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Metalloproteinases of the extracellular matrix and their inhibitors

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Abstract

The dynamic equilibrium between the synthesis and degradation of the extracellular matrix is to a large extent mediated by matrix metalloproteinase (MMP) enzymes, which are antagonized by tissue inhibitors of metalloproteinases (TIMPs). Tissue-degrading enzymes of the metalloproteinase family have been implicated in the pathogenesis of several conditions involving the extracellular matrix. MMPs are a family of zinc-dependent endopeptidases capable of degrading practically all components of the extracellular matrix. Recent insights suggest that MMPs may also have a broader spectrum of functions, including regulation of the inflammatory response and cytokine signaling. MMPs have been subdivided according to their main degradation activity and the continuously growing list of known substrates. Metalloproteinases are promising drug targets, and they are subjected to pharmacological inhibition by clinically available drugs such as tetracyclines and bisphosphonates. Interest in MMPs has recently increased, because their expression is frequently related to tumor progression. As such, metalloproteinases have diagnostic potential as markers to predict the outcome of disease processes. This review introduces the members of the MMP family and discusses their domain structure and function, their significance in physiology and pathology and the mechanism of inhibition by TIMPs.

Key words: extracellular matrix, metalloproteinase, degradation, substrate, tissue inhibitors of metalloproteinases

Introduction

Matrix metalloproteinases (MMPs), also called matrixins, are calcium-dependent multidomain zinc-containing enzymes. The criterion for belonging to this family of endoproteases is the presence of sequences homologous to the catalytic domain of fibroblast collagenase (collagenase 1, MMP-1) (Murphy and Nagase, 2008).

A total of 28 matrix metalloproteinases have been identified, 23 of which are present in humans (Konopka and Brzezińska-Błaszczyk, 2008; Kowalski et al., 2008; Murphy and Nagase, 2008; Rottenberger and Kolev, 2011). In humans, MMPs are synthesized in several cells, e.g. fibroblasts, mastocytes, osteoblasts, odontoblasts, dendritic cells, microglial cells, smooth muscle myocytes, keratinocytes, endothelial cells, macrophages, T lymphocytes, monocytes, neutrophils, and cancer cells (Dziankowska-Bartkowiak et al., 2004; Śliwowska and Kopczyński, 2005; Konopka and Brzezińska-Błaszczyk, 2008; Kwiatkowski et al., 2008; Zygmunt and Zygmunt, 2013). Matrixins are also found in fruit flies, nematodes, sea urchins, hydras and plants (Murphy and Nagase, 2008). MMP numbering starts with 1 and ends with 28, but does not include the numbers 4, 5, 6, 18 and 22. This is due to the duplicated simultaneous discovery of these enzymes by different research groups (Kwiatkowski et al., 2008).

Nuclear magnetic resonance and X-ray crystallography have enabled the determination of the spatial structure of many MMPs. In their construction one can distinguish a characteristic domain common to all the

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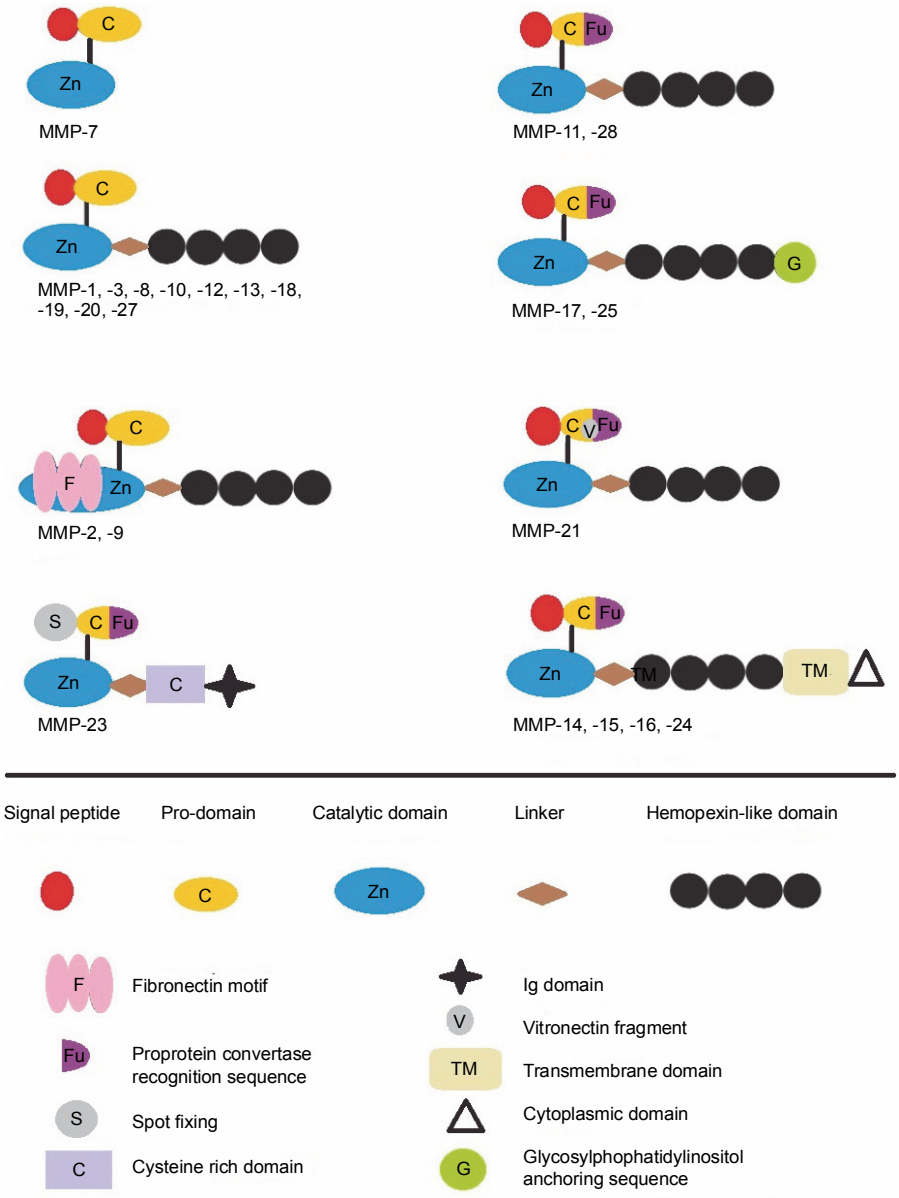

Fig. 1. Metalloproteinases and their domains. Own study based on Murphy G., Nagase H. (2008)

family and a specific domain determining different characteristics of individual enzymes (Fig. 1) (Kwiatkowski et al., 2008; Murphy and Nagase, 2008; Tallant et al. 2010).

Formerly, MMPs had been divided into 6 subgroups mainly depending on their construction and substrate specificity: collagenase, gelatinase, stromelysin, matrilysin, membrane-type MMPs and other classified MMPs (Table 1). At present, bioinformatic methods allow us to compare the primary sequences of MMPs, so that the six evolutionarily differentiated subgroups can be distinguished (Kwiatkowski et al., 2008; Murphy and Nagase, 2008):

A) MMP-19, -26, -28;
B) MMP-11, -21, -23;
C) MMP-17, -25;
D) MMP-1, -3, -8, -10, -12, -13, -27;
E) MMP-14, -15, -16, -24;
F) MMP-2, -7, -9, -20.

MMP structure

All metalloproteinases are constructed of a propeptide consisting of about 80 amino acid residues and a catalytic domain comprising approximately 170 amino

Table 1. Division and functions of extracellular matrix metalloproteinases (Kwiatkowski et al., 2008; Lipka and Boratynski, 2008; Murphy and Nagase, 2008)

MMP	Enzymes	Chromosomal location (human)	Substrats
Collagenases			
MMP-1	interstitial collagenase: collagenase 1	11q22-q23	collagen types I, II, III, V, VII, VIII, X, gelatin, IL-1beta, MMP-2, MMP-9, fibronectin
MMP-8	neutrophil collagenase: collagenase 2	11q21-q22	
MMP-13	collagenase 3	11q22.3	
Gelatinases			
MMP-2	gelatinase A	16q13	gelatin, collagen I, II, III, IV, V, VII, X, XI, fibronectin, laminin, elastin, proMMP-9, -13, alpha-1-antiprotease, IL-1 beta, TGF-beta
MMP-9	gelatinase B	20q11.2-q13.1	gelatin, collagen III, IV, V, VII, X, XI, elastin, laminin, fibronectin, vitronectin, IL-1 beta, TGF-beta, plasminogen
Stromelysins			
MMP-3	stromelysin 1	11q23	proteoglycans, fibronectin, laminin, elastin, gelatin, vitronectin, plasminogen, fibrynnogen, fibrin, collagen type III, IV, V, antithrombin III, MMP-1, MMP-2, MMP-8, MMP-9, MMP-13
MMP-10	stromelysin 2	11q22.3-q23	
MMP-11	stromelysin 3	22q11.2	
Matrilysins			
MMP-7	matrilysin 1	11q21-q22	collagen type IV, glycoproteins, gelatin
MMP-26	matrilysin 2	11p15	
Membrane-type MMPs			
(A) Transmembrane-type			
MMP-14	MT1-MMP	14q11-q12	collagen I, II, III, gelatin, fibronectin, laminin, proteoglycans, pro-MMP2, pro-MMP13
MMP-15	MT2-MMP	15q13-q21	pro-MMP2
MMP-16	MT3-MMP	8q21	pro-MMP2
MMP-24	MT5-MMP	20q11.2	pro-MMP2
(B) GPI-anchored			
MMP-17	MT4-MMP	12q24.3	pro-MMP2
MMP-25	MT6-MMP	16p13.3	gelatin
Others			
MMP-12	macrophage elastase	11q22.2-q22.3	amelagenin, aggrecans, elastin, collagen IV
MMP-19	–	12q14	
MMP-20	enamelysin	11q22.3	
MMP-21	–	10	
MMP-23	CA-MMP	1p36.3	
MMP-27	–	11q24	
MMP-28	epilysin	17q21.1	

acids. In addition, there might exist a hemopexin-like domain of about 210 amino acids, responsible for the binding of extracellular matrix proteins involved in the activation and inhibition of the enzyme. A flexible hinge region (linker) made up of 15-65 amino acid residues is situated between the hemopexin-like domain and the catalytic domain. This stabilizes the enzyme's structure and affects substrate specificity. This region also plays an important role during degradation of some MMP substrates. In the process of collagen degradation by collagenases, interaction between the catalytical and hemopexin-like domains is necessary. Furthermore, it has been shown that this linker itself may take part in the binding of collagen and its degradation (Lipka and Boratyński, 2008; Tallant et al., 2010).

The catalytic domain consists of three α-helices (A-C), five β-sheets (I-V) and a connecting loop. In this domain, there is one catalytic and one structural zinc ion as well as typically three calcium ions. The active site is located in the cleft between the upper and lower subunit of the enzyme. The upper subunit consists of five β-sheets surrounded by three loops and α-helices A and B. The substrate-binding site is formed by β-sheet IV, α-helix B and one loop. Within the active center of the enzyme, the zinc ion is bound by three histidine residues in the conservative sequential motive HEXXHXXGXXH. The "Met-turn" motif, which is located below the catalytic zinc-binding site, is responsible for forming the correct structure around the zinc ion. The fourth ligand of the catalytic zinc is water and this initiates the activation mechanism of enzymatic hydrolysis (Lipka and Boratyński, 2008; Murphy and Nagase, 2008; Groblewska et al. 2010; Tallant et al. 2010; Rottenberger and Kolev, 2011).

The enzyme active site significantly affects the substrate specificity of metalloproteinases. In addition to the catalytic zinc ion, there is a specific S1 pocket, which interacts with the amino acid side chains. The prodomain contains a propeptide that keeps the enzyme in an inactive form (also called a proenzyme, zymogen, pro-MMP). This consists of three α-helices connected by loops and exposed to autoproteolysis. The propeptide has a characteristic amino acid sequence PRCGXPD, a motif called a "cysteine switch". Cysteine, present in this motif, binds one zinc atom and keeps the enzyme in an inactive state. The N-terminal propeptide signal sequence directs the secretion of the proenzyme from the endoplasmic reticulum to the extracellular matrix and undergoes proteolysis on the cell membrane. The hemopexin-like domain is characterized by its analogy to the sequence of the protein binding and transporting heme. It has the shape of an ellipsoidal disk and consists of four symmetrically arranged β-sheets. It has been shown that, in some MMPs, this domain contains calcium, sodium and chlorine ions, which most likely stabilize the enzyme's structure (Gohlke et al., 1996; Tallant et al., 2010; Klein and Bischoff, 2011).

MMP activation

Under physiological conditions, the activity of metalloproteinases can be controlled at several levels (Żebrowski et al., 2003; Dziankowska-Bartkowiak et al., 2004; Śliwowska and Kopczyński, 2005; Kowalski et al., 2008; Kwiatkowski et al., 2008; Łukasiewicz et al., 2008; Groblewska et al., 2010; Gorman et al., 2011; Rottenberger and Kolev, 2011):

1) by stimulating the transcription of genes encoding growth factors, cytokines (IL-1, TNF-α), hormones (parathyroid hormone) and bacterial products (lipopolysaccharide);
2) as a result of post-translational modifications (proenzyme activation);
3) through the action of a family of endogenous tissue inhibitors of metalloproteinases (TIMPs) and inhibitors of serine proteases (serpins);
4) by adjusting the level of enzymes through sequestration of intracellular vesicles;
5) through the acidity of the environment;
6) by the level of substrate specificity.

Metalloproteinases are synthesized as pre-pro-enzymes. Cleavage of signal peptides results in the release of MMPs as zymogens to the extracellular matrix. Thanks to the propeptide domain, these are kept in an inactive pro-enzyme form and as such are found in all tissues. The active site of the zinc-binding pro-enzyme is blocked by a cysteine coordinate bond. Activation of the pro-enzyme is caused by a variety of inorganic compounds, proteases, urea, plasmin, metal ions, detergents, and oxidants and through release of signal peptides and breaking bonds between the cysteine residue and the zinc ion. As a result, the active site is exposed, followed by conformational changes in the enzyme. The thiol group of cysteine is replaced by a water molecule. The removal of the propeptide occurs either autocata-

lytically or by proteolysis involving other proteases. Thus, an enzyme with an exposed active site containing a Zn atom is formed, which is about 10 kDa smaller than the pro-enzyme form. For full activation of the enzyme, the presence of calcium ions is required. The highest proteolytic activity of MMPs is observed at pH 8, while other proteases are active in acidic environments (Żebrowski et al., 2003; Dziankowska-Bartkowiak et al., 2004; Śliwowska and Kopczyński 2005; Kowalski et al., 2008; Kwiatkowski et al., 2008; Lipka and Boratyński, 2008; Tallant et al. 2010; Klein and Bischoff, 2011).

Activation of matrix metalloproteinases might also result from the action of active forms of MMPs and serine proteinases present in the extracellular environment; for example, a protease of the plasminogen activation pathway, kallikrein, cathepsin G, leukocyte elastase and trypsin produced by tumor cells (Dziankowska-Bartkowiak et al., 2004; Śliwowska and Kopczyński, 2005; Łukasiewicz et al., 2008).

As previously mentioned, metalloproteinases are activated by oxidation or nitrosylation. Myeloperoxidases are byproducts of oxidative stress and may cause conformational changes in catalytic domains of MMPs, by which these enzymes are activated (Gorman et al., 2011).

Peroxynitrite also directly activates MMP-1, -8, -9, and -2 through S-glutathionylation forming disulfides between cysteinyl thiol groups in propeptides, which interfere with the Cys-Zn interaction, without requiring cleavage of the propeptide. Thus, the microenvironment of cells can potentially alter the activity of MMPs independently from changes occurring during enzyme synthesis (Gorman et al., 2011).

Controlling the activity of metalloproteinases also occurs through phosphorylation. There is evidence that human MMP-2 is phosphorylated on serine and threonine residues. *In vitro* phosphorylation of MMP-2 by protein kinase C (Sariahmetoglu et al., 2007) and protein kinase CK2 (Filipiak et al., 2014) reduces their activity. The phosphorylation of the cytoplasmic domain of MMP-14 has also been reported, although the functional consequence of this phosphorylation is unknown. Since the effects of the phosphorylation of MMPs have not yet been well documented, the physiological roles of phosphorylation in the regulation of MMP expression or MMP activity remain to be determined (Gorman et al., 2011). Most MMPs are activated extracellularly, but metalloproteinases containing a specific sequence (RXK/RR) at the end of the C-prodomain are activated intracellularly in the Golgi apparatus by proprotein convertases or furins. These include MMP-11, MMP-21 and membrane-type MMPs (Dziankowska-Bartkowiak et al., 2004; Kowalski et al., 2008; Lipka and Boratyński, 2008).

The synthesis process of MMPs is primarily inhibited by steroid hormones and transforming growth factor beta (TGF-β). Tissue inhibitors of MMPs block the membrane-type metalloproteinase molecules and inhibit the activation of pro-enzymes. The imbalance between metalloproteinases and their tissue inhibitors causes an increased MMP activity which is associated with many diseases (Kowalski et al., 2008).

Silencing of MMP expression can be achieved through:

1) inhibition of signal transduction derived from protein kinases;
2) the use of specific antisense oligonucleotides;
3) the use of ribozymes with enzymatic activity against MMP mRNA.

MMP functions

The main role of MMPs is the degradation of basement membrane proteins and the extracellular matrix (ECM). MMP-2 and MMP-9 degrade the main component of vascular basement membrane-type IV collagen, which eases the migration of leukocytes and cells taking part in the course of morphogenesis. Through hydrolysis of ECM, angiogenesis, carcinogenesis and metastasis are also enabled (Dziankowska-Bartkowiak et al., 2004; Kwiatkowski et al., 2008). Hydrolyzing ECM by MMPs destroys the connective tissues and basement membrane which supports cancer growth due to the lack of a barrier. As a result, regions usually inaccessible to macromolecules may become unveiled. Migration of endothelial cells initiated by MMPs 14 and 2 is caused by hydrolysis of a specific sequence of laminin V, which interacts with the α3β1 integrin receptor (Dziankowska-Bartkowiak et al., 2004; Kwiatkowski et al., 2008). During the degradation of ECMs the release of numerous growth factors also occurs. TGF-β is bound to decorin, which maintains tissue integrity. Hydrolysis of decorin leads to the release of TGF-β and may, for example, regulate the expression of genes encoding for MMPs. This process involves, among others, MMP-2, MMP-3, and MPP-7 (Lipka and Boratyński, 2008).

In addition to their ability to hydrolyze ECMs, MMPs are able to degrade a number of other proteins, e.g. cell-surface receptors. They also hydrolyze molecules released from the cell membrane, so that they can inactivate and activate a number of cytokines, chemokines and growth factors (Lipka and Boratyński, 2008).

In physiological conditions, MMPs ensure a correct extracellular environment, appropriate interactions between cells by maintaining a proper ECM structure and regulation of extracellular signals. MMPs exercise control over the development, formation and remodeling of tissues, and the proliferation and differentiation of cells. Furthermore, MMPs are involved in the construction of tissues supporting all internal organs, maturation and follicular atresia, the aggregation of platelets, stimulation of neurite outgrowth and regeneration of connective tissue. Additionally, MMPs enable the course of cyclical changes in the endometrium, the implantation of trophoblast and the course of changes occurring during pregnancy, childbirth and child maturation (Śliwowska and Kopczyński, 2005; Lipka and Boratyński, 2008; Łukasiewicz et al., 2008; Wasilewska et al., 2009; Ziemiańska et al., 2012; Zygmunt and Zygmunt, 2013).

MMPs activate migration of cells involved in the inflammatory response to injured tissues, releasing cytokines and their receptors from cell membranes. MMPs allow wound healing and scar formation (Śliwowska and Kopczyński, 2005; Lipka and Boratyński, 2008; Łukasiewicz et al., 2008; Wasilewska et al., 2009; Zygmunt and Zygmunt, 2013). These enzymes exhibit excessive activity in pathological states, such as infiltration, metastasis and angiogenesis, liver cirrhosis, glaucoma, corneal ulceration, cardiovascular diseases, diseases of the nervous system (Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, meningitis), autoimmune diseases, periodontal diseases, dermatological diseases, osteoporosis, polycystic ovary syndrome, Crohn's disease, and stomach and duodenal ulcers (Żebrowski et al., 2003; Dziankowska-Bartkowiak et al., 2004; Śliwowska and Kopczyński, 2005; Kowalski et al., 2008; Lipka and Boratyński, 2008; Łukasiewicz et al., 2008; Zygmunt and Zygmunt, 2013).

Inhibitors of MMPs

Currently, in humans there are four known tissue specific inhibitors of metalloproteinases, numbered 1-4. Their genes are located on chromosomes Xp11.3-Xp11.23, 17q25, 22q12.1-Q13.2, and 3p25, respectively. TIMPs exist in the intercellular spaces and in body fluids. They are produced by the same cells as MMPs. Their expression is controlled during development and tissue differentiation (Dziankowska-Bartkowiak et al., 2004; Kowalski et al., 2008; Lipka and Boratyński, 2008; Murphy and Nagase, 2008; Rottenberger and Kolev, 2011).

TIMPs' general shape resembles a wedge, and they bind to the active site of MMPs in a manner similar to their substrates. TIMPs are characterized by a two-domain construction. The N-terminal domain is the same for all inhibitors consisting of 125 amino acids; it blocks the activity of metalloproteinases by binding to their active site. The amino group chelates the zinc atom and removes its associated water molecule, whereas the carboxyl group of the N-terminal cysteine associates with the zinc atom by which enzyme activity is blocked. The C-terminal domain composed of about 65 amino acids determines the binding of the inhibitor to the hemopexin-like domain of metalloproteinases. In both domains, there are three pairs of conserved disulfide bridges. Tissue inhibitors of metalloproteinases play a regulatory role in the degradation of extracellular matrix eliminating proteinases and in the inhibition of the activation of MMPs. This is effected by building non-covalent bonds with the latent and active forms of metalloproteinases in a 1:1 molar ratio. Metalloproteinase activity is inhibited by blocking the release of propeptides from pro-MMPs (Żebrowski et al., 2003; Kowalski et al., 2008; Lipka and Boratyński, 2008).

The most widespread tissue inhibitors of metalloproteinases include TIMP-1 and TIMP-2. TIMP-1 is a soluble glycoprotein with a molecular weight of 28 kDa, which is produced by most cells. TIMP-2 is also a soluble protein with a molecular weight of 21 kDa produced by fibroblasts and endothelial cells that have the ability to bind to progelatinase A and to control its activation. TIMP-2 has a higher affinity towards MMP-2, whereas TIMP-1 selectively binds to MMP-9. TIMP-1 does not possess inhibiting properties towards membrane-type MMPs. TIMP-3 is an insoluble inhibitor and is associated with the intracellular matrix. TIMP-2 and -3 bind to all types of MMPs (Żebrowski et al., 2003; Dziankowska-Bartkowiak et al., 2004; Łukasiewicz et al., 2008; Groblewska et al., 2010). Tissue metalloproteinase inhibitors play an important role in establishing a balance be-

tween the mechanisms of synthesis and degradation of the extracellular matrix. In the event of excess secretion of MMP, the secretion of TIMP is also increased. If the synthesis of matrix metalloproteinases is greater than the synthesis of tissue inhibitors, degradation processes become intensified (Dziankowska-Bartkowiak et al., 2004; Groblewska et al., 2010; Zygmunt and Zygmunt, 2013).

Expression of TIMP-1 is primarily controlled by interleukin 1 (IL-1), -6, -10, tumor necrosis factor α (TNF-α) and TGF-β. IL-1 stimulates the synthesis of matrix metalloproteinases and serine proteinases, but also inhibits the synthesis of TIMP-1. A similar kind of action has also been described for TNF-α. TIMP-2 shows no susceptibility to the activity of cytokines. TIMP-3 is regulated by TGF-β, and inhibited by TNF-α (Żebrowski et al., 2003; Dziankowska-Bartkowiak et al., 2004). It has been shown that, besides inhibiting the activity of metalloproteinases, TIMPs also possess other biological properties. TIMP-1 and -2 act as promoters of cell proliferation and inhibit apoptosis. TIMP-1 induces the proliferation of a variety of normal cells, including erythroid progenitor cell lines, keratinocytes, chondrocytes, fibroblasts, endothelial cells, and pathological proliferation of fibroblasts in the course of scleroderma, neoplasms of the liver and breast, bone sarcomas, and other malignancies. TIMP-2 inhibits the growth of endothelial cells induced by the basic fibroblast growth factor, enables the activation of MMP-2, and is involved in cell proliferation in bone sarcomas and fibromas. TIMP-3 is known to be an inducer of apoptosis. TIMP-4 plays an important role in the development of tissue, as it occurs mainly in the brain, heart, ovary and skeletal muscle. TIMPs are also involved in immune response (Konopka and Brzezińska-Błaszczyk, 2008; Lipka and Boratyński, 2008; Murphy and Nagase, 2008; Groblewska et al., 2010; Zygmunt and Zygmunt, 2013).

Typically, reduced expression of TIMPs increases the invasiveness of tumor cells and tumor growth, and its overexpression reduces this process and minimizes the risk of metastases. So far, attempts to develop a method to introduce constructs overexpressing TIMPs into body cells have failed (Zygmunt and Zygmunt, 2013).

Plasma non-specific inhibitors include α2-macroglobulin (produced by the liver), and α1-antiprotease. α2-macroglobulin is a natural inhibitor of all MMPs but its large size does not allow it to effectively penetrate through the blood vessel walls. Thus, the inhibiting effect is significantly reduced. Additionally, inhibition by α2-macroglobulin is irreversible, and the complex formed is removed by endocytosis (Dziankowska-Bartkowiak et al., 2004; Śliwowska and Kopczyński, 2005; Kowalski et al., 2008; Lipka and Boratyński, 2008; Murphy and Nagase, 2008; Groblewska et al., 2010). MMP synthesis is also inhibited by anti-inflammatory cytokines: interferon γ (IFN-γ), IL-4, dexamethasone, and indomethacin. These compounds reduce the production of intermediates in the synthesis of MMPs such as prostaglandin E2 (PGE2) and cyclic adenosine monophosphate (cAMP) (Żebrowski et al., 2003; Śliwowska and Kopczyński, 2005; Łukasiewicz et al., 2008).

Other recognized MMP inhibitors are procollagen C-proteinase enhancer 1, the β-amyloid precursor protein, and the RECK glycoprotein. Neovastat (AE-941) is a natural MMP inhibitor obtained from shark cartilage. It inhibits the activity of MMP-2, MMP-9, and MMP-12, the binding of vascular endothelial growth factor to endothelial cells and tyrosine phosphorylation. It, therefore, has antitumor activity (Śliwowska and Kopczyński, 2005; Gill and Parks, 2008; Kowalski et al., 2008; Lipka and Boratyński, 2008). Synthetic metalloproteinase inhibitors include tetracyclines (doxocycline, oxotetracycline, minocycline) and anthracyclines administered in low doses, chlorhexidine, bisphosphonates, thiols and collagen mimetic peptides (Żebrowski et al., 2003; Śliwowska and Kopczyński, 2005; Łukasiewicz et al., 2008; Gorman et al., 2011). Bisphosphonates have high affinity for bone hydroxyapatite and are primarily used in anticancer therapies. Collagen mimetics include batimastat (BB-94) and marimastat (BB-2516). These imitate the structure of collagen so that the MMPs join them (Śliwowska and Kopczyński, 2005; Konopka and Brzezińska-Błaszczyk, 2008). Doxocycline inhibits gene expression, activation of MMPs and their catalytic activity (Konopka and Brzezińska-Błaszczyk, 2008). Chlorhexidine is a biguanide class antiseptic. It directly inhibits the activity of MMPs (Konopka and Brzezińska-Błaszczyk, 2008).

Trochate (Ro32-3555), AG 3340, and BAY 12-9566 are synthetic MMP inhibitors. Another promising compound is BMS-27291 – a non-protein MMP inhibitor with a broad spectrum of action. Importantly, it does not possess a toxic effect towards skeletal muscles (Śliwowska and Kopczyński, 2005).

Conclusions

Information collected in this review confirms the extremely wide range of functions of MMPs. Their function is not limited only to proteolysis of the extracellular matrix scaffold. The relationship between MMP activity and a number of physiological processes, such as apoptosis, angiogenesis, cell migration etc., is closely related to pathological conditions and, therefore, has resulted in numerous studies into this group of enzymes.

MMPs are involved in maintaining a balance between proteolytic and anti-proteolytic activities. When this balance is disturbed, many diseases occur, ranging from tissue destruction in chronic inflammatory conditions to cancer metastasis and neurological, cardiological or nephrological disorders.

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