MINIREVIEW

Role of Matrix Metalloproteinase-7 (Matrilysin) in Human Cancer Invasion, Apoptosis, Growth, and Angiogenesis

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Matrix metalloproteinase (MMP)-7, also known as matrilysin, is a "minimal domain MMP" that exhibits proteolytic activity against components of the extracellular matrix (ECM). Matrilysin is frequently overexpressed in human cancer tissues and is associated with cancer progression. Tumorigenesis is a multistep process involving cell growth, invasion, metastasis, and angiogenesis. Matrilysin has been shown to play important roles not only in degradation of ECM proteins, but also in the regulation of several biochemical processes such as activation, degradation, and shedding of non-ECM proteins. This minireview provides a summary of the current literature on the roles of matrilysin in tumorigenesis with a focus on the roles of modifications of non-ECM proteins by matrilysin and other related MMPs in tumorigenesis. Proteolysis of insulin-like growth factor binding protein by matrilysin results in increased bioavailability of insulin-like growth factors and enhanced cellular proliferation. Matrilysin has also been implicated in the ectodomain shedding of several cell surface molecules. Heparin-binding epidermal growth factor precursor (proHB-EGF) is cleaved by matrilysin into mature HB-EGF, which promotes cellular proliferation. Membrane-bound Fas ligand (FasL) is cleaved into soluble FasL, which increases apoptosis of cells adjacent to tumor cells. E-cadherin is converted to soluble E-cadherin to promote invasion. Tumor necrosis factor (TNF)-alpha precursor is cleaved to release soluble TNF-alpha to increase apoptosis. We propose that these matrilysin-mediated pathways provide the *necessary* and logical mechanisms to promote cancer progression. Exp Biol Med 231:20–27, 2006

Key words: matrix metalloproteinase matrilysin; cancer; ectodomain shedding; apoptosis; growth

Introduction

The extracellular matrix (ECM) provides a structural framework to support cells and maintains cellular functions by mediating cell-cell or cell-ECM interactions. The ECM is composed of collagen, elastin, proteoglycans, and other molecules. Cellular growth and migration are critically dependent on turnover and remodeling of the ECM, which is regulated by an exquisite balance between the synthesis and degradation of ECM proteins. Degradation of ECM components is mostly controlled by proteolytic enzymes called matrix metalloproteinases (MMP)s. The MMP family consists of at least 25 zinc-dependent endopeptidases that function at neutral pH. Almost all MMPs share homologous protein sequences and domain structures. In addition to these conserved domains, MMPs have diverse domains that are related to substrate specificity and recognition of other proteins. However, MMP-7 (matrilysin), MMP-23, and MMP-26 lack a C-terminal hemopexin domain common to other MMP members, and they have distinctively smaller molecular weights.

MMPs are synthesized as latent enzymes (zymogens) that are secreted or membrane-associated, and must be proteolytically processed to their active forms. As for matrilysin, this protein is secreted as a 28-kDa proenzyme and can be activated through proteolytic removal of a 9-kDa prodomain from the N-terminus. Zymography can separate

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proteinases on the basis of molecular weight under denaturing conditions. Thus, inactive and active forms can be distinguished according to molecular weight by zymography. Promatrilysin can be activated by endoproteinases, plasmin, and trypsin (1–4). Experimentally, activation of promatrilysin can be achieved by incubation with mercurial compounds such as 4-aminophenyl mercuric acetate (APMA). Recently developed *in situ* zymography using a carboxymethylated transferrin as a substrate enables determination of the localization of active matrilysin *in vivo* (5). This may be a useful method to further understand the functions of matrilysin in pathophysiological conditions.

Several excellent reviews have already addressed the roles of matrilysin in tumorigenesis (1–4). Therefore, this minireview summarizes recent knowledge about the roles of matrilysin in tumorigenesis, highlighting modifications of non-ECM proteins by matrilysin and other related MMPs.

Association of MMPs with Cancers

Matrix metalloproteinases play a key role not only in normal processes of ECM degradation, but also in pathological processes such as tissue remodeling of inflammatory diseases, cancer invasion, and metastasis. Expression of MMPs is generally up-regulated in a wide range of malignant tumors. There is substantial evidence that overexpression of MMPs correlates with a more aggressive phenotype of tumor cells and poorer prognosis.

It was initially believed that MMPs, through degradation of ECM components, were primarily involved in tumor invasion, intravasation into the blood or lymphatic circulation, extravasation from the circulation, and local migration at metastatic sites (3). There is a general correlation between the levels of MMP expression and the stage of tumor progression. However, there is growing evidence that MMPs have expanded roles, as they are necessary for the creation and maintenance of a microenvironment that facilitates growth and angiogenesis of tumors at primary and metastatic sites (3).

As scientific understanding of MMPs has advanced, therapeutic strategies that inhibit activities of MMPs have rapidly developed. RNA interference (RNAi) is a process in which double-stranded RNA triggers the degradation of a homologous messenger RNA. RNAi-mediated gene-silencing technology has recently been used to inhibit the activities of MMPs (6, 7).

Roles of MMPs Other than in ECM Degradation

Aside from degrading ECM substrates, certain MMPs are involved in the regulation of activities of bioactive molecules associated with cell physiology (Fig. 1). These molecules include cytokines and cytokine receptors, growth factors and growth factor receptors, and cell adhesion molecules. For example, cell surface–anchored MMP-9 activates transforming growth factor-β (TGF-β) and facilitates tumor invasion and angiogenesis (8).

Furthermore, several MMPs have been implicated in ectodomain shedding. Ectodomain shedding, often referred to simply as "shedding," is a process by which the extracellular domain of a transmembrane molecule is proteolytically removed from the cell surface (Fig. 2). This process can alter cell surface signaling by cleavage of a transmembrane molecule or provoke a cell-tissue interaction by subsequent release of a soluble ectodomain.

Biochemical Processes Mediated by Matrilysin

Matrilysin is one of the few MMP family members expressed in polarized glandular epithelium (3). Therefore, the function of matrilysin may be influenced by its release to either the apical or basolateral compartments (or both), through which matrilysin would act on its various substrates (9). Matrilysin has been shown to be constitutively expressed in the ductal and glandular epithelium of normal mammary and parotid glands, liver, pancreas, prostate, and the peribronchial glands and conducting airways in the lung (9). Immunohistochemical analyses have shown matrilysin staining in the glandular epithelium to be primarily apical and lumenal with little or no basolateral staining within the cells or at the cell surface (9). Matrilysin also plays an important role in the maintenance of innate immunity in organs such as the lung and intestine, where matrilysin proteolytically activates antibacterial peptides such as prodefensins (10, 11). The precursor of mouse Paneth cell α-defensins (cryptdins), antimicrobial propeptides that are relevant to intestinal host defense, is cleaved by matrilysin to generate mature defensin (11). During tumor progression, matrilysin is expressed in benign and malignant tumors that arise from the glandular epithelium. Matrilysin has a broad substrate specificity against ECM components, including elastin, type IV collagen, fibronectin, vitronectin, aggrecan, and proteoglycans (Table 1) (1–4). Matrilysin is also involved in the regulation of several bioactive substances other than ECM components. Like several other MMPs, recent studies have indicated that matrilysin plays an important role in ectodomain shedding of cell-surface molecules, such as tumor necrosis factor-α (TNF-α) precursor (12, 13), Fas ligand (FasL) (14, 15), heparin-binding epidermal growth factor (HB-EGF) (16), E-cadherin (17), and β4-integrin (18). Tumor necrosis factor-α, FasL, and HB-EGF are localized apically; and E-cadherin, β4-integrin, and various ECM components are localized basolaterally. The mechanism by which matrilysin secretion is regulated in a polarized system has been partially elucidated (9). Using an *in vitro* model system, Harrell *et al.* (9) examined the pattern of matrilysin secretion in the polarized epithelium. Latent matrilysin was secreted primarily to the basolateral compartment, as would be expected for a matrix-degrading protease. However, matrilysin was more active in the apical compartment, suggesting the co-release of matrilysin activator(s). These findings warrant

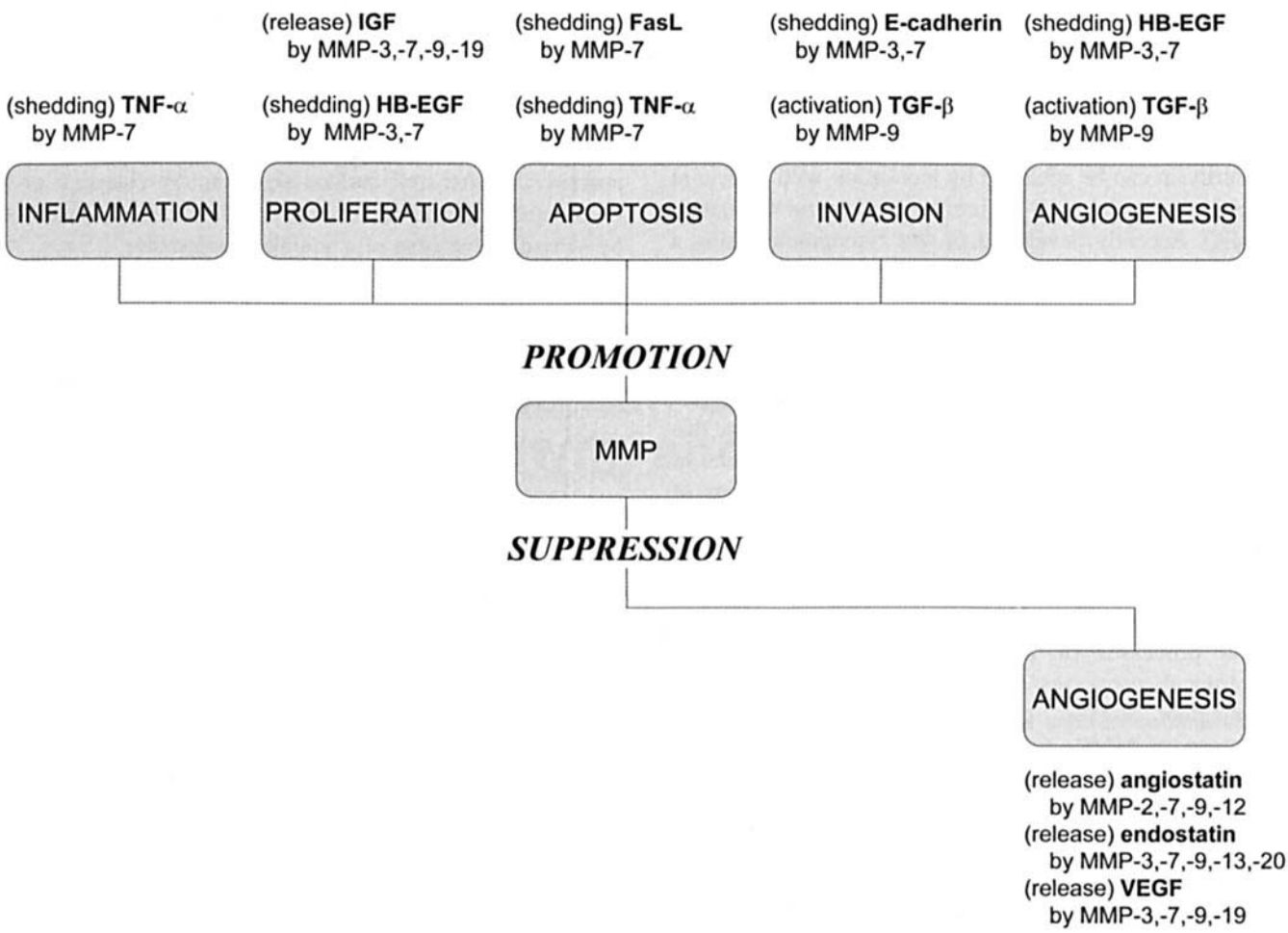

Figure 1. Regulation of the activities of bioactive molecules by MMPs. All references are cited in the text. TNF-α, tumor necrosis factor-α; IGF, insulin-like growth factor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; FasL, Fas ligand; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

further investigation to better understand the mechanism of action of matrilysin *in vivo*.

Features of Matrilysin in Cancers

Distribution of Matrilysin in Cancers. Matrilysin appears to be quite unique in its restricted expression in tumor cells. Although the majority of MMPs are produced predominantly by stromal cells, such as stromal fibroblasts, macrophages, and endothelial cells, only a few MMPs, including matrilysin, are expressed by tumor cells themselves, indicating that matrilysin is expressed in a tumor-associated fashion. The production by tumor cells themselves could be useful as a biological marker of an aggressive phenotype and as a target of therapeutic intervention.

Matrilysin is overexpressed in a variety of epithelial tumors and mesenchymal tumors. We and other researchers have demonstrated that matrilysin is overexpressed in invasive cancers of the digestive organs, such as the esophagus (19), stomach (20), colon (21–23), liver (24), and pancreas (25, 26). There is substantial evidence that the expression of matrilysin is associated with advanced clinicopathological stages and unfavorable prognosis (19, 22–26). Matrilysin is also overexpressed in cancers of other organs (1–4) such as the lung (27), skin (28), breast (29), prostate (30), and head and neck (31). In colorectal cancer, we have shown that the lumenal surface of neoplastic glands in the superficial layer was apically stained, whereas the cytoplasm of cancer cells at the invasive front was diffusely and basolaterally stained for matrilysin (22). Basolateral staining of matrilysin in cancer cells at the invasive front has been observed in a variety of epithelial tumors, suggesting a direct role of matrilysin as a matrix-degrading protease.

The functional polymorphism in the matrilysin promoter (–181A/G) has, interestingly, been shown to increase susceptibility to esophageal squamous cell carcinoma, gastric cardiac adenocarcinoma, and non–small-cell lung carcinoma (32). It would be interesting to analyze whether this polymorphism also increases susceptibility to other tumors characterized by matrilysin overexpression.

Role of Matrilysin in Cancer Invasion. Like other MMPs, matrilysin can promote cancer invasion by proteolytic cleavage of the ECM substrates. Matrilysin also

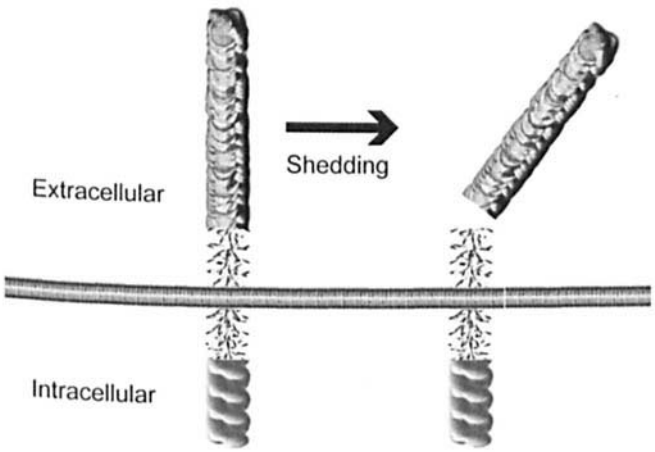

Figure 2. Proteolytic shedding of a transmembrane molecule. The substrate is cleaved by MMPs in the juxtamembrane region of the extracellular domain. This releases soluble protein into the pericellular space.

activates other MMPs, such as proMMP-2 and proMMP-9, to facilitate tumor invasion (Table 1) (33, 34). We and other researchers previously reported that matrilysin promotes *in vitro* invasiveness of cancer cells of the stomach, colon, and pancreas, and that matrilysin expression is correlated with invasiveness of cancer tissues of the esophagus, stomach, colon, liver, and pancreas (19, 21–26, 35).

Matrilysin is also involved in tumor invasion through regulation of the activities of non-ECM proteins. E-cadherin, a transmembrane protein, is involved in the positive regulation of cell adhesion by its interaction with the cytoplasmic tail of catenins. Matrilysin and MMP-3 release soluble E-cadherin through ectodomain shedding of E-cadherin (17) (Fig. 3). Resulting soluble E-cadherin inhibits E-cadherin function in a paracrine way, promoting the migration and invasion of tumor cells.

In a rodent model that mimics the osteoblastic and osteolytic changes associated with human metastatic prostate cancer, matrilysin produced by osteoclasts was capable of processing the receptor activator of nuclear factor–kappa B ligand (RANKL) to a soluble form that promoted osteoclast activation (36). Thus, this study demonstrated a molecular mechanism by which matrilysin promotes prostate cancer-induced bone resorption.

Role of Matrilysin in Cancer Growth. Matrilysin has been shown to influence the early stage of tumorigenesis (3, 37, 38). Modification of non-ECM proteins by matrilysin is one of the mechanisms by which matrilysin plays a role in early tumorigenesis. Matrilysin sheds the ectodomain of HB-EGF precursor (proHB-EGF) to yield mature HB-EGF, which promotes cellular proliferation by activating the ErbB4 receptor and inhibits apoptosis (16).

The insulin-like growth factor (IGF) system, through its mitogenic and antiapoptotic effects, plays an important role in tumorigenesis. The bioavailability of IGFs is regulated by interactions with IGF binding proteins (IGFBPs). Proteolytic modification of IGFBPs increases the bioavailabilty of IGFs. MMP-3 (39, 40), matrilysin (41), MMP-9 (40), and MMP-19 (42) are involved in the regulation of the IGF axis through their proteolytic action on IGFBPs such as IGFBP-3. Importantly, it has recently been shown that matrilysin degrades all six IGFBPs (IGFBP-1 to IGFBP-6), thus increasing the bioavailability of IGFs, and thereby favoring cancer cell growth and survival (43). ADAM28, a member of the disintegrin and metalloproteinase (ADAM) family, is also a substrate of matrilysin (44). It has been reported that secreted form ADAM28 activated by matrilysin also digests

Table 1. Biochemical Process Mediated by Matrilysin[a]

Function	Substrate	Localization
Degradation	Elastin	ECM
	Type IV collagen	ECM
	Fibronectin	ECM
	Vitronectin	ECM
	Aggrecan	ECM
	Proteoglycans	ECM
	IGFBP-1,-2,-3,-4,-5,-6	Serum
	Plasminogen	Serum
Activation	ADAM28	Lymphocytes, some cancer cells
	Intestinal a-defensin	Paneth cells in small intestinal crypts
	proMMP-2	Miscellaneous
	proMMP-9	Miscellaneous
Shedding	β4 integrin	Cell surface
	E-cadherin	Cell surface
	FasL	Cell surface
	proHB-EGF	Cell surface
	TNF-α precursor	Cell surface

[a] All references are cited in the text.

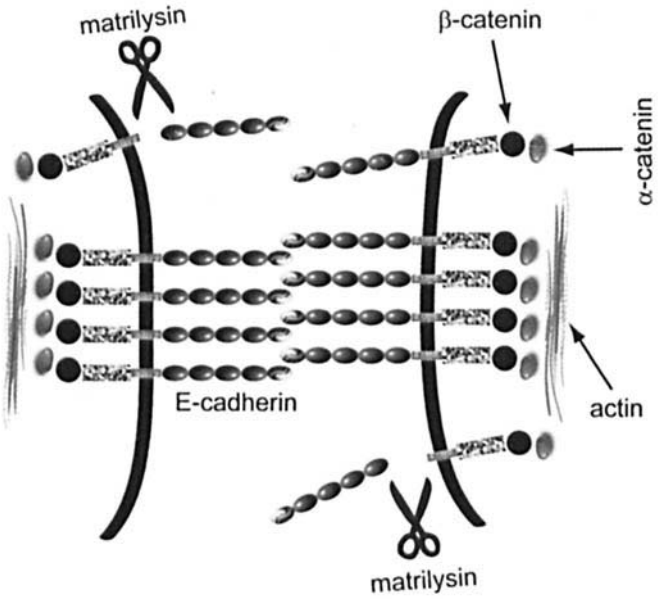

Figure 3. Disruption of the E-cadherin adherence junctions by matrilysin. The extracellular domain of E-cadherin forms a "molecular zipper" via the interaction with other E-cadherin proteins on adjacent cells. The cytoplasmic domain of E-cadherin interacts directly with β- and γ-catenin in a protein complex that is linked to the actin cytoskeleton via α-catenin. Matrilysin mediates cleavage of the E-cadherin ectodomain, resulting in disruption of the E-cadherin/catenin complex.

IGFBP-3 in both free and complex forms with IGF-I or IGF-II.

In the *in vitro* model system mentioned above, apically active matrilysin increased cell proliferation and cell saturation density (9). Therefore, identifying matrilysin substrates specifically at the apical cellular membrane domain of the glandular epithelium will allow us to further understand the mechanism of action of matrilysin *in vivo* (9).

Role of Matrilysin in Apoptosis. Programmed cell death or apoptosis is a physiological process by which unwanted cells are removed. Apoptosis can be triggered by a wide variety of stimuli. FasL, a transmembrane stimulator of the death receptor Fas, is one of the major apoptosis inducers.

Previous studies have shown that matrilysin sheds the ectodomain of membrane-bound FasL (mFasL) from non-cancer and cancer cell membranes to generate soluble FasL (sFasL) (14, 15). Released sFasL increases apoptosis in surrounding cells through the activation of Fas (Fig. 4A). However, cancer cells are refractory to this proapoptotic signal (Fig. 4B). Possible reasons for the discrepancy between the apoptotic action of normal surrounding cells and the antiapoptotic action of cancer cells are that sFasL conveys a reduced apoptotic potency compared with mFasL (45) and that most cancer cells are relatively resistant to Fas-mediated apoptosis as a result of abnormalities in the level of several proteins involved in the signal transduction cascade (46).

Tumor necrosis factor-α can be slowly cleaved from the cell surface by matrilysin, producing a bioactive cytokine, soluble TNF-α (13), which may increase apoptosis through binding to the TNF-receptor 1. However, the cleavage of TNF-α by matrilysin showed about 30-fold lower specificity constant relative to TNF-α converting enzyme (TACE) (13). The functional significance of the cleavage of TNF-α by matrilysin *in vivo* needs to be further clarified.

Role of Matrilysin in Angiogenesis. Angiogenesis, also referred to as neovascularization, is a process of growth or development of new blood vessels. This phenomenon is essential for cancer cells to enlarge and invade surrounding tissues. During angiogenesis, MMPs are assumed to play a role in the formation of openings within the ECM through which *de novo* capillaries can expand and extend. Previous studies showed that several MMPs are expressed in vascular endothelial cells adjacent to tumor cells, suggesting their involvement in angiogenesis. For example, MMP-2 and MMP-9 were immunostained in the vascular structures of human astrocytic and oligodendroglial gliomas (47). Matrilysin mRNA and protein were detected among the vascular endothelial cells near matrilysin-positive tumor cells by *in situ* hybridization and immunohistochemistry (48). Furthermore, matrilysin has been shown to accelerate the proliferation of human umbilical vein endothelial cells in a dose-dependent manner *in vitro* (49). Recent investigation using immunohistochemistry in gastric cancer has revealed that microvessel density was correlated with matrilysin expression (50). Another study showed that matrilysin stimulates DNA synthesis of cultured vascular endothelial cells estimated by thymidine uptake (51). Moreover, matrilysin-induced angiogenesis at the site at which human colon cancer cells were implanted in a mice model was inhibited by a matrilysin-specific antisense oligonucleotide (51). These results suggest that matrilysin directly induces angiogenesis, at least in part, through proliferative action on vascular endothelial cells.

On the other hand, MMPs also serve to inhibit angiogenesis by generating polypeptides that have anti-angiogenic effects. MMP-2 (52), matrilysin (53, 54), MMP-9 (53, 54), and MMP-12 (55) are capable of cleaving human plasminogen to produce an angiostatin fragment that is a circulating inhibitor of angiogenesis. Resulting angiostatin reduces endothelial cell proliferation and promotes endothelial cell apoptosis, and thus acts as a potent inhibitor of tumor growth (56). Endostatin, another angiogenesis inhibitor, also has the potential to inhibit the growth of blood vessels. An endostatin-containing fragment was generated from collagen type XVIII by MMP-3, matrilysin, MMP-9, MMP-13, and MMP-20 *in vitro* (57) and by matrilysin *in vivo* (58). Moreover, neostatin-7, the C-terminal 28-kDa endostatin-spanning proteolytic fragment, is generated from the proteolytic action of matrilysin on type XVIII collagen. Antiangiogenic properties of neostatin-7 have recently been characterized (59). However, the contribution of MMP-mediated generation of these cleavage

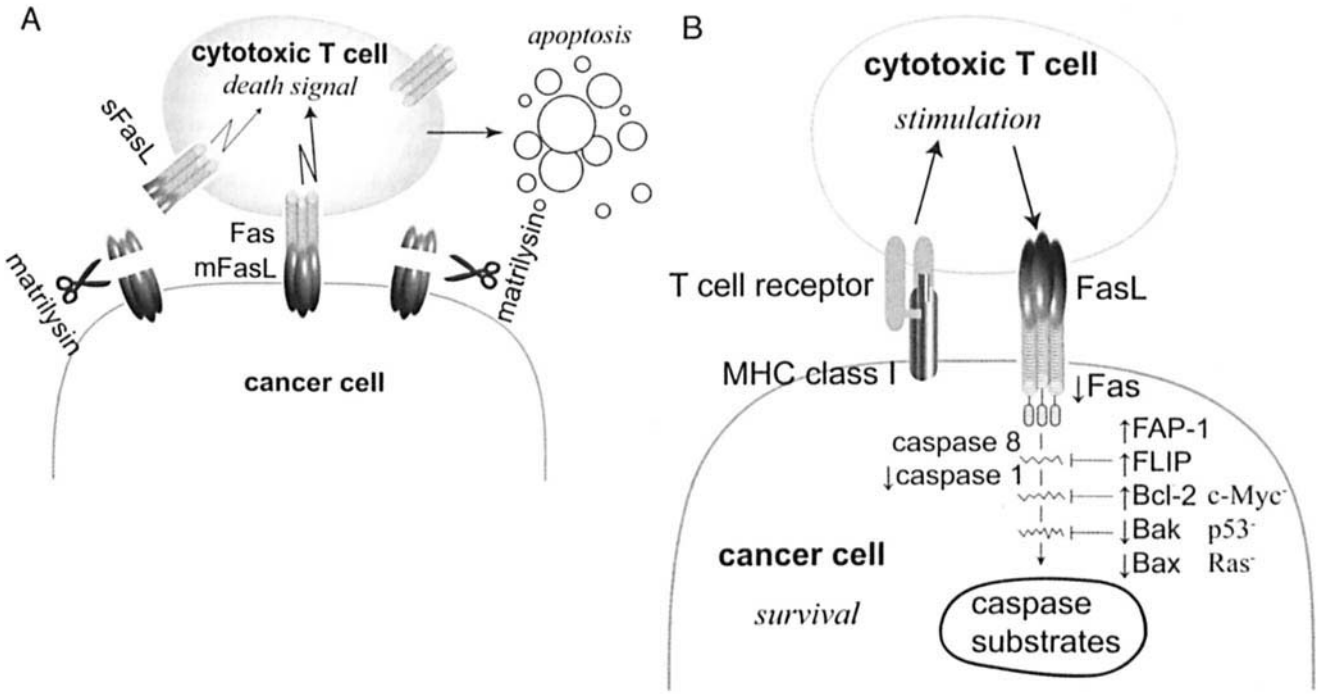

Figure 4. (A) Apoptosis of a cytotoxic T cell (CTL) mediated by a cancer cell. Membrane-bound FasL (mFasL) on the cancer cell plasma membrane binds to its receptor, Fas, on the T cell, and thereby induces apoptosis of Fas-expressing CTLs. Matrilysin mediates the shedding of mFasL from the cell membrane to generate soluble FasL, and this may further contribute to the apoptotic signal acting on the CTL. (B) Model of cancer cell resistance to Fas-mediated apoptosis. The activated CTL expresses FasL, which binds to the Fas-expressing cancer cell. Several proteins involved in the Fas signal transduction cascade have the potential for abnormal function or anomalous expression, each of which may result in failure to induce apoptosis of the target cell. In addition, mutation of some oncogenes and tumor suppressor genes can potentially impair Fas signaling (p53 and Ras), or cooperate with Fas resistance (c-Myc). (adapted from Reference 46, with permission from Elsevier).

products to the control of physiological and tumor angiogenesis remains to be determined.

Vascular endothelial growth factor (VEGF) is one of the most potent mediators of angiogenesis. A recent study has shown that MMP-3, matrilysin, MMP-9, and MMP-19 can cleave matrix-bound isoforms of VEGF, releasing it from the matrix as soluble fragments (60). Thus, soluble VEGF is made by either MMP-dependent cleavage or by messenger RNA splicing, which removes the matrix attachment region. However, contrary to expectations, soluble VEGF was less effective than matrix-bound VEGF in supporting the vessel growth needed for tumor survival, suggesting that soluble VEGF and matrix-bound VEGF provide different signaling outcomes even though they act through the same cell surface receptor, VEGFR2. The relative levels and availability of MMPs may explain the heterogeneous nature of vessels in different tumors (60).

Thus, matrilysin and other MMPs are not always proangiogenic, and the mechanisms by which MMPs regulate tumor angiogenesis are complicated. Further analysis is required to clarify how the balance between proangiogenic and antiangiogenic effects exerted by matrilysin and other MMPs affects tumor angiogenesis.

Conclusions

More than 25 members of the human MMP family have so far been identified. Although MMPs have different substrate specificities, there seems to be considerable overlaps among their behaviors, because most MMP knockout mice develop normally. A series of MMPs may have a well-organized and integrated modifying capacity rather than exhibit inconsistent capabilities independently. Nevertheless, matrilysin has many unique and important characteristics, and there is substantial evidence that matrilysin contributes to tumor invasion and metastasis by degrading ECM components. Moreover, recent research advances have revealed that matrilysin plays an important role in the activation, degradation, release, and shedding of non-ECM proteins. The research field is progressing rapidly, and understanding the distinct temporal control of matrilysin and its spectrum of substrates and modulators would be indispensable for developing novel therapeutic strategies that target matrilysin in human tumors.

Recently, a number of MMP inhibitors have been developed as a new generation of anticancer drugs. Although many phase III studies have failed to meet their primary end points, a therapeutic benefit of an MMP inhibitor has been reported in patients with gastric cancer (61). The effectiveness of MMP inhibitors is more likely to be observed in patients with less advanced disease. Therapeutic agents that inhibit the expression or function (or both) of matrilysin may prove efficacious in the treatment of a variety of tumors characterized by matrilysin overexpression. Recent studies have shown that RNAi-

mediated MMP gene silencing inhibits invasion of some human tumors (6, 7). It is tempting to adopt RNAi technology for potential application to develop matrilysin-targeted anticancer drugs.

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