REVIEW Libri Oncol., Vol. 40 (2012), No 1-3, 49 – 55

POTENTIAL OF MATRIX METALLOPROTEINASES AND THEIR INHIBITORS IN COLORECTAL CARCINOMA PATIENTS

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Summary

Colorectal carcinoma (CRC) is the third most common type of cancer worldwide. Early stages of colorectal cancer are associated with good survival rates. However, most colorectal cancers are diagnosed at advanced stages when disease is no longer limited to bowel wall. Penetration through the bowel wall is partly attributed to disfunctionate extracellular matrix (ECM) remodeling.

Matrix metalloproteinases (MMPs) are enzymes that have an important role in ECM degradation. Activity of MMPs is controlled by tissue inhibitors of metalloproteinases or TIMPs. MMP-1, -2, -3. -7, -9, -13 blood levels correlate with the stage of disease. In fact, determining the concentrations of MMPs and TIMPs in plasma/serum may differentiate colorectal adenomas from colorectal carcinomas. Furthermore, a correlation between the anastomotic leakage in colorectal cancer surgery and levels of TIMP-1, MMP-8 and MMP-9 has been found. TIMP-1 was also considered in monitoring chemotherapy effects.

In this paper we review current applications of quantifying MMPs and TIMPs and their implications for clinical practice.

KEY WORDS: *Extracellular matrix, matrix metalloproteinase, tissue inhibitors of metalloproteinases, colorectal carcinoma*

POTENCIJAL MATRIKS METALOPROTEINAZA I NJIHOVIH INHIBITORA KOD BOLESNIKA S KOLOREKTALNIM KARCINOMOM

Sažetak

Kolorektalni karcinom je treći oblik tumora prema učestalosti u svijetu. Rani stadiji kolorektalnog karcinoma povezuju se s višom stopom preživljenja. Međutim, kod značajnog broja bolesnika s kolorektalnim karcinomom bolest se dijagnosticira u već uznapredovalom stupnju bolesti, koji karakterizira prodor tumora u stijenku crijeva, što dijelom doprinosi poremećaju pregradnje izvanstaničnoga matriksa.

Matriks metaloproteinaze (MMP) su enzimi koji imaju značajnu ulogu u pregradnji izvanstaničnog matriksa. Njihova je aktivnost regulirana posredstvom tkivnih inhibitora metaloproteinaza (TIMP). Koncentracije MMP-1, -2, -3. -7, -9, -13 u krvi koreliraju sa stupnjem bolesti. Mjerenjem koncentracija MMP i TIMP u plazmi /serumu može se razlikovati kolorektalni adenom od karcinoma. Nadalje, kod bolesnika s kolorektalnim karcinomom je pronađena povezanost između popuštanja anastomoze i koncentracija TIMP-1, MMP-8 i MMP-9. Dodatna moguća primjena TIMP-1 jest i praćenje učinka terapije.

U ovome je članku prikaz trenutno mogućih potencijala određivanja koncentracija MMP i TIMP te njihove primjene u kliničkoj praksi.

KLJUČNE RIJEČI: *Izvanstanični matriks, matriks metaloproteinaze, tkivni inhibitori metaloproteinaza, kolorektalni karcinom.*

INTRODUCTION

The extracellular matrix (ECM) is secreted by cells and surrounds the cells in tissues. It has long been believed to be merely the structural support to cells since its characteristics are specific to certain tissue morphology. Iextracellular matrix was shown not to be simply a passive, mechanical support for cells, but in fact an extraordinarily complex scaffold composed of a variety of biologically active molecules that are highly regulated and critical for determining the action and fate of the cells that it surrounds.

Degradation of ECM macromolecules is an important feature of morphogenesis, developement, tissue remodeling and repair. While, regulated in homeostasis, disregulation in degradation is observed many pathophysiological conditions (arthritis, nephritis, fibrosis, atherosclerosis, heart failure) as well as in carcinogenesis (1,2).

Heterogenous types of proteinases are involved in ECM degradation, but the key enzymes are considered to be matrixins or matrix metalloproteinases (MMPs), large family of calcium-requiring zinc endopeptidases. Activity of MMPs is specifically controlled by their inhibitors known as tissue inhibitors of metalloproteinases (TIMPs). In fact, balance between MMPs and TIMPs is essential in remodeling of ECM enviroment (3,4).

This review describes biological properties, structure, function of both, MMP and TIMP with the emphasis, their possible application as a diagnostic and prognostic tool in patients with colorectal cancer.

Extracellular matrix

Extracellular matrix is a complex mixture of negatively charged polysaccharides (glycosaminoglycans), adhesive glycoproteins (such fibronectin and lamin) and fibrous proteins (elastin, collagens), which is secreted by cells and surrounds them in tissues (5,6). ECM represents both structural support for cells (which is tissue specific mechanical support (through collagen, laminin, proteoglycan and fibronectin) and a signaling platform composed of diverse biologically active molecules which are strictly regulated and are critical in determining the function of these cells (proliferation *vs.* cell cycle arrest, motility *vs.* immobility, survival *vs.* apoptosis) (7).

In most carcinomas, ECM proteins are overexpressed: increasing crosslinked collagen type I is a marker of metastatic potential of tumor and poor prognosis in women with breast cancer; laminin expression positively correlates with invasiviness of tumors; proteoglycans are involved in cell adhesion and they are over-expressed in epithelial tumors; increased stroma fibronectin is an indicator of tumor progression in prostate cancer (8,9).

The communication between cells and between cells and their ECM is established through ligand-receptor interactions, which are the triggers of communication cascades which finaly result in changes in gene expression and consequently changes in ECM. One mechanism would be fibronectins binding to the integrins and transmitting the signal for cytoskeletal remodeling; growth factors bind to their receptors and initiate the cell growth. In fact, some proteins, like collagen and fibronectin, can imitate transforming growth factors (i.e. TGF- β) and activate its signaling pathway even in the absence of TGF-β receptors (10). The other mechanism would be that matrix proteins themselves apart from providing mechanical support, contain growth factor-like domains, which can bind to growth factor receptors, and thus stimulate the the cell growth.

Apart from extracellular growth stimulation tumours require new blood vessels for further growth. In normal tissue pro-angiogenic factors and endogenous inhibitors of angiogenesis are in balance. Tumor cells produce pro-angiogenic factors, such as angiogenic growth factors VEGF-A and FGF-2 which control matrix-degrading proteinases (11). When tumor cells secrete VEGF-A and FGF-2 in their microenvironment, they increase the activity of matrix-degrading proteinases and results in remodeling of ECM. Therefore, the inhibition of matrix-degrading proteinase activity may also stop or slow down neoangiogenesis and thereby slow down the tumor progression. This might be a new therapeutic strategy for antineoplastic treatment (12,13).

Matrix metalloproteinases

The matrix metalloproteinase family includes 24 proteinases. MMPs remodel tissue via degradation of ECM. MMPs are synthesized as proenzymes (in inactive form, proMMP). Proenzyme contains propeptide (part of about 80 amino ac-

ids), catalytic metalloproteinase domain (170 amino acids), a linker peptide variable length (hinge region) and hemopexin domain (200 amino acids) (14,15). MMPs secondary structure elements are three alpha-helixes and connecting loops. Position of alpha-helix and loops form MMP substrate binding catalytic domain. In accordance with their substrate specificity and structure MMPs are divided into 5 groups: collagenases, gelatinases, membrane type, stromelysins, matrilysins (16). Members of MMP family are described in detail in Table 1.

MMPs identify a hydrophobic amino acids (Leu, Ile, Met, Phe, Tyr) in target proteins and cleave a peptide bond before that part. MMP-12 is an exception, it cleaves in X-Lys bound (17). The hydrophobic amino acid residues fit into the enzyme active site S1′ pocket with variable depth depending on particular member of MMPs family. Other, noncatalitic domains also participate in the enzyme activity and specifity. For example, fibronectin domains of MMP-2 and MMP-9 are important for enzyme activity on type IV collagen, gelatin, and elastin. The loop region in MMP-1 just before the catalytic site helix is neccesery for collagenolytic activity (18).

MMPs are zinc-dependent endopeptidases. The essential zinc atom in the catalytic domain

Table 1.

FEATURES OD MATRIX METALLOPROTEINASES (1-17)

Designation	Common name	Chromosomal location	Structural class	Substrates
MMP-1	Collagenase-1, interstital collagenase, fibroblast collagenase, tissue collagenase	11q22-q23	Simple hemopexin domain	Type I and II fibrillar collagens
MMP-2	Gelatinase A, 72-kDa gelatinase, 72-kDa type IV collagenase, neutrophil gelatinase	16q13	Gelatin-binding	CCL2 CXCL 12
MMP-3	Stromelysin-1, transin-1, proteoglycanase, procollagenase-activating protein	11q23	Simple hemopexin domain	E-cadherin Laminin, type IV collagen Latent TGF β1
MMP-7	Matrilysin, matrin; PUMP1, small uterine metalloproteinase	11q21-q22	Minimal domain	Pro-α-defensins FAS ligand (CD95L) Latent TNF,Syndecan-1 E-cadherin,Elastin
MMP-8	Collagenase-2, neutrophil collagenase, granulocyte collagenase	11q21-q22	Simple hemopexin domain	Mouse CXCL5
MMP-9	Gelainase B, 92-kDa gelatinase, 92-kDa type IV collagenase	20q11,2-q13,1	Gelatin- binding	Zona occudens 1 α1-Antiproteinase Latent TGF-β1,Latent VEGF Fibrin,NG2 proteoglycan
MMP-10	Stromelysin-2, transin-2	11q22,3-q23	Simple hemopexin domain	/
MMP-11	Stromelysin-3	22q11,2	Furin-activated and secreted	/
MMP-12	Metalloelastase, macrophage elastase, macrophage metalloelastase	11q22,2-q22,3	Simple hemopexin domain	Lantent TNF
MMP-13	Collagenase-3	11q22,3	Simple hemopexin domain	Type I and II fibrillar collagens
MMP-14	MT1-MMP, MT-MMP1	14q11-q12	Transmembrane	ProMMP2,Fibrillar collagens Fibrin,Syndecan-1 γ 2-Subunit of laminin-5
MMP-15	MT2-MMP, MT-MMP2	15q13-q21	Transmembrane	Fibrin
MMP-16	MT3-MMP, MT-MMP3	8q21	Transmembrane	Fibrin Syndecan-1
MMP-17	MT4-MMP, MT-MMP4	12q24,3	GPI-linked	/

makes an intramolecular complex with the single cysteine residue in MMPs propeptide domain, a complex that blocks the activation of enzyme. After secretion, proMMPs can be activated with proteinases or nonproteolytic pathway (19,20). The most important event is the disassociation of the cysteine residue from the complex.

Activation of certain members of MMP family by plasmin is a part of fibrinolitic pathway in *in vivo* conditions. Plazmin is a product of plasminogen activation by tissue plasminogen activator and urokinase. It is known that plasmin can activate proMMP-1, proMMP-3, proMMP-7, proMMP-9, proMMP-10, and proMMP-13 (21,22). Activation of MMPs and interactions between fibrinolytic system and MMPs is shown in Figure 1.

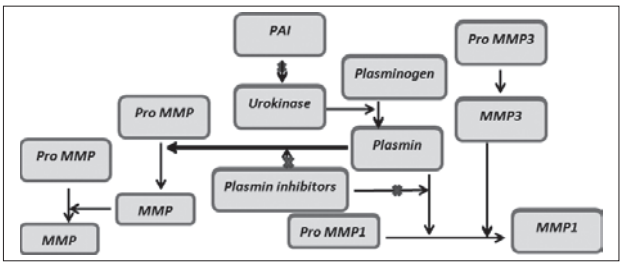

Figure 1. Interaction between fibrinolytic and metalloproteinase (MMP) systems

Activation of proMMPs is gradual: α_2-macroglobulin and TIMPs are types of regulatory mechanisms that inhibit and regulate MMP activity. Plasma glycoprotein (α_2-macroglobin) inhibits MMPs by entrapping them within the macroglobulin structure (23). The complex MMP- α_2-macroglobin is rapidly cleared by endocytosis (by LDL receptor-related protein-1) (24,25). TIMPs interfere with MMPs activation by interacting with the intermediate MMP before it is completely activated.

Tissue inhibitors of metalloproteinases

Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors of MMPs. Their expression influences development and tissue remodeling. In pathological conditions, such as carcinogenesis, changes of TIMP levels are important because of they effect on MMP activity.

TIMPs (21 to 29 kDa) are group of 4 proteins: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Protein N-domain consist about 125 and C-terminal domain 65 amino acids. TIMP has a wedge like shape like a wedge and binds to the catalytic metalloproteinase domain similar like a supstrate. The N-terminal four amino acid residues and the CD-loop region next to them on TIMP-2 molecule are main points of interaction with MMP. Two of four amino acid residues are strictly conserved cysteines that make disulfide bonds. Cysteins is important in chelating the zinc in catalytic domain by expelling the water molecule bound to the zinc. They are connected to one another in the stoichiometric ratio 1:1.

It has been proved that TIMPs inhibit all members of metalloproteinase family, except TIMP-1 which is a poor inhibitor for MT1-MMP, MT3-MMP, MT5-MMP and MMP-19. TIMP-3 inhibits ADAM-17 (TACE), ADAM-10, ADAM-12, and the aggrecanases (ADAMTS-4 and ADAMTS-5) in contrast to other TIMP (26,27). α –macroglobulins inhibit most proteinases in plasma. In solution MMP-1 prefers to react with α_2-macroglobulin more than with TIMP-1. Some other protein also have been reported to inhibit metalloproteinases. MMP-2 can be inhibited by the procollagen C-terminal proteinase enhancer protein and the secreted form of membrane-bound β-amyloid precursor protein. RECK, a GPI-anchored glycoprotein, may inhibit proteolytic activity of MMP-2, MMP-9, and MT1-MMP. Just MMP-2, but not MMP-1, MMP-3, and MMP-9, is inhibited by a scorpion toxin- chlorotoxin (28,29). Unfortunately, the accurate mechanisms of MMP inhibition by these proteins are yet not explained.

Relations of MMPs, TIMPs and colorectal cancer

Globally, colorectal carcinoma is the third most prevalent cacer worldwide. The highest risk of CRC development is observed in genetic predisposing people or with sporadic adenomatous polyp. Colorectal carcinogenesis is a complex, long-term, and multi-step malignant transformation process from normal epithelium to cancer cells, which includes numerous genetic changes and results in various phenotypic alterations.

Despite the continual improvement in surgical techniques and procedures as well as perioperative approach, colorectal cancer operations are accompanied by high mortality (5%), morbidity rates (20-40%) and postoperative complications (30,31).

The role of TIMP-1 in tumorogenesis was linked to inhibition of apoptosis, cell growth stimulation and angiogenesis disregulation (32,33,34). Furthermore, it seems that TIMP-1 has a promising prognostic potential (higher values are connected with shorter survival) (35,36).

On the other hand, significant over expression of MMP-1, -2, -3. -7, -9, -13 in colorectal carcinoma patients was noted along with the correlation of their concentration with the stage of disease (37,38). Moreover, colorectal carcinoma cells themselves produce MMP-7. Mutation of APC gene causes nuclear beta-Catenin/TCF complex accumulation, which then acts as transcriptional factor for MMP over expression (39). Association between increased expression of MMP-3 in colorectal cancer and levels of microsatelite instability and poor prognosis was also described (40). Furthermore, increased levels of MMP-9 were noted in early transition from colon adenoma to adenocarcinoma.

On the other hand, MMP-12 over-expression is associated with the better survival rates in colorectal carcinoma patients, probably through its inhibitory effect on angiogenesis.

Attempt of designing the drug with MMPs inhibitory properties were promising in animal model, but transition to humans proved disappointing, stressing once again multifactoriality and complexity of carcinogenesis. Recent research focus were matrix metalloproteinases MMPs-2 (gelatinase A) and -9 (gelatinase B) inhibitors due to their role in signal transduction via cell surface integral membrane proteins (CD44, αVβ/αβ1/αβ2 integrins and Ku protein) (41).

There are four types of TIMPs (1-4) in humas, with high degree of structural homology, but with quite different functions. While TIMP-1 inhibits angiogenesis directly through MMP-9 and VEGF, TIMP-2 selectively blocks the growth of microvascular endotel which is response to FGF-2 and VEGF-A. TIMP-3 promotes apoptosis, through caspase-8 pathway inhibits migration of endotel cells in vitro (42).

There are already several possible clinical apllications of MMPs and TIMPs levels in prognosis and treatment reponse. Immunohistochemistry depicted higher MMP-9 expression in moderately and poorly differentiated tumors compared with well differentiated ones. Over-expression of MMP-2 and MMP-9 is associated with worse five-year survival. These two gelatinases are prognostically significant in both colon and rectal carcinoma (37). Gradual increase in immunostaining positivity for MMP-2, MMP-9, TIMP-1 and TIMP-2 was associated with tumor progression.

Plasma/serum concentration of MMPs and TIMPs may differentiate colorectal adenomas from colorectal carcinomas. Clinical trials are opened which explore their elligability for standard tumor stage markers. On the other hand, connection between elevated intraperitoneal concentration of MMP-8 and MMP-9 and the possibility of anastomotic leakage development after rectal cancer surgery has been researched for prediction of anastomotic leak risk (43). Another posible use of TIMP-1, due to its increased levels in apoptosis, could be the monitoring of the chemotherapy effect.

CONCLUSION

Cancer cells and normal human cells are surrounded by extracellular matrix (ECM). ECM used to be considered a passive cells environment, but now it is viewed as a dynamic communication matrix which may play a role in cancer development and progression. Heterogenous types of proteinases are involved in ECM degradation amongst which are matrix metalloproteinases (MMPs). Their inhibitors are TIMPs - tissue inhibitors of metalloproteinases. Changes in MMPs and TIMPs concentrations in serum/plazma correlate with patient's survival. Intraperitoneal concentrations correlate with the risk of anastomotic leak in patient after rectal cancer surgery. Therefore, these parameters might be introduced in anastomotic leak assessment and monitoring chemotherapy effect.

LITERATURE

1. Parangi S, O'Reilly M, Christofori G, Holmgren L, Grosfeld J, Folkman J, Hanahan D. Antiangiogenic therapy of transgenic mice impairs de novo tumor growth. Proc Natl Acad Sci U S A. 1996;93(5):2002-7.
2. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell. 1996;86(3):353-64.
3. Meijer MJ, Mieremet-Ooms MA, van der Zon AM, van Duijn W, van Hogezand RA, Sier CF, Hommes DW,

Lamers CB, Verspaget HW. Increased mucosal matrix metalloproteinase-1, -2, -3 and -9 activity in patients with inflammatory bowel disease and the relation with Crohn's disease phenotype. Dig Liver Dis. 2007; 39(8):733-9.

4. Kapsoritakis AN, Kapsoritaki AI, Davidi IP, Lotis VD, Manolakis AC, Mylonis PI, Theodoridou AT, Germenis AE, Potamianos SP. Imbalance of tissue inhibitors of metalloproteinases (TIMP) - 1 and - 4 serum levels, in patients with inflammatory bowel disease. BMC Gastroenterol. 2008;8:55.
5. Iozzo RV. Matrix proteoglycans: from molecular design to cellular function. Annu Rev Biochem. 1998;67: 609-52.
6. Stetler-Stevenson WG. Dynamics of matrix turnover during pathologic remodeling of the extracellular matrix. Am J Pathol. 1996;148(5):1345-50.
7. Nelson CM, Bissell MJ. Of Extracellular Matrix, Scaffolds, and Signaling: Tissue Architecture Regulates Development, Homeostasis, and Cancer. Annu Rev Cell Dev Biol. 2006;22:287-309.
8. Denys H, Braems G, Lambein K, Pauwels P, Hendrix A, De Boeck A, Mathieu V, Bracke M, De Wever O. The extracellular matrix regulates cancer progression and therapy response: implications for prognosis and treatment. Curr Pharm Des. 2009;15(12):1373-84.
9. Riaz M, Sieuwerts AM, Look MP, Timmermans MA, Smid M, Foekens JA, Martens JW. High TWIST1 mRNA expression is associated with poor prognosis in lymph node-negative and estrogen receptor-positive human breast cancer and is co-expressed with stromal as well as ECM related genes. Breast Cancer Res. 2012;14(5):R123.
10. Dang D, Yang Y, Li X, Atakilit A, Regezi J, Eisele D, Ellis D, Ramos DM. Matrix metalloproteinases and TGFbeta1 modulate oral tumor cell matrix. Biochem Biophys Res Commun. 2004;316(3):937-42.
11. Cheng N, Chytil A, Shyr Y, Joly A, Moses HL. Transforming growth factor-beta signaling-deficient fibroblasts enhance hepatocyte growth factor signaling in mammary carcinoma cells to promote scattering and invasion. Mol Cancer Res. 2008;6(10):1521-33.
12. Hanada M, Feng J, Hemmings BA. Structure, regulation and function of PKB/AKT-a major therapeutic target. Biochim Biophys Acta. 2004;1697(1-2):3-16.
13. Kelly RJ, Morris JC. Transforming growth factor-beta: a target for cancer therapy. J Immunotoxicol. 2010; 7(1):15-26.
14. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. Annu Rev Cell Dev Biol. 2001;17:463-516.
15. Amălinei C, Căruntu ID, Bălan RA. Biology of metalloproteinases. Rom J Morphol Embryol. 2007;48(4): 323-34.
16. Murphy G, Houbrechts A, Cockett MI, Williamson RA, O'Shea M, Docherty AJ. The N-terminal domain of tissue inhibitor of metalloproteinases retains metalloproteinase inhibitory activity. Biochemistry. 1991;30 (33):8097-102.
17. Gronski TJ Jr, Martin RL, Kobayashi DK, Walsh BC, Holman MC, Huber M, Van Wart HE, Shapiro SD. Hydrolysis of a broad spectrum of extracellular matrix proteins by human macrophage elastase. J Biol Chem. 1997;272(18):12189-94.
18. Murphy G, Nguyen Q, Cockett MI, Atkinson SJ, Allan JA, Knight CG, Willenbrock F, Docherty AJ. Assessment of the role of the fibronectin-like domain of gelatinase A by analysis of a deletion mutant. J Biol Chem. 1994;269(9):6632-6.
19. Giannelli G, Falk-Marzillier J, Schiraldi O, Stetler-Stevenson WG, Quaranta V. Induction of cell migration by matrix metalloprotease-2 cleavage of laminin-5. Science. 1997;277(5323):225-8.
20. Kajita M, Itoh Y, Chiba T, Mori H, Okada A, Kinoh H, Seiki M. Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. J Cell Biol. 2001;153(5):893-904.
21. Baramova EN, Bajou K, Remacle A, L'Hoir C, Krell HW, Weidle UH, Noel A, Foidart JM. Involvement of PA/plasmin system in the processing of pro-MMP-9 and in the second step of pro-MMP-2 activation. FEBS Lett. 1997;405(2):157-62.
22. Ramos-DeSimone N, Hahn-Dantona E, Sipley J, Nagase H, French DL, Quigley JP. Activation of matrix metalloproteinase-9 (MMP-9) via a converging plasmin/stromelysin-1 cascade enhances tumor cell invasion. J Biol Chem. 1999;274(19):13066-76.
23. Oleksyszyn J, Augustine AJ. Plasminogen modulation of IL-1-stimulated degradation in bovine and human articular cartilage explants. The role of the endogenous inhibitors: PAI-1, alpha 2-antiplasmin, alpha 1-PI, alpha 2-macroglobulin and TIMP. Inflamm Res. 1996;45(9):464-72.
24. Cáceres LC, Bonacci GR, Sánchez MC, Chiabrando GA. Activated α(2) macroglobulin induces matrix metalloproteinase 9 expression by low-density lipoprotein receptor-related protein 1 through MAPK-ERK1/2 and NF-κB activation in macrophage-derived cell lines. J Cell Biochem. 2010;111(3):607-17.
25. Barchowsky A, Frleta D, Vincenti MP. Integration of the NF-kappaB and mitogen-activated protein kinase/AP-1 pathways at the collagenase-1 promoter: divergence of IL-1 and TNF-dependent signal transduction in rabbit primary synovial fibroblasts. Cytokine. 2000; 12(10):1469-79.
26. Brennan FM, Green P, Amjadi P, Robertshaw HJ, Alvarez-Iglesias M, Takata M. Interleukin-10 regulates TNF-alpha-converting enzyme (TACE/ADAM-17) involving a TIMP-3 dependent and independent mechanism. Eur J Immunol. 2008;38(4):1106-17.
27. Wei S, Kashiwagi M, Kota S, Xie Z, Nagase H, Brew K. Reactive site mutations in tissue inhibitor of metalloproteinase-3 disrupt inhibition of matrix metalloproteinases but not tumor necrosis factor-alpha-converting enzyme. J Biol Chem. 2005;280(38):32877-82.

28. Oh J, Takahashi R, Kondo S, Mizoguchi A, Adachi E, Sasahara RM, Nishimura S, Imamura Y, Kitayama H, Alexander DB, Ide C, Horan TP, Arakawa T, Yoshida H, Nishikawa S, Itoh Y, Seiki M, Itohara S, Takahashi C, Noda M. The membrane-anchored MMP inhibitor RECK is a key regulator of extracellular matrix integrity and angiogenesis. Cell. 2001;107(6):789-800.
29. Herman MP, Sukhova GK, Kisiel W, Foster D, Kehry MR, Libby P, Schönbeck U. Tissue factor pathway inhibitor-2 is a novel inhibitor of matrix metalloproteinases with implications for atherosclerosis. J Clin Invest. 2001;107(9):1117-26.
30. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22(4):191-7.
31. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010;46(4):765-81.
32. Baker AH, Zaltsman AB, George SJ, Newby AC. Divergent effects of tissue inhibitor of metalloproteinase-1, -2, or -3 overexpression on rat vascular smooth muscle cell invasion, proliferation, and death in vitro. TIMP-3 promotes apoptosis. J Clin Invest. 1998;101 (6):1478-87.
33. Thorgeirsson UP, Yoshiji H, Sinha CC, Gomez DE. Breast cancer; tumor neovasculature and the effect of tissue inhibitor of metalloproteinases-1 (TIMP-1) on angiogenesis. In Vivo. 1996;10(2):137-44.
34. Ikenaka Y, Yoshiji H, Kuriyama S, Yoshii J, Noguchi R, Tsujinoue H, Yanase K, Namisaki T, Imazu H, Masaki T, Fukui H. Tissue inhibitor of metalloproteinases-1 (TIMP-1) inhibits tumor growth and angiogenesis in the TIMP-1 transgenic mouse model. Int J Cancer. 2003;105(3):340-6.
35. Dechaphunkul A, Phukaoloun M, Kanjanapradit K, Graham K, Ghosh S, Santos C, Mackey JR. Prognostic significance of tissue inhibitor of metalloproteinase-1 in breast cancer. Int J Breast Cancer. 2012;2012:290854.
36. Lee JH, Choi JW, Kim YS. Plasma or serum TIMP-1 is a predictor of survival outcomes in colorectal cancer: a meta-analysis. J Gastrointestin Liver Dis. 2011;20(3): 287-91
37. Langers AM, Verspaget HW, Hawinkels LJ, Kubben FJ, van Duijn W, van der Reijden JJ, Hardwick JC, Hommes DW, Sier CF. MMP-2 and MMP-9 in normal mucosa are independently associated with outcome of colorectal cancer patients. Br J Cancer. 2012;106(9):1495-8.
38. Bendardaf R, Buhmeida A, Hilska M, Laato M, Syrjänen S, Syrjänen K, Collan Y, Pyrhönen S. MMP-9 (gelatinase B) expression is associated with disease-free survival and disease-specific survival in colorectal cancer patients. Cancer Invest. 2010 Jan;28(1):38-43.
39. Hlubek F, Spaderna S, Jung A, Kirchner T, Brabletz T. Beta-catenin activates a coordinated expression of the proinvasive factors laminin-5 gamma2 chain and MT1-MMP in colorectal carcinomas. Int J Cancer. 2004;108(2):321-6.
40. Ortega P, Morán , de Juan C, Frías C, Hernández S, López-Asenjo JA, Sánchez-Pernaute A, Torres A, Iniesta P, Benito M. Differential Wnt pathway gene expression and E-cadherin truncation in sporadic colorectal cancers with and without microsatellite instability.Clin Cancer Res. 2008;14(4):995-1001.
41. Bauvois B. New facets of matrix metalloproteinases MMP-2 and MMP-9 as cell surface transducers: outside-in signaling and relationship to tumor progression. Biochim Biophys Acta. 2012;1825(1):29-36.
42. Yuan LQ, Liu YS, Luo XH, Guo LJ, Xie H, Lu Y, Wu XP, Liao EY. Recombinant tissue metalloproteinase inhibitor-3 protein induces apoptosis of murine osteoblast MC3T3-E1.Amino Acids. 2008;35(1):123-7.
43. Pasternak B, Matthiessen P, Jansson K, Andersson M, Aspenberg P. Elevated intraperitoneal matrix metalloproteinases-8 and -9 in patients who develop anastomotic leakage after rectal cancer surgery: a pilot study. Colorectal Dis. 2010;12:e93-8.

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