loss of basement membrane type IV collagen is associated with increased expression of metalloproteinases 2 and 9 (MMP-2 and MMP-9) during human colorectal tumorigenesis. Carcinogenetics 1999; 20: 749–55.
9 Reeb E, Dieterich CG, Winograd R et al. Activity and cellular origin of gelatinases in patients with colon and rectal carcinoma differential activity of matrix metalloproteinase-9. Cancer 2001; 92: 2680–91.
10 Pucci-Minafra I, Minafra S, La Rocca G et al. Zymographic analysis of circulating and tissue forms of colon carcinoma gelatinase A (MMP-2) and B (MMP-9) separated by mono- and two-dimensional electrophoresis. Matrix Biol 2001; 20: 419–27.
11 Strongin AY, Collier I, Bannikov G et al. Mechanism of cell surface activation of 72-kDa type IV collagenase. Isolation of the activated form of the membrane metalloprotease. J Biol Chem 1995; 270: 5311–8.
12 Butler GS, Butler MJ, Atkinson SJ et al. The TIMP2 membrane type 1 metalloproteinase ‘receptor’ regulates the concentration and efficient activation of gelatinase A. A kinetic study. J Biol Chem 1998; 273: 871–80.
13 Kinoshita T, Sato H, Okada A et al. TIMP-2 promotes activation of progelatinase A by membrane-type 1 matrix metalloproteinase immobilized on agarose beads. J Biol Chem 1998; 273: 16098–103.
14 Kudo T, Takino T, Miyamori H et al. Substrate choice of membrane-type 1 matrix metalloproteinase is dictated by tissue inhibitor of metalloproteinase-2 levels. Cancer Sci 2007; 98: 563–8.
15 Nishida Y, Miyamori H, Thompson EW, Takino T, Endo Y, Sato H. Activation of matrix metalloproteinase-2 (MMP-2) by membrane-type 1 matrix metalloproteinase through an artificial receptor for proMMP-2 generates active MMP-2. Cancer Res 2008; 68: 9096–104.
16 Takino T, Koshikawa N, Miyamori H et al. Cleavage of metastasis suppressor gene product KiSS-1 protein/metastin by matrix metalloproteinases. Oncogene 2005; 22: 4617–26.
17 Endo K, Takino T, Miyamori H et al. Cleavage of syndecan-1 by membrane type matrix metalloproteinase-1 stimulates cell migration. J Biol Chem 2003; 278: 40764–70.
18 Nakada M, Yamada A, Takino T et al. Suppression of membrane-type 1 matrix metalloproteinase (MMP)-mediated MMP-2 activation and tumor invasion by scintillating 3 and its splicing variant gene product, N-Tes. Cancer Res 2001; 61: 8896–902.
19 Li Y, Aoki T, Mori Y et al. Cleavage of lumican by membrane-type matrix metalloproteinase-1 abrogates the proteoglycan-mediated suppression of tumor cell colony formation in soft agar. Cancer Res 2004; 64: 7058–64.
20 Chellahah MA, Ma T. Membrane localization of membrane type matrix metalloproteinase by CD44 regulates the activation of pro-matrix metalloprotease 9 in osteoclasts. Biomed Res Int 2013; 2013: 302392.
21 Sato H, Kinoshita T, Takino T et al. Activation of a recombinant membrane type 1-matrix metalloproteinase (MT1-MMP) by furin and its interaction with tissue inhibitor of metalloproteinases (TIMP)-2. F E B S Lett 1996; 393: 101–4.
22 Fridman R, Toth M, Pena D, Mobashery S. Activation of progelatinase B (MMP-9) by gelatinase A (MMP-2). Cancer Res 1995; 55: 2548–55.
23 Murphy G. Tissue inhibitors of metalloproteinases, Genome Biol 2011; 12: 233–9.
24 Toth M, Chytrykova I, Bernardo MM et al. Pro-MMP-9 activation by the MT1-MMP/PPM-2 axis and MMP-3: role of TIMP-2 and plasma membranes. Biochem Biophys Res Com 2003; 308: 386–95.
25 Lambert E, Bridoux L, Dey J et al. TIMP-1 binding to proMMP-9/CD44 complex localized at the cell surface promotes erythrocyt cell survival. Int J Biochem Cell Biol 2009; 41: 1102–15.