TOPICAL REVIEW

Matrix metalloproteinases: their biological functions and clinical implications

Hijova E

Institute of Experimental Medicine, Faculty of Medicine, Safarikiensis University, Kosice, Slovakia. **hijova@pobox.sk**

Abstract

Matrix metalloproteinases (MMPs), which are also known as matrixins, are proteinases that participate in extracellular matrix remodelling and degradation. Under normal physiological conditions, the activities of MMPs are precisely regulated at the level of transcription, at that of activation of the pro-MMP precursor zymogenes as well as at that of inhibition by endogenous inhibitors (tissue inhibitors of metalloproteinases, TIMPs). Alterations in the regulation of MMP activity are implicated in diseases such as cancer, fibrosis, arthritis and atherosclerosis. The pathological effects of MMPs and TIMPs in cardiovascular diseases involve vascular remodelling, atherosclerotic plaque instability and cardiac remodelling in congestive heart failure or after myocardial infarction. Since excessive tissue remodelling and increased matrix metalloproteinases activity have been demonstrated during atherosclerotic lesion progression (including plaque disruption), MMPs represent a potential target for therapeutic intervention aimed at the modification of vascular pathology by restoring the physiological balance between MMPs and TIMPs. Recent findings suggest that MMPs are also involved in cancer initiation, invasion and metastasis; MMP inhibitors could be considered for evaluation as cancer chemopreventive molecules. This review describes the members of MMP and TIMP families and discusses the structure, function and regulation of MMP activity. *(Tab. 1, Ref. 45.)*

Key words: matrix metalloproteinases, tissue inhibitors of metalloproteinases, cancer, atherosclerosis, heart failure.

Matrix metalloproteinases (MMPs) constitute a family of human zinc-dependent proteolytic enzymes. They take part in the degradation of extracellular matrix (ECM) and basement membranes (BM) during morphogenesis, cell migration, angiogenesis and proteolytic activation of growth factors. All these events are needed in fetal development and in normal tissue remodelling as well as in epidermal wound healing, inflammation and tumor invasion. According to their substrate specificity and structure, MMPs can be divided into six subgroups: interstitial collagenases, stromelysins, matrilysins, type IV collagenases also called gelatinases, membrane-type MMPs (MT-MMPs) and other MMPs. In normal cellular environment, specific tissue inhibitors of metalloproteinases-TIMPs, strictly regulate MMP activity.

Matrix metalloproteinases, regulation of MMPs, inhibitors of MMPs

Matrix metalloproteinases (MMPs) are zinc-dependent endoproteinases that are involved in the degradation of proteins in the extracellular matrix and basement membrane (Tab. 1).

Physiologically, these enzymes play a role in normal tissue remodelling events such as embryonic development, angiogenesis, ovulation, mammary gland involution and wound healing. Abnormal expression appears to contribute to various pathological processes including rheumatoid arthritis and osteoarthritis, pulmonary emphysema, atherosclerosis, and tumor growth, invasion and metastasis.

MMPs are generally divided into six subgroups: interstitial collagenases (MMP-1, -8, and MMP-13), stromelysins (MMP-3, -10, -11 and MMP-12), matrilysins (MMP-7 and MMP-26), type IV collagenases (MMP-2 and MMP-9), membrane-type MMPs (MMP-14, -15, -16, -17, -24 and MMP-25) and others (MMP-19, -23, and MMP-28) (Nagase and Woessner, 1999; Uria and

Institute of Experimental Medicine, Faculty of Medicine, Safarikiensis University, Kosice, Slovakia

Address for correspondence: E. Hijova, MVD, Institute of Experimental Medicine, Faculty of Medicine LF UPJS, Trieda SNP 1, SK-040 11 Kosice, Slovakia.
Phone: +421.55.6424606, Fax: +421.55.6420253

Tab. 1. MMPs and their substrates.

Enzyme	Substrates
Collagenase-1 (MMP-1)	Col I, II, III, VII, VIII, X, aggrecan, entactin/nidogen, MBP, serpins, α2M, perlecan, vitronectin, tenascin,fibrinogen, TNF precursor, IGFBP
Collagenase-2 (MMP-8)	Col I, II, III, aggrecan, serpins, α2M, fibrinogen
Collagenase-3 (MMP-13)	Col I, II, III, IV, IX, X, XIV, aggrecan, fibrillin, fibronectin, gelatin, Laminin (Ln-1), large tenascin C, osteonectin, serpins, PAI, fibrinogen
Gelatinase-A (MMP-2)	Col I, IV, V, VII, X, gelatin, fibronectin, tenascin, fibrillin, osteonectin, entactin, aggrecan, vitronectin, decorin, MBP, α1PI, plasminogen, α2M, Ln-5, IGFBP, TNF precursor, pro-TGF-ß
Gelatinase-B (MMP-9)	Col I, IV, V, VII, XI, XIV, gelatin, elastin, fibrillin, osteonectin, aggrecan, fibronectin, vitronectin, decorin, MBP, α2M, TNF precursor, IGFBP, plasminogen, pro-TGF-ß, α1PI
Stromelysin-1 (MMP-3)	Col III, IV, V, VII, IX, X, elastin, fibronectin, fibrillin, fibrinogen, gelatin, aggrecan, Ln-1, nidogen, vitronectin, osteonectin, decorin, tenascin, α1PI, TNF precursor, MBP, E-cadherin, IGFBP, plasminogen, osteopontin
Stromelysin-2 (MMP-10)	Col III, IV, V, IX, X, elastin, fibronectin, gelatin, aggrecan, Ln-1, nidogen
Stromelysin-3 (MMP-11)	α1PI, IGFBP
Metalloelastase (MMP-12)	Elastin, col IV, fibronectin, Ln-1, gelatin, vitronectin, entactin, proteoglycan, heparan and chondroitin sulfates, TNF precursor, plasminogen, fibrillin, fibrinogen, α1PI
Matrilysin (MMP-7)	Col IV, elastin, fibronectin, Ln-1, entactin, tenascin, osteonectin, aggrecan, vitronectin, MBP, decorin, versican, α1PI, osteopontin, E-cadherin, plasminogen, ß4 integrin, α-prodefensin, Fas ligand, pro-TNF-α
Matrilysin-2 (MMP-26)	Col IV, gelatin, fibronectin, fibrin, α1PI, ß-casein, TACE-substrate
MT1-MMP (MMP-14)	Col I, II, III, gelatin, fibronectin, Ln-1, vitronectin, aggrecan, tenascin, nidogen, perlecan, fibrinogen/fibrin, fibrillin, α1PI, α2M, Ln-5, CD44, tTG
MT2-MMP (MMP-15)	Fibronectin, Ln-1, gelatin, aggrecan, tenascin, nidogen, perlecan, vitronectin, tTG
MT3-MMP (MMP-16)	Col III, fibronectin, gelatin, laminin, aggrecan, casein, vitronectin, α2M, α1PI, tTG
MT4-MMP (MMP-17)	Gelatin, TNF-α precursor, fibrillin, fibronectin
MT5-MMP (MMP-24)	ND
MMP-19	Col IV, gelatin, Ln-1, nidogen, tenascin, fibronectin, aggrecan, fibrinogen, COMP
Enamelysin (MMP-20)	Amelogenin, aggrecan, COMP
MMP-21	ND
MMP-23	gelatin
MMP-27	ND
MMP-28	casein

ND = not determined (Modified from Kerkelä and Saarialho-Kere, 2003; Lohi et al, 2001)

Lopez-Otin, 2000; Lohi et al, 2001). At least eight of the known human MMP genes (MMP-1, MMP-3, MMP-7, MMP-8, MMP-10, MMP-12, MMP-13, and MMP-20) are clustered in chromosome 11 at 11q21-23 (Shapiro, 1998). Other known MMP genes are scattered along chromosomes 1, 8, 12, 14, 16, 20 and 22.

The basic structure of MMPs consists of a catalytic domain and additional amount of variable inserts depending on the specific MMP. These variable inserts include the signal peptide, propeptide, furin-cleavage site insert, fibronectin-like repeats, hinge region, hemopexin domain, cystein-rich region, cytoplasmatic tail, and transmembrane domain.

Transcriptional regulation of MMP genes. In normal tissue, the secretion and activity of MMPs is very low, but their production and release are rapidly induced when tissue remodelling is needed (Nagase and Woessner, 1999). The regulation of MMPs occurs at many levels, including transcription, modulation of mRNA half-life, secretion, localization, zymogen activation and inhibition of proteolytic activity. The control at the level of transcription is the major level of MMP regulation (Fini et al, 1998). Various effectors including growth factors and cytokines /epidermal growth factor (EGF), tumor necrosis factor-α (TNF-α), interleukin 1ß (IL-1ß), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), interleukin-6 (IL-6) and transforming growth factor-ß (TGF-ß) chemical agents, psychical stress, oncogenic cellular transformation as well as cell-cell and cell-matrix interactions regulate MMP gene expression. Extracellular stimuli affect MMP expression via signal transduction pathways that lead to activator protein-1 (AP-1) binding site activation. AP-1 site is in the genes of MMPs-1, -3, -7, -8, -9, -10, -12 and MMP-13. MMP-2, MMP-11, MMP-28 and MT1-MMP genes do not have AP-1 site. MMP-1, -3 and MMP-9 have also another AP-1 site, but the role of this site is not clear. The expression of AP-1 transcription factors are induced by mitogen activated proteine kinase (MAPK) pathways, i.e. extracellular signal-regulated kinase (ERK 1,2), stress activated proteinase kinase/Jun N-terminal kinase (SAPK/JNK) and p38. ERK 1,2 pathway plays a crucial role in growth factor-induced mitogenesis, differentiation and cellular transformation, but it can also be induced by stress stimuli. SAPK/JNK and p38 are merely activated by cytokines and stress such as UV-light (Karin et al, 1997). TGF-ß inhibitory elements (TIE) are described in some MMP gene promoters (MMPs -1, -7 and -13), but their role is not clear. TGF-ß and (TNF-α) might stimulate MMP-1 expression as shown in cultured keratinocytes (Mauviel et al, 1996; Johansson et al, 1997). MMP-7 can be both up- and downregulated by TGF-ß. In rats, TGF-ß is a down-regulated gene expression of MMP-3. MMP-10 is responsive for EGF, keratinocyte growth factor (KGF), TNF-α, TGF-ß1, TGF-α, and MMP-12 is up-regulated by IL-1, TNF-α, macrophage colony stimulating factor (M-CSF), vascular endothelial growth factor (VEGF), PDGF-BB, and inhibited by TGF-ß (Windsor et al, 1993; Madlener et al, 1996; Feinberg et al, 2000). MMP-13 is induced by TPA, IL-1ß and TGF-ß in human fibroblasts (Uria et al, 1997,1998).

Activation of proMMPs. Most proMMPs are secreted from cells and activated extracellularly, but some of them are stored in and released from intracellular granules (MMP-8, MMP-9). ProMMPs secreted as inactive zymogens can be activated by proteinases or by non-proteolytic agents (Nagase, 1997). In vitro, the activation can be set off by plasmin, trypsin, furin, kallikrein, chymase, mast cell tryptase as well as by other, such as bacterial proteinases. The activation of proMMPs by plasmin is a relevant pathway in vivo. Plasmin is generated from plasminogen by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Plasmin has been reported to activate proMMP-1, proMMP-3, proMMP-7, proMMP-9, proMMP-10, and proMMP-13 (Lijnen, 2001). ProMMP-1 can also be activated by MMP-3, MMP-7 or by MMP-10. Many MMPs are activated by other MMPs. ProMMP-2 is activated by MT-MMPs, including MT1-MMP, MT2-MMP, MT3-MMP, MT5-MMP and MT6-MMP (Visse and Nagase, 2003). MT4-MMP does not activate proMMP-2 (English et al, 2000). MMP-2 activation with active MT1-MMP needs TIMP-2, but MT2-MMP is independent of it (Morrison et al, 2001). During MMP-2 activation, MT1-MMP forms dimers or multimers on the cellular surface through interaction of hemopexin domains, and then binds TIMP-2. ProMMP-2 binds with the C-terminal domain of TIMP-2 through its hemopexin domain. The second, active, MT1-MMP then cleaves proMMP-2, thereby partly activating it. The MMP-2 dissociates from the membrane and is fully activated by intermolecular processing. Thus TIMP-2 enhances the activation of MMP-2 at low levels, but inhibits it at high levels. ProMMP-11 possesses a furin recognition sequence and it is activated intracellularly by furin (Pei and Weiss, 1995). MT-MMPs (Sternlicht and Werb, 2001), MMP-21, MMP-23, and MMP-28 (Marchenko and Strongin, 2001; Lohi et al, 2001; Ahokas et al, 2002) have a similar basic motif in the propeptide. ProMMP-13 can be activated by MMP-3, MMP-10, MT2-MMP as well as by MT1-MMP (Knäuper et al, 1996; d'Ortho et al, 1997; Murphy et al, 1999) and MMP-13 itself is able to active gelatinases (Knäuper et al, 1997). MMP-26 is an exception, because it is auto-activated (Marchenko et al, 2003).

The ADAMs (a disintegrin and metalloproteinase like) are a group of molecules that are related to the MMPs. Currently, 23 members of the ADAM family are known to exist, and at least three of these (i.e. ADAM-10, -12 and -17) have been shown to possess proteinase activity (Stone et al, 1999).

Tissue inhibitors of metalloproteinases (TIMPs) are a family of secretory proteins that are able to inhibit MMP activity through non-covalent binding of active forms of MMPs in the extracellular space in 1:1 molar stoichiometry. Four TIMPs have been identified in vertebrates, namely TIMP-1, -2, -3 and -4 (Edwards et al, 1996; Gomez et al, 1997; Duffy and McCarthy, 1998). TIMPs are expressed in various tissues and by many cell types, and their expression is regulated during development and tissue remodelling (Brew et al, 2000). TIMP-1, TIMP-2 and TIMP-4 stay in secreted form in ECM whereas TIMP-3 is associated with it (Leco et al, 1994). All TIMPs are capable of inhibiting all MMPs, with the following exceptions: at least one of ADAMs (tumor necrosis factor-α-converting enzyme (ADAM-17 (TACE)) is not inhibited by TIMP-1, -2 or - 4, TACE activity, however, is

blocked by TIMP-3 (Amour et al, 1998). Some TIMPs appear to act as multifunctional molecules. Thus, in addition to the inhibition of MMP activity, TIMP -1 and TIMP-2 can stimulate cell proliferation, at least in vitro. Furthermore, although both TIMP-1 and TIMP-2 have been found to inhibit apoptosis (Guedez et al, 1998; Valente et al, 1998), TIMP-3 was shown to promote this process (Baker et al, 1999). TIMPs have N- and C-terminal domains and the MMP inhibition occurs through folding the N-domain and binding it to the active site of MMP. TIMPs play an important role in many biological processes, including fetal development, angiogenesis and cancer. An imbalance between TIMP and MMP activities is believed to result in excessive degradation of matrix components in tumor invasion, but the balance between various TIMPs may also be a critical factor in determining the degrading potential of cells in normal and pathological conditions. Overexpression of different TIMPs can inhibit malignant cells in vivo and in vitro. Therefore, adenovirus-mediated gene delivery of TIMP-1, -2 and -3 inhibits tumor invasion (Ahonen et al, 1998). However, the lack of effective methods for gene delivery has limited the clinical utility of this approach.

Role of MMPs in tumors, atherosclerosis and heart failure

Cancer may be comprehended as a disease where abnormalities in genes result in gain-of-function oncogenes or loss-of-function tumor-suppressor genes. Together with other inducers, these mutations cause failure in regulating proliferation, differentiation, cell death, and expression of many cell-type-specific functions properly, and result in an altered phenotype of cell and eventually in cancer. MMPs can regulate the tumor microenvironment, and their expression and activation are increased in almost all human cancers compared with normal tissue. MMPs in tumors are expressed by tumor cells but even more often by surrounding stromal and inflammatory cells. There is no single MMP consistently overexpressed in any tumor type, or a consistent pattern of MMP expression across the variety of human cancer. At least MMP -1, -2, -3, -7, -9, -10, -11, -13 and -14 are frequently overexpressed in many human tumors (Kerkelä and Saarialho-Kere, 2003). The increased MMP expression in tumors is most likely due to transcriptional changes, which result from the activation of oncogenes or loss of tumor-suppressors (Egeblad and Werb, 2002).

It is generally assumed that the primary mechanism by which MMPs promote the spreading of cancer is carried out by degradation of ECM, which consists of two main components: basement membranes and interstitial connective tissue. Although collagen IV is the main component of basement membranes, it is thought to be degraded mostly by MMP-2 and MMP-9. Other proteins such as laminin, proteoglycans, entactin and osteonectin are also present in this structure. The interstitial connective tissue is composed of cells distributed in a meshwork of collagen fibres, glycoproteins, proteoglycans and hyaluronic acid. The main forms of collagen found here are types I, II and III. During cancer dissemination, the interstitial connective tissue is believed to be broken down mainly by interstitial collagenases and some of the stromelysins.

MMPs promote both primary tumor growth and metastasis by activating growth factors, inactivating growth-factor binding proteins, cleaving receptors involved in cell adhesion, unmasking cryptic sites of interaction, and by acting on ECM components or other proteins to uncover hidden biological activities which can affect cell proliferation, migration and angiogenesis.

Angiogenesis is necessary for a tumor to grow up to a size greater than approximately 2 mm in diameter. The process begins with local degradation of the basement membranes that surround capillaries, followed by invasion of the surrounding stroma by the underlying endothelial cells in the direction of the angiogenic signal. MMPs may promote angiogenesis by at least two different mechanisms: by degrading barriers and thereby allowing endothelial cell invasion, and by liberating factors that promote or maintain the angiogenic phenotype (Stetler-Stevenenson, 1999). It is important to point out that, although clear evidence exists that MMPs potentiate angiogenesis, these proteases also have the potential to inhibit this process. For example, MMP-3, -7, -9 and -12, can degrade plasminogen, generating the angiogenesis inhibitor angiostatin. Another potent inhibitor of angiogenesis is endostatin, which is a breakdown product of collagen XVIII. It is presently unknown as to whether MMPs play a role in generating endostatin. Endostatin, which is a C-terminal fragment of the basement membrane collagen XVIII, is probably produced by MMP-3, -9, -12, -13 and -20 (Hanahan et al, 1996; Hojilla et al, 2003).

Atherosclerosis is the major cause of coronary heart disease, and matrix metalloproteinases play an important role in atherosclerosis by degrading the extracellular matrix, which results in cardiovascular remodelling. Recent studies have identified an enhanced expression of MMPs in an atherosclerotic lesion and their contribution to the weakening of vascular wall by degrading the extracellular matrix. Both, animal experiments and clinical sample analysis have shown that balance in expression and activation of MMPs and inhibition by TIMPs is a critical point in the development of stenotic and aneurysmal changes. Polymorphism in MMP gene promoter contributes to inter-individual differences in susceptibility to coronary heart disease. The development of therapeutic drug specifically targeting MMPs may thus be useful in the prevention of atherosclerotic lesion progression, plaque rupture, and restenosis (Watanabe and Ikeda, 2004).

Myocardial remodelling is a milestone in the progression of congestive heart failure (CHF). Left ventricular remodelling during the progression of CHF is accompanied by changes in the structure of the myocardial extracellular matrix. The myocardial extracellular matrix is composed of structural proteins and biologically active molecules that contribute to the maintenance of left ventricular myocardial architecture and function. A family of proteolytic enzymes responsible for myocardial extracellular protein degradation is the matrix of metalloproteinases. A number of MMP species have been identified within the human myocardium and are increased with the development of CHF. Cer-

tain MMPs that are expressed at very low levels in normal myocardium such as collagenase-3 (MMP-13) and the membrane-type MMPs (MT-MMPs) are substantially up-regulated in CHF and likely to contribute to the pathologic remodelling that occurs within the myocardium. However, not all MMP species are uniformly increased in patients with end-stage CHF, suggesting that a specific portfolio or cassette of MMPs are expressed in the failing myocardium. Changes in MMP/TIMP levels are likely to reflect the progression and/or acceleration of the left ventricular remodelling process in CHF. Thus serial measurements of plasma MMP/TIMP levels may hold diagnostic/prognostic significance in CHF patients.

The further necessary steps in improving our understanding of this myocardial MMP system include the following:

1) The identification of MMP species that are up-regulated in CHF.
2) Elucidation of the upstream signalling the pathways that contribute to MMP induction.
3) The development of methods of detecting the early myocardial MMP activation in patients with developing CHF.
4) The examination of the effects of pharmacologic modulators of the MMP system on animal models with CHF.

The results from these future studies may yield some novel therapeutic strategies by which to control myocardial extracellular remodelling and thereby slow down the progression of the CHF process (Spinale et al, 2002).

Despite the intensive research the precise biological activities of MMPs and TIMPs remains enigmatic and therefore the mentioned next steps in improving our understanding of MMPs and TIMPs do not focused only on congestive heart failure but are necessary also in the development of other human diseases.

References

Ahokas K, Lohi J, Lohi H et al. Matrix metalloproteinase-21, the human orthologue for XMMP, is expressed during development and in cancer. Gene 2002; 301: 31—41.

Ahonen M, Baker AH, Kähäri VM. Adenovirus-mediated gene delivery of tissue inhibitor of metalloproteinases-3 inhibits invasion and induces apoptosis in melanoma cells. Cancer Res 1998; 58: 2310—2315.

Amour A, Slocombe PM, Webster A et al. TNF-α converting enzyme (TACE is inhibited by TIMP-3. FEBS Lett 1998; 435: 39—41.

Baker AH, George SJ, Zaltsman AB, Murphy G, Newby AC. Inhibition of invasion and induction of apoptotic cell death of cancer cell lines by overexpression of TIMP-3. Br J Cancer 1999; 79: 1347—1355.

Brew K, Dinakarpandian D, Nagase H. Tissue inhibitors of metalloproteinases: evolution, structure and function. Biochim Biopys Acta 2000; 1477: 267—283.

Duffy MJ, McCarthy K. Matrix metalloproteinases in cancer: prognostic markers and targets for therapy. Int J Oncol 1998; 12: 1343—1348.

Edwards D, Beaudry PP, Laing TD et al. The roles of tissue inhibitors of metalloproteinases in tissue remodelling and cell growth. Int J Obes Relat Metab Disord 1996; 3: 9—14.

Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer 2002; 2: 161—174.

English WR, Puente XS, Freije JM et al. Membrane type 4 matrix metalloproteinese (MMP-17) has tumor necrosis factor-convertase activity but does not activate pro-MMP2. J Biol Chem 2000; 275: 14046—14055.

Feinberg MW, Jain MK, Werner F et al. Transforming growth factor-beta 1 inhibits cytokine-mediated induction of human metalloelastase in macrophages. J Biol Chem 2000; 275: 25766—25773.

Fini ME, Cook JR, Mohan R. Proteolytic mechanisms in corneal ulceration and repair. Arch Dermatol Res 1998; 290: S12—23.

Gomez D, Alonso DF, Yoshiji H, Thorgeirsson UP. Tissue inhibitors metalloproteinases: structure, regulation and biological function. Eur J Cell Biol 1997; 74: 111—122.

Guedez L, Stetler-Stevenson WG, Wolff L et al. In vitro suppression of programmed cell death of B cells by tissue inhibitors of metalloproteinase-1. J Clin Invest 1998; 102: 2002—2010.

Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic swich during tumorigenesis. Cell 1996; 86: 353—364.

Hojilla CV, Mohammed FF, Khokha R. Matrix metalloproteinases and their tissue inhibitors direct cell fate during cancer development. Br J Cancer 2003; 89: 1817—1821.

Johansson N, Westermarck J, Leppä S et al. Collagenase-3 (MMP-13) gene expression by HaCat keratinocytes is enhanced by tumor necrosis factor- and transforming growth factor-β. Cell Growth Differ 1997; 8: 243—250.

Karin M, Liu ZG, Zandi E. AP-1 function and regulation. Curr Opin Cell Biol 1997; 9: 240—246.

Kerkelä E, Saarialho-Kere U. Matrix metalloproteinases in tumor progression: focus on basal and squamous cell skin cancer. Exp Dermatol 2003; 1: 109—125.

Knäuper V, Lopez-Otin C, Smith B, Knight G, Murphy G. Biochemical characterization of human collagenase-3. J Biol Chem 1996; 271: 1544—1550.

Knäuper V, Cowell S, Smith B et al. The role of the C-terminal domain of human collagenase-3 (MMP-13) in the activation of procollagenase-3, substrate specificity, and tissue inhibitor of metalloproteinase interaction. J Biol Chem 1997; 272: 7608—7616.

Leco KJ, Khokha R, Pavloff N, Hawkes SP, Edwards DR. 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 Biol Chem 1994; 269: 9352—9360.

Lijnen HR. Plasmin and matrix metalloproteinases in vascular remodeling. Thromb Haemost. 2001; 86: 324—333.

Lohi J, Wilson CL, Roby JD, Parks WC. Epilysin, a novel human matrix metalloproteinase (MMP-28) expressed in testis and keratocytes and in response to injury. J Biol Chem 2001; 276: 10134—10144.

Madlener M, Mauch C, Conca W, Brauchle M, Parks WC, Werner S. Regulation of the expression of stromelysin-2 by growth factors in keratinocytes: implications for normal and impaired wound healing. Biochem J 1996; 320: 659—664.

Marchenko GN, Strongin AY. MMP-28, a new human matrix metalloproteinase with an unusual cysteine-switch sequence is widely expressed in tumors. Gene 2001; 265: 87—93.

Marchenko GN, Marchenko ND, Strongin AY. The structure and regulation of the human and mouse matrix metalloproteinase-21 gene and protein. Biochem J 2003; 372: 503—515.

Mauviel A, Chung KY, Agarwal A, Tamai K, Uitto J. Cell-specific induction of distinct oncogenes of the Jun family is responsible for differential regulation of collagenase gene expression by transforming growth factor-beta in fibroblasts and keratinocytes. J Biol Chem 1996; 271: 10917—10923.

Morrison CJ, Butler GS, Bigg HF, Roberts CR, Soloway PD, Overall CM. Cellular activation of MMP-2 (gelatinase A) by MT2-MMP occurs via a TIMP-2 independent pathway. J Biol Chem 2001; 276: 47402—47410.

Murphy G, Stanton H, Cowell S et al. Mechanisms for pro matrix metalloproteinase activation. APMIS 1999; 107: 38—44.

Nagase H. Activation mechanisms of matrix metalloproteinases. Biol Chem 1997; 378: 151—160.

Nagase H, Woessner JF. Matrix metalloproteinases. J Biol Chem 1999; 274: 21491—21494.

dOrtho MP, Will H, Atkinson S et al. Membrane-type matrix metalloproteinases 1 and 2 exhibit broad-spectrum proteolytic capacities comparable to many matrix metalloproteinases. Eur J Biochem 1997; 250: 751—757.

Pei D, Weiss SJ. Furin-dependent intracellular activation of the human stromelysin-3 zymogen. Nature 1995; 375: 244—247.

Shapiro SD. Matrix metalloproteinase degradation of extracellular matrix: biological consequences. Curr Opin Cell Biol 1998; 10: 602—608.

Spinale FG, Gunasinghe H, Sprunger PD, Baskin JM, Bradham WC. Extracellular degradation pathway in myocardial remodeling and progression to heart failure. J Card Fail 2002; 8(6 Suppl): 332—338.

Sternlicht M, Werb Z. How matrix metalloproteinases regulate cell behavior. Annu Rev Cell Dev Biol 2001; 17: 463—516.

Stetler-Stevenenson W. Matrix metalloproteinases in angiogenesis: a moving target for therapeutic intervention. J Clin Invest 1999; 103: 1237—1241.

Stone AL, Kroeger M, Amy Sang QX. Structure-function analysis of the ADAM family of disintegrin-like and metalloproteinase-containing proteins. J Prot Chem 1999; 18: 447—465.

Uria JA, Stahle-Backdahl M, Seiki M, Fueyo A, Lopez-Otin C. Regulation of collagenase-3 expression in human breast carcinomas is mediated by stromal-epithelial cell interactions. Cancer Res 1997; 57: 4882—4888.

Uria JA, Werb Z. Matrix metalloproteinases and their expression in mammary gland. Cell Res 1998; 8: 187—194.

Uria JA, Lopez-Otin C. Matrilysin-2, a new matrix metalloproteinase expressed in human tumors and showing the minimal domain organization required for secretion, latency, and activity. Cancer Res 2000; 60: 4745—4751.

Valente P, Fassima G, Melchiori A et al. TIMP-2 overexpression reduces invasion and angiogenesis and protects B16F10 melanoma cells from apoptosis. Int J Cancer 1998; 75: 246—253.

Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 2003; 92: 827—839.

Watanabe N, Ikeda U. Matrix metalloproteinases and atherosclerosis. Curr Atheroscler Rep 2004; 6: 112—120.

Windsor LJ, Grenett H, Birkedal-Hansen B, Bodden MK, Engler JA, Birkedal-Hansen H. Cell type-specific regulation of SL-1 and SL-2 genes. Induction of the SL-2 gene but not the SL-1 gene by human keratinocytes in response to cytokines and phorbolesters. J Biol Chem 1993; 268: 17341—17347.

Received February 26, 2005.
Accepted March 12, 2005.