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REVIEW

Matrix Metalloproteinases of Normal Human Tissues

P. Z. Khasigov[1]*, O. V. Podobed[1], S. A. Ktzoeva[1], T. M. Gatagonova[1], S. V. Grachev[1], S. S. Shishkin[2], and T. T. Berezov[3]

[1]Sechenov Moscow Medical Academy, ul. Bol'shaya Pirogovskaya 2/6, Moscow, 119881 Russia; fax: (095) 248-0181
[2]Research Center of Medical Genetics, Russian Academy of Medical Sciences, ul. Moskvorech'e 1, Moscow, 115478 Russia; fax: (095) 324-0702
[3]Russian University of People's Friendship, ul. Miklukho-Maklaya 6, Moscow, 117198 Russia; fax: (095) 434-0412

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Abstract—This review considers biochemical properties of the family of matrix metalloproteinases (MMPs) of normal human tissues and the involvement of these enzymes in morphogenesis. Four main MMP subfamilies are characterized, and a group of other MMPs is described. Data on mechanisms of activation and inhibition of MMPs in certain tissues during various physiological processes (embryogenesis, angiogenesis, tissue growth and involution) are considered. Information about tissue inhibitors of MMP is presented, and the ability of these inhibitors to regulate the activity of MMPs is analyzed.

Key words: matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, extracellular matrix

Matrix metalloproteinases (MMPs), also known as matrixins, are members of a family of Zn-dependent endopeptidases that are responsible for degradation of various protein components of the intercellular matrix and basal membranes at neutral pH values. So far, 20 different human MMPs have been characterized [1-7] including data on their primary structure. The present work analyzes the biochemical properties of MMPs with regard to specific features of this family of proteins.

Based on primary structure, substrate specificity, and cell localization, these enzymes may be divided into at least four main subfamilies: collagenases, gelatinases, stromelysins, and membrane-bound MMP (MB-MMP). However, some recently described enzymes, such as macrophagal metalloelastase MMP-12 [8], MMP-7 [9], stromelysin 3 [10], MMP-18 [11], MMP-19 [12], MMP-20 [13], and MMP-23 [4], cannot be assigned to any of these subfamilies. Taking into account their specific structural and/or functional properties, these seven MMPs are combined into the group "other enzymes" (table).

The table shows that genes of metalloproteinases 1, 3, 7, 8, 10, 12, 13, and 20, i.e., of nearly a half of the known enzymes of this family, are located in the same q22.3 region of chromosome 11. Consequently, they probably represent a cluster of genes of the same family. The common location of the MMP-2 and MMP-15 genes (16q13-21) and of the MMP-9 and MMP-24 genes (20q11.2) also attracts attention. Thus, it is likely that matrix metalloproteinases are products of expression of the same superfamily of genes. Moreover, the MMP genes were probably generated by the divergence of a single gene cluster during evolution [5, 13].

The subfamily of collagenases includes the interstitial collagenase (MMP-1), the collagenase of neutrophils (MMP-8), and collagenase-3 (MMP-13). These enzymes disintegrate native fibrillar interstitial collagens by cleaving the single peptide bond in α-chains, and this results in fragments of about 1/4 and 3/4 of the length of an intact molecule [14-16]. Collagenases can also hydrolyze other substrates (table), but fibrillar collagens can be destroyed only by these enzymes. The collagenase of neutrophils predominantly cleaves type I collagen, while the interstitial collagenase cleaves type III collagen [15].

The subfamily of gelatinases includes gelatinase A (MMP-2, 72 kD) and gelatinase B (MMP-9, 92 kD). Gelatinases cleave type IV and type V collagens and elastin inside basal membranes and denatured collagen

Abbreviations: MMP) matrix metalloproteinase; MB-MMP) membrane-bound matrix metalloproteinase; TIMP) tissue inhibitor of metalloproteinases; HGF) hepatocyte growth factor; EM) extracellular matrix.

* To whom correspondence should be addressed.

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Family of matrix metalloproteinases (MMPs) of normal human tissues

Enzyme subfamily	Enzyme	Symbol	Gene location on the chromosome*	Substrates and/or functions	Expression and/or tissue localization	References
1	2	3	4	5	6	7
I. Collagenases (type I collagenases)	Interstitial collagenase (EC 3.4.24.7)	MMP-1	11q22.3	Collagens I, II, III, VII, X; gelatins, entactin, aggrican, casein, α_2-macroglobulin, binding protein	Stroma cells of menstrual and proliferative endometrium, liver, fibroblasts, chondrocytes, epithelial cells, macrophages	[15, 45, 90-94, 97]
	Collagenase of neutrophils (EC 3.4.24.34)	MMP-8	11q22.3	Collagens I, II, III; aggrican, binding protein	Neutrophilic leukocytes, chondrocytes of articular cartilage	[15, 95]
	Collagenase 3 (EC 3.4.24.-)	MMP-13	11q22.3	Collagens I, II, III; aggrican, gelatins	Cartilaginous and bone cells	[96]
II. Gelatinases (type IV collagenases)	Gelatinase A (EC 3.4.24.24)	MMP-2	16q13-q21	Gelatins, collagens I, IV, V, VII, X, XI; fibronectin, laminin, aggrican, elastin, large tenascin – C-protein, vitronectin, β-amyloid protein precursor	Stroma cells of menstrual, late secretory, secretory, and proliferative endometrium; liver, aorta	[93, 97, 98]
	Gelatinase B (EC 3.4.24.35)	MMP-9	20q11.2-q13.1	Gelatins, collagens III, IV, V, XIV; aggrican, elastin, entactin, vitronectin	Stroma cells of menstrual endometrium, liver, small blood vessels of brain tissue	[93, 97, 99]
III. Stromelysin	Stromelysin 1 (EC 3.4.24.17)	MMP-3	11q22.3	Proteoglycans, gelatins, fibronectin, laminin, collagens III, IV, V, IX, X; large tenascin – C-protein, vitronectin, aggrican	Stroma cells of menstrual and proliferative endometrium, liver	[93, 97]
	Stromelysin 2 (EC 3.4.24.22)	MMP-10	11q22.3	Proteoglycans, gelatins, fibronectin, laminin, collagens III, IV, V, IX; aggrican, entactin, large tenascin – C-protein	Stroma cells of menstrual and late secretory endometrium, mature macrophages (mononuclear phagocytes)	[97, 100]

Contd.

1	2	3	4	5	6	7
IV. Membrane-bound MMP (MB-MMP)	MB1-MMP (EC 3.4.24.-)	MMP-14	14q11-q12	Laminin-1, dermatan sulfate proteoglycan, collagens I, II, III; vitronectin, fibronectin; activates proMMP-2 and proMMP-13	Lung, placenta, kidney, ovary, prostate, spleen, thymus, testicle, large intestine	[34]
	MB2-MMP (EC 3.4.24.-)	MMP-15	16q13-q21	Activates proMMP-2	Liver, placenta, testicle, large intestine, small intestine, pancreas, kidney, lung, heart, skeletal muscle	[34]
	MB3-MMP (EC 3.4.24.-)	MMP-16	8q21	Activates proMMP-2	Placenta, brain, lung	[101]
	MB4-MMP	MMP-17	12q24	Unknown**	Brain, leukocytes, large intestine, ovary, testicle	[102]
	MB5-MMP	MMP-24	20q11	Activates proMMP-2	Brain, kidney, pancreas, lung	[5]
	MB6-MMP, leukolysin	MMP-25	Not established	Gelatinolytic activity. This enzyme is suggested to be a component of the proteolytic arsenal of leukocytes during inflammation	Leukocytes	[103]
V. Other MMPs	Matrilysin (EC 3.4.24.23)	MMP-7	11q22.3	Proteoglycans, gelatins, fibronectin, laminin, elastin, entactin, collagen IV, small tenascin – C-protein, vitronectin, aggrican	Epithelial cells of menstrual, late secretory, and proliferative endometrium; prostate, early promonocytes, microglia-like cells of brain tissue, articular cartilage	[97, 99, 104-106]
	Stromelysin 3 (EC 3.4.24.-)	MMP-11	22q11.2	Fibronectin, laminin, gelatins, collagen IV, aggrican, α_1-proteinase inhibitor, α_2-macroglobulin	Stroma cells of menstrual, late postsecretory, and proliferative endometrium; liver	[93, 97]
	Metalloelastase (EC 3.4.24.65)	MMP-12	11q22.2-q22.3	Elastin	Macrophages, stroma cells, placenta	[8]

Contd.

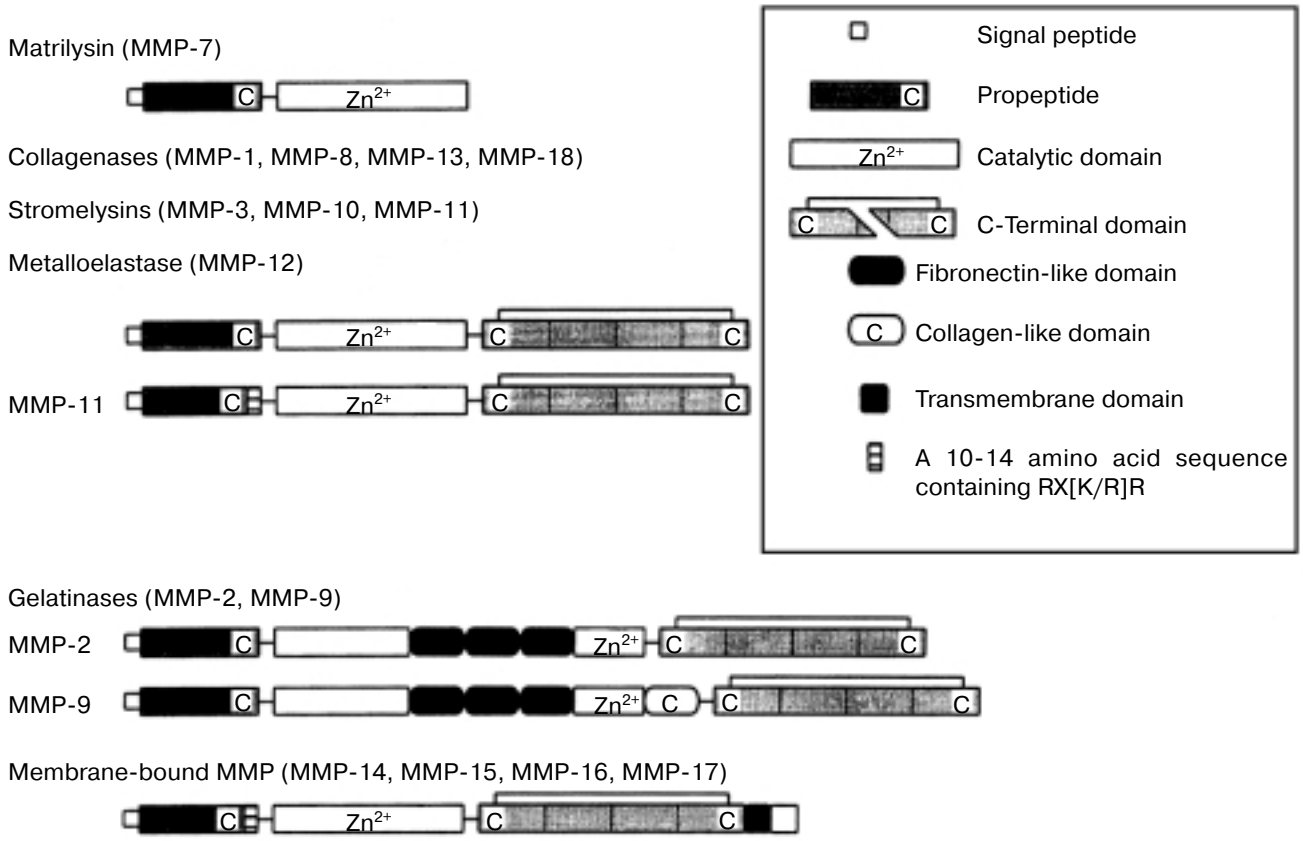
1	2	3	4	5	6	7
	Unnamed	MMP-18	Not established	Unknown	Mammary gland, placenta, lung, pancreas, ovary, small intestine, large intestine, spleen, thymus, testicle, heart	[11]
	Unnamed	MMP-19	12q14	Unknown	Placenta, lung, pancreas, ovary, spleen, small intestine	[12]
	Enamelysin	MMP-20	11q22.3	Amelogenin, other proteins of this family, and synthetic peptides	Odontoblasts	[13]
	Unnamed	MMP-23	1p36.3	Unknown	Ovary, testicle, prostate, heart, small intestine, large intestine, placenta, lung, pancreas	[4]

* Data on the mapping of metalloproteinase genes are given following Genbank (http:/www.ncbi.nlm.nih.gov/) (Benson, D. A., Boguski, M. S., Lipman, D. J., et al. (1999) *Nucleic Acids Res.*, **27**, 12-17). Search system Locus Link NCBI.

** It has been recently found that MMP-17 is anchored in the cell membrane structure through glycosyl phosphatidylinositol and can be released from the cell surface under the influence of endogenous metalloproteinases (Itoh, Y., Kajita, M., Kinoh, H., et al. (1999) *J. Biol. Chem.*, **274**, 34260-34266).

(gelatin). Due to the latter property, gelatinases complement collagenases during the degradation of fibrillar collagens [17, 18]. Moreover, gelatinases hydrolyze other types of collagens and certain proteins of the connective tissue matrix (table). Stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and matrilysin (MMP-7) have low substrate specificity and are involved in the degradation of many proteins of the intercellular matrix including proteoglycans and glycoproteins, such as laminin and fibronectin [9, 19-23]. Stromelysin-3 (MMP-11), elastase (MMP-12), and membrane-bound MMP (MB-MMP) (MMP-14 and MMP-15) seem to have higher substrate specificity [24]. Although, according to the literature [25], recombinant MB1-MMP and MB2-MMP cleaved fibronectin, tenascin, nidogen, aggrican, and perlecan, MB2-MMP is also active toward laminin. MB1-MMP was first characterized as an activator of progelatinase A [26], and only later it was shown to destroy such components of the intercellular matrix as collagens I, II, and III [27], fibronectin, laminin, vitronectin, and dermatan sulfate proteoglycan [28]. In some cases the substrate specificity of MMP is lower, for instance, they can catalyze the splitting of interleukin 1β [29] and of tumor necrosis factor precursor [30].

All MMPs are synthesized as proenzymes, and many of them are secreted by cells in latent forms. The proenzymes are activated *in vivo* by proteases [9, 31]. A common feature of MMPs is the presence of Zn^{2+} in the active site and the requirement for Ca^{2+} for stabilization of the molecule [32]. The primary structures of MMPs are very similar and have a common conserved sequence [15]. Molecules of nearly all MMPs contain several various domains, each of which is responsible for a certain function: the maintenance of the latent form of the enzyme, secretion, substrate recognition, and catalysis [15, 26, 33-35]. The domain structure of MMP proenzymes is presented in the figure. The prodomain that contains the conserved sequence PRCGXPD is necessary for the maintenance of MMP in the latent form and it is cleaved off during activation of the proenzyme. The



The domain structure of proenzymes of certain matrix metalloproteinases (MMP) of human tissues (after [13]).

adjacent catalytic domain includes a motif with three conserved histidine residues that complex with Zn^{2+} [36]. The C-terminal region of the MMP molecule contains a hemopexin-like domain that seems to determine the substrate specificity or the interaction with the cell surface receptor [26, 34, 35, 37]. Gelatinase molecules contain an additional fibronectin-like domain that helps during their binding to their substrate, gelatin [38, 39]. Moreover, molecules of gelatinase B contain a domain with a sequence similar to α_2-chain of the collagen V. MB-MMP are characterized by a specific transmembrane domain in the C-terminal and by a sequence recognizable by a convertase furin that has been also found in molecules of stromelysin 3 molecule [26, 34, 35].

MECHANISMS OF MMP ACTIVATION

Specific inhibitors control the activity of MMP in tissues by regulating their synthesis, stimulation, and suppression of activity. On the transcription level, the synthesis of many MMP is regulated by cytokines, hormones, growth factors, tumor promotors, and by the products of matrix degradation [9, 15].

The posttranslational regulation includes, first, activation of the proenzyme, which is now believed to take different pathways. These pathways include stepwise activation of the membrane-bound proenzyme by the so-called cysteine-switch mechanism [9, 40], its activation on the cell surface, and intracellular activation [9]. The maintenance of MMP in its latent form is mainly provided by tissue inhibitors of metalloproteinases (TIMP). Thus, it has been shown that TIMP 1 and TIMP 2 can bind to thee C-terminal domains of progelatinases, and in these complexes, MMPs are inactive [41-44].

Activation of the latent enzyme is one of the most important steps in the regulation of MMP activity [45]. Conversion of the proenzyme into the active form can occur under the influence of proteinases, denaturing agents (urea, SDS, NaSCN), and modifiers (iodoacetate, 4-aminophenylmercuric acetate (APMA), HOCL, oxidized glutathione), and heating [46]. The activation of prostromelysin 1 (proMMP-3) induced by APMA occurs in a stepwise manner with the involvement of some intermediates [9, 47, 48]. The activation of proMMP by proteinases occurs similarly, namely, the proteinase initially attacks a bond in the middle of the propeptide and thus promotes a subsequent proteolytic

reaction. The next stage can be catalyzed by a particular MMP. Thus, MMP-3 converts a partially activated collagenase (MMP-1) into the completely activated form by splitting the Gln80–Phe81 bond [49]. However, proMMP-7 is immediately activated on the splitting of the Glu79–Tyr78 bond under the influence of MMP-3 [50] and of proMMP-8 on splitting of the Glu78–Phe79 bond under the influence of MMP-3 or MMP-10 [16, 51]. It has been suggested [36, 40] that the SH-group of Cys in the sequence PRCG[V/N]PD, which is common for all proMMPs, interacts with Zn^{2+} in the active site and thus prevents the binding of water to Zn^{2+}. Thus, the proenzyme remains inactive. The activation in the pericellular and extracellular space of MMPs that have been secreted in the inactive form starts by limited proteolysis of the N-terminal domain of the propeptide, and this initiates conformational changes and destruction of the Zn^{2+}–Cys bond. Then the modified MMP autocatalytically splits the peptide bond after the PRCGVPD sequence, and this produces a molecule of the activated enzyme [40].

It has been reliably established that posttranslational regulation of the activity of gelatinase A, i.e., the activation of the latent enzyme, involves MB1-MMP. MB1-MMP, which not only activates progelatinase A, but also its receptor [26, 35, 52], has been found on the surface of invasive tumor cells. Strongin et al. [52] suggested that MB1-MMP is also a cell surface receptor for TIMP-2 that is also involved in the activation of proMMP-2. There is much evidence that the activation of progelatinase A in the pericellular space includes the complexing of TIMP-2 and MB1-MMP [26, 52, 53]. And the N-terminal domain of TIMP-2 actively binds to the catalytic domain of MB1-MMP resulting in a complex on the cell surface [54]. And then the C-terminal domain of progelatinase A seems to interact with the available C-terminal domain of TIMP-2, and thus a complex of three molecules is produced [52]. According to this hypothesis, a free (not bound with TIMP-2) molecule of MB1-MMP attacks a single bond in the progelatinase A molecule, and autocatalytic breaking of a peptide bond results in activation of the proenzyme [55, 56]. However, this hypothesis is contradicted by findings [57] that the C-terminal domain of proMMP-2 is not involved in the splitting of the Asn37–Leu38 bond in the progelatinase A molecule under the influence of the catalytic domain of MB1-MMP. It has recently been shown that the prodomain of MB1-MMP plays the main role in the binding of TIMP-2 and the subsequent activation of the progelatinase A [58].

Progelatinase A can also be activated *in vitro* by the soluble form of MB2-MMP, but it should be noted that this reaction is suppressed in the presence of TIMP-2 and TIMP-3 and only partially in the presence of TIMP-1. It is likely that progelatinase A can be activated by various MB-MMPs depending on tissue localization [56].

MB1-MMP is also involved in activation of other MMPs; thus, it activates procollagenase 3 (proMMP-13) on the cell surface. Gelatinase A somehow influences this activation, this being indicated by an increase in the activation rate in its presence [16]. MMP-3 is also involved in the activation of proMMP-9, which is inactive inside the complex with TIMP-1 [44]. The generation of a complex that includes proMMP-9, TIMP-1, and MMP-3 results in a decreased interaction between proMMP-9 and TIMP-1. The leukocyte elastase that selectively splits TIMP-1 and thus promotes the activation of proMMP-9 by MMP-3 is also suggested to be involved in the activation [59].

Immediate activation of progelatinase B under the influence of collagenase 3 has been shown *in vitro* [60]. The reaction proceeded in two steps and resulted in the complete cleavage of the propeptide, and the rate of the reaction did not depend on the interaction between the C-domains of progelatinase B and of the activating enzyme.

Thus, the activation of proMMP on the cell surface is a complicated multi-step process, and its molecular mechanism is not yet clear. The activation of MMP on the cell surface is very important for degradation of the matrix in the pericellular space that is necessary for the migration and proliferation of cells. The special role of MB-MMP should be emphasized because these proteinases are not only involved in matrix degradation in regions of their location on the cell surface but, through the activation of collagenase-3 and gelatinase A, can also trigger a cascade of MMP-catalyzed proteolytic reactions by initiating and increasing matrix degradation.

The intracellular activation of stromelysin 3 (MMP-11) under the influence of the Golgi apparatus-associated subtilisin-like proteinase furin was shown in [61]. The sequence recognizable by furin is also found in the MB-MMP molecule [61]. Intracellular activation of a mutant type MB1-MMP under the influence of furin has been shown [28], but it is not clear whether such activation occurs in the case of the full-size MB1-MMP molecule [62].

It should be emphasized that the main fraction of MMP is converted into the active form by a complicated multi-step process, and many steps seem to occur outside the cell.

TISSUE INHIBITORS OF MATRIX METALLOPROTEINASES

To elucidate the role of MMP in the normal metabolism of basal membranes and of the intercellular matrix and especially in the development of various diseases, available data should be considered concerning features of TIMP that regulate both the enzymatic activity of

MMPs and their *in vivo* activation [63-65]. To provide normal physiological processes, balance should be maintained between the activities of MMPs and of their inhibitors [65]. Disorders in this balance can severely influence the composition of the intercellular matrix and various functions of cells including adhesion, migration, and differentiation [63-65]. Studies on the structure and functions of TIMPs are reviewed in detail in [65]. Consider in brief some features of TIMPs that are important for understanding the mechanism of inhibition of the enzymatic activity of MMPs and of their activation.

The currently known four members of the TIMP family have in common a number of specific structural features [64-69]. Thus, the conserved region of a TIMP molecule has twelve cysteine residues that form six disulfide bridges. The NH_2-terminal domain of all TIMPs, which is responsible for the inhibitory activity, contains the consensus sequence VIRAK. During the processing of a TIMP, a leader sequence of 29 amino acid residues is cleaved from the propeptide molecule. The complete amino acid sequence of TIMP-1 was determined by Carmichael et al. [70]. Later the structures of other TIMPs were studied, and the conserved sequences were determined, as well as differences in amino acid sequences of various members of the family [65].

It has been shown that TIMPs can interact with the conserved sequence of MMPs; however, during the reaction with MMP-2 and MMP-9 they also seem to interact with other sequences [67, 71, 72]. TIMPs complex with MMPs via noncovalent bonds; during the dissociation of the complex the intact enzyme and inhibitor are liberated [73]. It has been recently shown that, during inhibition, TIMP-1 initially binds reversibly with the C-terminal sequence of MMP-1, and then a tight complex of the inhibitor with MMP slowly forms [74]. Based on studies of the recombinant TIMP-1 molecule, the sequence for the N-terminal domain of TIMP-1 was suggested [69] to determine its ability to inhibit enzymatic reactions with the involvement of MMPs. Later, by directed mutagenesis, a sequence located between Cys3 and Cys13 of the N-terminal domain was shown to be essential for the inhibitory activity of TIMP-1 [75]. The inhibitory activity of TIMP-2 is also associated with its N-terminal sequence [76]. Then it was shown that the region GCEEC surrounding two disulfide bonds (Cys13–Cys124, Cys127–Cys174) in the TIMP-1 molecule was involved in the inhibition of the enzymatic activity of fibroblast collagenase [66].

As mentioned above, TIMP-1 maintains proMMP-9 in its latent form via the formation of a bimolecular complex. The interaction of this complex with MMP can inhibit the activity of the latter due to formation of a more stable complex proMMP-9/TIMP-1/MMP [77]. TIMP-2 was shown to activate proMMP-2 along with MB1-MMP, but no such activity was found for TIMP-1 [78-80]. These findings indicate that TIMPs play various roles in the regulation of MMP activity.

Many cell types express TIMPs. TIMP-1 and TIMP-2 exist in soluble forms, while TIMP-3 is insoluble and occurs only bound with the extracellular matrix (EM) [81, 82]. The synthesis of TIMP-1 is influenced by various external stimuli, such as phorbol esters, growth factors, and cytokines, whereas the expression of TIMP-2 is mainly constitutive [83]. The inhibitory activity of TIMP-3 appears to increase in the presence of certain heparin sulfate proteoglycans [84].

TIMP-1 and TIMP-2 can function as growth factors and stimulate the growth of erythroid cells, fibroblasts, and keratinocytes [85-87]. To explain this finding, it was suggested that specific TIMP receptors should exist on the cell surface. Another mechanism that seems to deserve attention suggests that intercellular signals generated in response to changes in the state of the EM and transmitted through integrin receptors should be changed when the activity of MMP is modified [88]. The stimulation of secretion of TIMP-3 by hepatocyte growth factor (HGF) seems to be the first stage in the rearrangement of the extracellular matrix under the influence of external stimuli during various physiological and pathological processes [89].

THE INVOLVEMENT OF MMP AND TIMP IN PHYSIOLOGICAL REARRANGEMENT OF TISSUES

The great bulk of studies on MMPs are designed to elucidate their role during various pathological processes and especially in carcinogenesis. However, these enzymes are also actively involved in many processes associated with the maintenance of homeostasis and with histogenesis that is convincingly shown by specific features of expression and/or location of MMPs in human normal tissues [90-106] (table).

Local degradation of the intercellular matrix is necessary for the migration and proliferation of cells during the remodeling of tissues. Changes in MMP expression are especially pronounced in tissues where intense cyclic rearrangements occur, e.g., in human endometrium and in the mouse post-delivery uterus. In epithelial cells of the human endometrium, the activity of matrilysin is high during the proliferative, late secretory, and menstrual phases of the cycle when the endometrium structure is changing and the level of estrogen is increased relative to the level of progesterone [107]. During this period, fibroblasts are found to contain mRNA for stromelysin-1 and collagenase [97]. Expression of matrilysin in glandular epithelial cells of the mouse uterus is highest within 6 h to 1.5 days after delivery, when the shape and size of the uterus are especially changing [108]. Thus, the induction of transcription of various MMPs changes

similarly, but their expression depends on cell type. The expression of MMP-1 in endometrium cells depends on the levels of estradiol and progesterone, whereas MMP-2 and TIMP-1 seem to be synthesized constitutively [109]. The different regulation of expression of MMP-1 and MMP-2 is suggested to be due to the presence of regulatory elements AP-1 and PEA-3 in the gene promotor of MMP-1; such elements were not found in the gene promotor of MMP-2.

Morphogenesis and remodeling of mammary gland during lactation and involution were studied, and MMP and TIMP were shown to influence interactions between epithelial cells and basal membranes [110, 111]. MMP and TIMP were expressed at different times during mammary gland involution. The inhibitory activity of TIMP-1 helped to maintain the structural integrity of the basal membranes and to prevent their degradation [110].

Collagenase synthesized by osteoblasts is important during bone resorption that is associated with bone growth [112]. The production of TIMP-1 by osteoblasts is controlled by such mediators of bone remodeling as parathyroid hormone [113], *trans*-retinoic acid, and TGFβ-1 [83].

Basal keratinocytes at the edges of wounds were found to contain mRNA for collagenase, and mRNA for stromelysin was found near the basal keratinocytes and fibroblasts of the derma [114]. It is likely that stromelysin-1 is involved in the remodeling of derma during the elimination of granular tissue and resorption of scar tissue, similar to its involvement in restructuring of basal membranes around basal keratinocytes. Collagenase is suggested to destroy matrix collagen, which prevents migration of basal keratinocytes involved in the formation of epithelium. During wound healing, increased expression of MB1-MMP is also observed [115].

MMPs play an important role in embryogenesis, in particular in nephrogenesis. Increased expression of MB1-MMP was recorded in embryonal mouse kidney [116] and human kidney [35]. An *in vitro* model of development of renal tubules using the MDCK cells (dog renal epithelium cells) grown on a collagen gel support was studied, and HGF was shown to induce the expression of mRNA for MB1-MMP, which is immediately involved in tubulogenesis [117]. During metanephrogenesis, mRNAs for MB1-MMP and for MMP-2 are expressed in both epithelial and mesenchymal tissues, while corresponding proteins were found in epithelial tissue [118]. The authors conclude that these enzymes together with their inhibitor TIMP-2 are involved in paracrine/juxtacrine interaction of these tissues during embryogenesis. MMP-2 and TIMP play important roles in the remodeling of basal membranes associated with epithelial structures of the kidney during its development. Using immunohistochemistry, the location of MMP-2 was found in structures of immature nephrons during epithelial differentiation, and MMP-9 was found only in vascular structures of immature glomerules [119]. However, *in situ* hybridization revealed transcripts for MMP-2 in undifferentiated mesenchyme, but they were absent in structures at the stage of epithelial differentiation. Transcripts for MB1-MMP were found in epithelial structures during their development. The expression of TIMP-2 and TIMP-3 was similar to that of MMP-2. Thus, MMP-2 and TIMP are involved in the remodeling of the basal membranes associated with epithelial structures in the kidney during its development. MB1-MMP is suggested to be a receptor and/or a modifier of the activity of the MMP-2/TIMP complex.

Proteolytic fragments of fibronectin can be involved in regulatory processes in the cell [120]. They have been shown to be involved in the induction of specific genes, particularly, of those of proteases implicated in the degradation of EM [121]. On the other hand, fibronectin fragments are known to direct the migration of fibroblasts [121] and monocytes [122] towards wounds. Consequently, because MB-MMP can destroy fibronectin, they can be involved in wound healing. The insoluble fibrillar fibronectin can also be destroyed by matrilysin [120]. It is suggested that a 58-kD fragment resulting from the matrilysin-induced degradation of fibronectin should function as a signal molecule [120].

Nidogen is suggested to provide stability of basal membranes by forming bridges between laminin and type IV collagen and by anchoring various macromolecules such as collagen and perlecan [123]. Therefore, the degradation of nidogen under the influence of MB-MMP affects the stability of membranes. MB-MMP cleaves perlecan molecules at certain points [25]. Because perlecan is involved in the binding of growth factor, MB-MMP and other MMPs [124] play a special role in HGF release and, consequently, are mediators of regulatory reactions that occur under the influence of the latter.

MMPs are key enzymes of metabolism of connective tissue constituents and are involved in various physiological and pathological processes associated with the proliferation and migration of cells and, thus, with rearrangements in EM. Although very variable, MMPs have in common many structural and functional features that allow us to distinguish them as a separate family of endopeptidases. Under physiological conditions, the synthesis, activity, and inhibition of MMPs are strictly controlled on both autocrine/paracrine and hormonal levels. The proteolytic activity of MMPs is a result of the interaction of many factors regulating the expression of mRNA for the proenzyme, activation of the latent enzyme form, inhibition of the active enzyme, and inactivation and degradation of the enzyme and its inhibitors. A very low level of MMP activity in tissues under their balanced state can increase during normal rearrangements of tissues and under various pathological conditions.

The degradation of EM is a result of a complicated cascade of reactions with various MMPs acting as synergists. Gelatinases seem to play the main role in the final stages of this process due to their ability to digest denatured collagen. In the pericellular space these MMPs can interact with various matrix proteins through their fibronectin-like fragment. This results in a feedback between the matrix conditions and the potential activation of MMPs and, possibly, determines their *in vivo* mechanism.

It should be emphasized that MB-MMPs play a specific role in the metabolism of EM because they not only catalyze the proteolysis of EM proteins, but also can indirectly affect their degradation due to the activation of MMPs.

The interaction between activities of MMPs and of their inhibitors can be followed in various physiological and pathological situations in tissues. The ability of the inhibitors to complex with the inactive enzymes suggests that the function of TIMPs is more complicated than the simple suppression of MMP activity. Disorders in the expression of TIMPs that regulate not only the proteolytic activity of MMP but also their activation are significant during the development of various diseases associated with disorders in connective tissue metabolism.

The majority of data available about the properties of MMPs, especially data on the mechanisms of activation and inhibition of these enzymes, have been obtained *in vitro* or using recombinant MMP and TIMP molecules. To develop these studies further, efforts will be required to use these data to understand processes in the living organism. Studies on changes in MMP gene expression and on the activity of MMPs in models of various diseases are especially important. No doubt, such studies are very important because they are promising for the elucidation of molecular mechanisms of development of many diseases that in one way or another are associated with disorders in the metabolism of EM and for elaboration of approaches for their correction.

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REFERENCES

1. Kleiner, D. E., and Stetler-Stevenson, W. G. (1999) *Cancer Chemother. Pharmacol.*, **43**, Suppl., S42-51.
2. Stetler-Stevenson, W. G., Aznavoorian, S., and Liotta, L. A. (1993) *Ann. Rev. Cell Biol.*, **9**, 541-573.
3. Gururajan, R., Grenet, J., Lahti, J. M., and Kidd, V. J. (1998) *Genomics*, **52**, 101-106.
4. Velasko, G., Pendas, A. M., Fueyo, A., Knauper, V., Murphy, G., and Lopez-Otin, C. (1999) *J. Biol. Chem.*, **274**, 4570-4576.
5. Llano, E., Pendas, A. M., Freije, J. P., Nakano, A., Knauper, V., Murphy, G., and Lopez-Otin, C. (1999) *Cancer Res.*, **59**, 2570-2576.
6. Mertens, P. R., Alfonso-Jaume, M. A., Steinmann, K., and Lovett, D. H. (1998) *J. Biol. Chem.*, **273**, 32957-32965.
7. Pei, D. (1999) *Cell Res.*, **9**, 291-303.
8. Belaaouaj, A., Shipley, J. M., Kobayashi, D. K., Zimonjic, D. B., Popescu, N., Silverman, G. A., and Shapiro, S. D. (1995) *J. Biol. Chem.*, **270**, 14568-14575.
9. Nagase, H. (1997) *Biol. Chem.*, **378**, 151-160.
10. Basset, P., Bellocq, J. P., Wolf, C. X., Stoll, I., Hutin, P., Limacher, J. M., Podhajcer, O. L., Chenard, M.-P., Rio, M.-C., and Chambon, P. (1990) *Nature*, **348**, 699-704.
11. Cossins, J., Dudgeon, T. J., Catlin, G., Gearing, A. J., and Clements, J. M. (1996) *Biochem. Biophys. Res. Commun.*, **228**, 494-498.
12. Pendas, A. M., Knauper, V., Puente, X. S., Llano, E., Mattei, M. G., Apte, S., Murphy, G., and Lopez-Otin, C. (1997) *J. Biol. Chem.*, **272**, 4281-4286.
13. Llano, E., Pendas, A. M., Knauper, V., Sorsa, T., Salo, T., Salido, E., Murphy, G., Simmer, J. P., Bartlett, J. D., and Lopez-Otin, C. (1997) *Biochemistry*, **36**, 15101-15108.
14. Welgus, H. G., Heffrey, J. J., and Eisen, A. Z. (1981) *J. Biol. Chem.*, **256**, 9511-9515.
15. Matrisian, L. M. (1992) *BioEssays*, **14**, 455-463.
16. Knauper, V., Will, H., Lopez-Otin, C., Smith, B., Atkinson, S. J., Stanton, H., Hembry R., and Murphy, G. (1996) *J. Biol. Chem.*, **271**, 17124-17131.
17. Collier, I. E., Wilheim, S. M., Eisen, A. Z., Marmer, B. L., Grand, G. A., Seltzer, J. L., Kronberger, A., Hauer, E. A., and Goldberg, G. (1988) *J. Biol. Chem.*, **263**, 6579-6587.
18. Wilheim, S. M., Collier, I. E., Marmer, B. L., Eisen, A. Z., Grant, G. A., and Goldberg, G. (1989) *J. Biol. Chem.*, **264**, 17213-17221.
19. Nagase, H., and Okada, Y. (1996) in *The Textbook of Rheumatology* (Kelly, W. N., Harris, E. D., Jr., Ruddy, S., and Siedge, C. B., eds.) 5th ed., Saunders Co., Philadelphia, PA, USA, pp. 323-341.
20. Woessner, J. F., Jr. (1994) *Ann. N. Y. Acad. Sci. USA*, **732**, 11-21.
21. Whitham, S. E., Murphy, G., Angel, P., Rahmsdorf, H.-J., Smith, B. J., Lyons, A., Harris, T. J. R., Reynolds, J. J., Herrlich, P., and Docherty, A. J. P. (1986) *Biochem. J.*, **240**, 913-916.
22. Wilheim, S. M., Collier, I. E., Kronberger, A., Eisen, A. Z., Marmer, B. L., Grant, G. A., Bauer, E. A., and Goldberg, G. (1987) *Proc. Natl. Acad. Sci. USA*, **84**, 6725-6729.
23. Muller, D., Quantin, B., Gesnel, M.-C., Milon-Collard, R., Abecassis, J., and Breathnach, R. (1988) *Biochem. J.*, **253**, 187-192.
24. Heppner, K. J., Matrisian, L. M., Jensen, R. A., and Rodgers, H. (1996) *Am. J. Pathol.*, **149**, 273-282.
25. D'Orto, M.-P., Will, H., Atkinson, S., Butler, G., Messent, A., Gavrilovic, E., Smith, B., Timpl, R., Zardi, L., and Murphy, G. (1997) *J. Biol. Chem.*, **250**, 751-757.
26. Sato, H., Takino, T., Okada, Y., Cao, J., Schinagawa, A., Yamamoto, E., and Seiki, M. (1994) *Nature*, **370**, 61-65.
27. Ohuchi, E., Imai, K., Fujii, Y., Sato, H., Seiki, M., and Okada, Y. (1997) *J. Biol. Chem.*, **272**, 2446-2451.
28. Pei, D., and Weiss, S. J. (1996) *J. Biol. Chem.*, **271**, 9135-9140.
29. Ito, A., Mukaiama, A., Itoh, Y., Nagase, A., Thorgesen, I. B., Enghild, J. J., Sasguri, Y., and Mori, Y. (1996) *J. Biol. Chem.*, **271**, 14657-14660.

30. Gearing, A. J. H., Beckett, P., Christodoulou, M., Churchill, M., Clements, J., Davidson, A. H., Drummond, A. H., Galloway, W. A., Gilbert, R., Gordon, J. L., Leber, T. M., Mangan, M., Miller, K., Nayee, P., Owen, K., Patel, S., Thomas, W., Wells, G., Wood, L. M., and Wooley, K. (1994) *Nature*, **370**, 555-557.
31. Kleiner, D. E., Jr., and Stetler-Stevenson, W. G. (1993) *Curr. Opin. Biol.*, **5**, 891-897.
32. Bode, W., Reinemer, P., Huber, R., Kleine, T., Schnierer, S., and Tschesche, H. (1994) *EMBO J.*, **13**, 1263-1269.
33. Docherty, A. J. P., and Murphy, G. (1990) *Ann. Reum. Dis.*, **51**, 469-479.
34. Will, H., and Hinzmann, B. (1995) *Eur. J. Biochem.*, **231**, 602-608.
35. Takino, T., Sato, H., Shinagava, A., and Seiki, M. (1995) *J. Biol. Chem.*, **270**, 23013-23020.
36. Springman, E. B., Angelton, E. L., Birkedal-Hansen, H., and van Wart, H. E. (1990) *Proc. Natl. Acad. Sci. USA*, **87**, 364-368.
37. Schnierer, S., Kleine, T., Gote, T., Hillemann, A., Knauper, V., and Tschesche, H. (1993) *Biochem. Biophys. Res. Commun.*, **19**, 319-326.
38. O'Connell, J. P., Willenbrjck, F., Docherty, A. J. P., Eaton, D., and Murphy, G. (1994) *J. Biol. Chem.*, **269**, 14967-14973.
39. Murphy, G., Nguyen, Q., Cockett, M. J., Atkinson, S. J., Allan, J. A., Knight, C. G., Willenbrjck, F., and Docherty, A. J. P. (1994) *J. Biol. Chem.*, **269**, 6632-6636.
40. Van Wart, H. E., and Birkedal-Hansen, H. (1990) *Proc. Natl. Acad. Sci. USA*, **87**, 5578-5582.
41. Stetler-Stevenson, W. G., Krutsch, H. C., and Liotta, L. A. (1989) *J. Biol. Chem.*, **264**, 17374-17378.
42. Kolkenbrock, H., Orgel, D., Hecker-Kia, A., Noack, W., and Ulbrich, N. (1991) *Eur. J. Biochem.*, **198**, 775-781.
43. Goldberg, G. I., Stpongin, A., Collier, I. E., Genrich, L. T., and Marmer, B. L. (1992) *J. Biol. Chem.*, **267**, 4583-4591.
44. Ogata, Y., Itoh, Y., and Nagase, H. (1995) *J. Biol. Chem.*, **270**, 16518-16521.
45. Woessner, J. F. (1991) *FASEB J.*, **5**, 2145-2154.
46. Koklitis, P. A., Murphy, G., Sutton, C., and Angal, S. (1991) *Biochem. J.*, **276**, 217-221.
47. Nagase, H., Enghild, J. J., Suzuki, K., and Salvesen, G. (1990) *Biochemistry*, **29**, 5783-5789.
48. Cameron, P. M., Marcy, A. I., Rokosz, L. L., and Hermes, J. D. (1995) *Bioorg. Chem.*, **23**, 415-426.
49. Suzuki, K., Enghild, J. J., Morodomi, T., Salvesen, G., and Nagase, H. (1990) *Biochemistry*, **29**, 10261-10270.
50. Imai, K., Yokohama, Y., Nakanishi, I., Ochuchi, E., Fujii,Y., Nakai, N., and Okada, Y. (1995) *J. Biol. Chem.*, **270**, 6691-6697.
51. Knauper, V., Wilhelm, S. M., Seperack, P. K., DeClerck, Y. A., Langle, K. E., Osthues, A., and Tschesche, H. (1993) *Biochem. J.*, **295**, 581-586.
52. Strongin, A. Y., Collier, I., Bannicov, G., Marmer, B. L., Grant, G. A., and Goldberg, G. I. (1995) *J. Biol. Chem.*, **270**, 5331-5338.
53. Sato, H., Kinoshita, T., Takino, T., Nakayama, K., and Seiki, M. (1996) *FEBS Lett.*, **393**, 101-104.
54. Zucker, S., Drews, M., Conner, C., Foda, H. D., DeClerck, Y. A., Langley, K. E., Bahou, W. F., Docherty, A. J. P., and Cao, J. (1998) *J. Biol. Chem.*, **273**, 1216-1222.
55. Atkinson, S. J., Crabbe, T., Cowell, S., Ward, R. V., Butler, M. J., Sato, H., Seiko, V., Reynolds, J. J., and Murphy, G. (1995) *J. Biol. Chem.*, **270**, 30479-30485.
56. Butler, G. S., Butler, M. J., Atkinson, S. J., Will, H., Tamura, T., van Westrum, S. S., Crabbe, T., Clemens, J., d'Orto, M.-P., and Murphy, G. (1998) *J. Biol. Chem.*, **273**, 871-880.
57. Will, H., Atkinson, S. J., Butler, G. S., Smith, B., and Murphy, G. (1996) *J. Biol. Chem.*, **271**, 17119-17123.
58. Cao, J., Drews, M., Lee, H. M., Corner, C., Bahou, W. F., and Zucker, S. (1998) *J. Biol. Chem.*, **273**, 34745-34752.
59. Itoh, Y., and Nagase, H. (1995) *J. Biol. Chem.*, **270**, 16518-16521.
60. Knauper, V., Smith, B., Lopez-Otin, K., and Murphy, G. (1997) *Eur. J. Biochem.*, **248**, 369-373.
61. Pei, D., and Weiss, S. J. (1995) *Nature*, **375**, 244-247.
62. Cao, J., Rehemtulla, Bahou, W., and Zucker, S. (1996) *J. Biol. Chem.*, **271**, 30174-30180.
63. Murphy, G., and Docherty, A. J. (1992) *Am. J. Respir. Cell Mol. Biol.*, **7**, 120-125.
64. Denhardt, D. T., Feng, B., Edwards, D. R., Cocuzzi, E. T., and Malyankar, U. M. (1993) *Pharmacol. Ther.*, **59**, 329-341.
65. Gomez, D. E., Alonso, D. F., Yoshiji, H., and Thorgeirsson, U. P. (1997) *Eur. J. Cell Biol.*, **74**, 111-122.
66. Bodden, M. K., Harber, G. J., Birkedal-Hansen, B., Windsor, L. J., Caterina, N. C. M., Engler, J. A., and Birkedal-Hansen, H. (1994) *J. Biol. Chem.*, **269**, 18943-18952.
67. MacDougall, J., and Matrisian, L. M. (1995) *Cancer Metastasis Rev.*, **14**, 351-362.
68. Green, J., Wang, M., Liu, Y. E., Raymond, L. A., Rosen, S., and Shi, Y. E. (1996) *J. Biol. Chem.*, **271**, 30375-30380.
69. Murphy, G., Houbrechts, A., Cockett, M. I., Williamson, R. A., O' Schea, M., and Docherty, A. J. (1991) *Biochemistry*, **30**, 8097-8102.
70. Carmichael, D. F., Sommer, A., Thompson, R. C., Anderson, D. C., Smith, C. G., Welgus, H. G., and Stricklin, G. P. (1986) *Proc. Natl. Acad. Sci. USA*, **83**, 2407-2411.
71. Fridman, R., Fuerst, T. R., Bird, R. E., Hoyhtya, M., Delkust, M., Kraus, S., Komarek, D., Liotta, L. A., Berman, M. L., and Stetler-Stevenson, W. G. (1992) *J. Biol. Chem.*, **267**, 15398-15405.
72. Birkedal-Hansen, H. (1995) *Curr. Opin. Cell. Biol.*, **7**, 728-735.
73. Murphy, G., Koklitis, P., and Carne, A. F. (1989) *Biochem. J.*, **261**, 1031-1034.
74. Taylor, K. B., Windsor, L. J., Caterina, N. C. M., Bodden, M. K., and Engler, J. A. (1996) *J. Biol. Chem.*, **271**, 23938-23945.
75. O'Shea, M., Willenbrock, F., Williamson, R. A., Crocett, M. I., Docherty, A. J., and Murphy, G. (1992) *Biochemistry*, **31**, 10146-10152.
76. DeClerk, Y. A., Yean, T. D., Lee, Y., Tomich, J. M., and Langley, K. E. (1993) *Biochem. J.*, **289**, 65-69.
77. Kolkenbrock, H., Orgel, D., Hecker-Kia, A., Zimmermann, J., and Ulbrich, N. (1995) *Biol. Chem. Hoppe-Seyler*, **376**, 495-500.
78. Kinoshita, T., Sato, H., Takino, T., Itoh, M., Akizawa, T., and Seiki, M. (1996) *Cancer Res.*, **56**, 2535-2538.
79. Lichte, A., Kolkenbrock, H., and Tschesche, H. (1996) *FEBS Lett.*, **397**, 277-282.

80. Butler, G. S., Will, H., Atkinson, S. J., and Murphy, G. (1997) *Eur. J. Biochem.*, **244**, 653-657.
81. Striklin, G. P., and Welgus, H. G. (1983) *J. Biol. Chem.*, **258**, 12252-12258.
82. Leko, K. J., Hayden, L. J., Sharma, R. R., Rocheleau, H., Greenberg, A. H., and Edvards, D. R. (1994) *Gene*, **117**, 209-217.
83. Overall, C. M. (1994) *Ann. N. Y. Acad. Sci. USA*, **732**, 51-64.
84. Butler, G. S., Apte, S. S., Willenbrock, F., and Murphy, G. (1999) *J. Biol. Chem.*, **274**, 10846-10851.
85. Westbrook, C. A., Gasson, J. C., Gerber, S. E., Selsted, M. E., and Gold, D. V. (1984) *J. Biol. Chem.*, **259**, 9992-9996.
86. Docherty, A. J. P., Lyons, A., Smith, B. J., Wright, E. M., Stephens, P. E., Harris, T. J. R., Murphy, G., and Reynolds, J. J. (1985) *Nature*, **318**, 66-69.
87. Stetler-Stevenson, W. G., Bersch, N., and Gold, D. W. (1992) *FEBS Lett.*, **296**, 231-234.
88. Huhtala, P., Humphries, M. J., McCarthy, J. B., Tremble, P. M., Werb, Z., and Damsky, C. H. (1995) *J. Cell. Biol.*, **26**, 16011-16014.
89. Castagino, P., Soriano, J. V., Montensano, R., and Bottaro, D. P. (1998) *Oncogene*, **17**, 481-492.
90. Burkedal-Hansen, H., Moore, W. G., Bodden, M. K., Windsor, L. G., Burkedal-Hansen, B., De Carlo, A., and Engler, J. A. (1993) *Crit. Rev. Oral Biol. Med.*, **4**, 197-250.
91. Coussens, L. M., and Werb, Z. (1996) *Chem. Biol.*, **3**, 895-904.
92. Nagase, H. (1996) *Matrix Metalloproteinases*, in *Zinc Metalloproteinases in Health and Disease* (Hooper, N. M., ed.) Taylor and Francis, London, pp. 153-294.
93. Lichinghagen, R., Helmbrecht, T., Arndt, B., and Boker, K. H. (1995) *Eur. J. Clin. Chem. Clin. Biochem.*, **33**, 65-71.
94. Nicolson, G. L. (1991) *Semin. Cancer. Biol.*, **2**, 143-154.
95. Cole, A. A., Chubinskaya, S., Schumacher, B., Huch, K., Szabo, G., Yao, J., Mikecz, K., Hasty, K. A., and Kuettner, K. E. (1996) *J. Biol. Chem.*, **271**, 11023-11026.
96. Greenwald, R. A., Golub, L. M., Ramamurthy, N. S., Chowdhury, M., Moak, S. A., and Sorsa, T. (1998) *Bone*, **22**, 33-38.
97. Rodgers, W. H., Matrisian, L. M., Giudice, L. C., Dsupin, B., Cannon, P., Svitek, C., Gorstein, F., and Osteen, K. G. (1994) *J. Clin. Invest.*, **94**, 946-953.
98. McMillan, W. D., Patterson, B. K., Keen, R. R., and Pearce, W. H. (1995) *J. Vasc. Surg.*, **22**, 295-305.
99. Cossins, J. A., Clements, J. M., Ford, J. M., Miller, K. M., Pigott, R., Vos, W., Van der Walk, P., and De Groot C. J. (1997) *Acta Neuropathol. (Berl.)*, **94**, 590-598.
100. Welgus, H. G., Campbell, E. J., Cury, J. D., Eisen, A. Z., Senior, R. M., Wilhelm, S. M., and Goldberg, G. I. (1990) *J. Clin. Invest.*, **86**, 1496-1502.
101. Shimada, T., Nakamura, H., Ohuchi, E., Fujii, Y., Marakami, Y., Sato, H., Seiki, M., and Okada, Y. (1999) *Eur. J. Biochem.*, **262**, 907-914.
102. Puente, X. S., Pendas, A. M., Llano, E., Velasko, G., and Lopez-Otin, C. (1996) *Cancer Res.*, **56**, 944-949.
103. Pei, D. (1999) *Cell Res.*, **9**, 291-303.
104. Hashimoto, K., Yano, A., Tanabe, T., Usui, T., Kihira, Y., and Matsuo, Y. (1997) *Nippon Hinyokika Gakkai Zasshi.*, **88**, 852-857.
105. Busiek, D. F., Ross, F. P., McDonnell, S., Murphy, G., Matrisian, L. M., and Welgus, H. G. (1992) *J. Biol. Chem.*, **267**, 9087-9092.
106. Ohta, S., Imai, K., Yamashita, K., Matsumoto, T., Azumano, I., and Okada, Y. (1998) *Lab. Invest.*, **78**, 79-87.
107. Rodgers, W. H., Osteen, K. G., Matrisian, L. M., Navre, N., Giudice, L. C., and Gorstein, F. (1993) *Am. J. Obstet. Gynecol.*, **168**, 253-260.
108. Wilson, C. L., Heppner, K. J., Rudolph, L. A., and Matrisian, L. M. (1995) *Mol. Biol. Cell*, **6**, 851-869.
109. Lockwood, C. J., Krikun, G., Hausknecht, V. A., Papp, C., and Shatz, F. (1998) *Endocrinology*, **139**, 4607-4613.
110. Talhouk, R. S., Bissel, M. J., and Werb, Z. (1992) *J. Cell Biol.*, **118**, 1271-1281.
111. Boudreau, N. C., Sympson, C. J., Werb, Z., and Bissel, M. J. (1995) *Science*, **267**, 891-893.
112. Gack, S., Vallon, R., Schmidt, J., Grigoriadis, A., Tuckermann, J., Schenkel, J., Weiher, H., Wagner, E. F., and Angel, P. (1995) *Cell Growth Differ.*, **6**, 759-767.
113. Cook, T. F., Burke, J. S., Bergman, K. D., Quinn, C. O., Jeffrey, J. J., and Patridje, N. C. (1994) *Arch. Biochem. Biophys.*, **311**, 313-320.
114. Saarialho-Kere, U. K., Pentland, A. P., Birkedal-Hansen, H., Parks, W. C., and Welgus, H. G. (1994) *J. Clin. Invest.*, **94**, 79-88.
115. Okada, A., Bellocq, J. P., Rouyer, N., Chenard, M. P., Rio, M. C., Chambon, P., and Basset, P. (1995) *Proc. Natl. Acad. Sci. USA*, **92**, 2730-2734.
116. Kinoh, H., Sato, H., Tsunezuka, Y., Takino, T., Kawashima, A., Okada, Y., and Seiki, M. (1996) *J. Cell Sci.*, **109**, 953-959.
117. Kadono, Y., Shibahara, K., Namiki, M., Watanabe, Y., Seiki, M., and Sato, H. (1998) *Biochem. Biophys. Res. Commun.*, **251**, 681-687.
118. Ota, K., Stetler-Stevenson, W. G., Yang, Q., Kumar, A., Wada, J., Kashihara, N., Wallner, E. I., and Kanwar, Y. S. (1995) *Kidney Int.*, **54**, 131-142.
119. Tanney, D. C., Feng, L., Pollock, A. S., and Lovett, D. H. (1998) *Devel. Dynamics*, **213**, 121-129.
120. Von Bredow, D. C., Nagle, R. B., Bowden, G. T., and Cress, A. E. (1995) *Exp. Cell Res.*, **221**, 83-91.
121. Homandberg, G. A., Meyers, R., and Xie, D. L. (1992) *J. Biol. Chem.*, **267**, 3597-3604.
122. Clark, R. F. A. (1990) *J. Invest. Dermatol.*, **94**, 128S-134S.
123. Timpl, R., and Brown, J. C. (1996) *Bioassays*, **18**, 123-132.
124. Whitelock, J. M., Murdoch, A. D., Iozzo, R. V., and Underwood, P. (1996) *J. Biol. Chem.*, **271**, 10079-10086.