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REVIEW ARTICLE

Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs

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Abstract

The main group of enzymes responsible for the collagen and other protein degradation in extracellular matrix (ECM) are matrix metalloproteinases (MMPs). Collagen is the main structural component of connective tissue and its degradation is a very important process in the development, morphogenesis, tissue remodeling, and repair. Typical structure of MMPs consists of several distinct domains. MMP family can be divided into six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other non-classified MMPs. MMPs and their inhibitors have multiple biological functions in all stages of cancer development: from initiation to outgrowth of clinically relevant metastases and likewise in apoptosis and angiogenesis. MMPs and their inhibitors are extensively examined as potential anticancer drugs. MMP inhibitors can be divided into two main groups: synthetic and natural inhibitors. Selected synthetic inhibitors are in clinical trials on humans, e.g. synthetic peptides, non-peptidic molecules, chemically modified tetracyclines, and bisphosphonates. Natural MMP inhibitors are mainly isoflavonoids and shark cartilage.

Keywords

Angiogenesis, apoptosis, cancer, collagen, metalloproteinase, metalloproteinase inhibitor, metastasis

History

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Introduction

The most important function of the extracellular matrix (ECM) is to maintain tissues with their specific mechanical and biochemical properties. The tissue building cells are responsible for the biosynthesis of ECM components, but likewise the matrix has a direct impact on the cell function. Cell–matrix interactions are the result of the presence of a specific cell receptors and epitopes located on the matrix molecules and on the surface of binding cell. The receptors and epitopes play a dominant role not only in cells connection and migration, but also in regulation and stimulation of the cells differentiation and specific proteins expression on the gene level. Pericellular matrix creates a special physiological micro-environment for the cell protection against harmful, physical factors and facilitates the transmission of signals[1].

Collagen is the main structural component of connective tissue, that allows to maintain the stability of organs and support their structural integrity. In the last decade, knowledge of the collagen protein family and collagen-degrading enzymes has been significantly extended. Members of this protein family are characterized by a repeated tripeptide domain rich in proline, which is necessary to form a triplet-helix of collagen. However, the functionality of this diverse group of proteins is not limited to the formation of the structural scaffold of the ECM, but is much broader, due to the presence of additional domains[2,3]. The knowledge of the molecular structure and metabolism of various types of collagen in cells, tissues, and the whole organism is very important to understand the process of the embryo development and the pathologies associated with many human diseases. Molecular mechanisms of the expression and function of various types of collagen similarly allow for a better understanding the pathogenesis of diseases that result from the molecular defects in the gene encoding different molecules in collagen structure. These diseases include: achondroplasia, osteogenesis imperfecta, Alport syndrome, Ehlers–Danlos syndrome, and epidermolysis bullosa. The disorders in collagen metabolism and degradation are important in the course of osteoarthritis, osteoporosis, and oncogenesis. Extensive knowledge of the properties of different types of collagen and enzymes that participate in collagen degradation is very important due to their possible therapeutic use. Because of the collagen ability to bind to different molecules, it can be used as a drug delivery system. However, due to its capacity to create a network and its anchoring functions, collagen may be used in the process of the cytoskeleton forming in normal tissue and in accelerating the process of tissue regeneration[4,5].

Collagen degradation

The degradation of collagen as one of the components of the ECM is a very important process in the development, morphogenesis, tissue remodeling, and repair. It is tightly regulated in physiological conditions, and its dysregulation is among the causations of diseases such as cancer, rheumatoid arthritis, nephritis, encephalomyelitis, chronic ulcers, and fibrosis. The ECM degradation involves different types of proteases, however, the major are matrix metalloproteinase (MMPs) called matrixins[6].

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They belong to a group of endopeptidases, whose enzymatic activity is determined by Ca^{2+} and Zn^{2+} ions. The first identified enzyme in this group was collagenase-1 (now referred to as the MMP-1), discovered in 1962 by Gross and LaPiere in the experiment on the tissue material from the tail of a tadpole of North American frog species *Rana catesbiana*. Collagenase enables the distribution of a large amounts of collagen in the tail of tadpoles during metamorphosis, which in turn facilitates the transformation body into the adult specimen[7,8].

Currently there are 24 known MMPs identified in vertebrates, including 23 in humans. Common classification distinguishes a number of metalloproteinases, starting with MMP-1 and ending with MMP-28, but it does not include MMP-4, MMP-5, MMP-6, MMP-22, since these enzymes were discovered simultaneously by different research teams. MMPs are involved, among others, in trophoblast implantation, embryogenesis, bone growth, angiogenesis, wound healing, and tissue regeneration. The expression of MMPs' genes is observed in the connective tissue cells, primarily in fibroblasts, but also in neutrophils, monocytes, macrophages, and endothelial cells[9]. The biological activity of MMPs is regulated at the level of: gene transcription, the MMP mRNA half-life modulation, regulation of MMP secretion by cells, pro-enzymatic form activation (pro-MMP, zymogens), inhibition of catalytically active enzymes, and inhibition of enzyme activation. MMPs are also subject to neuroimmunohormonal control. The expression of MMPs is maintained in the tissues at a constant low level. Regulation of transcription at the cellular level is under the influence of growth factors, cytokines, hormones, interactions: cell–cell and cell–ECM, as well as physical factors such as UV radiation. Activation and inhibition of MMP is based on a cascade of controlled processes. Factors that increase the expression of MMP are: inflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor α [TNF-α]), hormones and growth factors (transforming growth factor [TGF-β], epidermal growth factor [EGF], platelet-derived growth factor [PDGF] and basic fibroblast growth factor [bFGF]). In contrast, the expression of MMP inhibitors (MMPI) include: corticosteroids, retinoic acid, heparin, and interleukin-4. MMPs are directly activated by the action of proteases (plasmin, trypsin, chymase, elastase) and certain metalloproteinases (MMP-1, MMP-2, MMP-8, MMP-9). Membrane-type MMPs (MT-MMPs) are likewise responsible for local activation of the enzyme system. The proteolytic properties of MMPs are controlled during activation of the inactive, catalytic proenzymes (pro-MMP) by the tissue inhibitors of metalloproteinases (TIMPs). In plasma, the largest part of the protease inhibitors are α2-macroglobulin and α1-antiprotease. In tissues, four TIMPs were extracted so far. TIMPs may inhibit the active forms of MMP and the process of activation or conversion of the pro-MMP into MMP. The expression of TIMP is regulated by the cytokines and growth factors[9].

MMPs structure

MMPs are ECM proteins, although some of them, e.g. MMP-1, MMP-2, and MMP-11 are found within cells and their activity toward to the intracellular proteins has been confirmed as well. Typical MMP consists of several distinct domains conserved among MMP family members (Figure 1). These domains are: predomain, propeptide, catalytic domain, and hemopexin domain. Predomain is absent in MT-MMPs. Propeptide domain, which usually consists of approximately 80 AAs, also contains highly conserved sequence PRCGVPDV. Catalytic domain consists of about 170 AAs and contains a conserved three histidine sequence, which is required for zinc chelation. A typical MMP contains a linker peptide known as a hinge region of variable length and hemopexin domain of approximately 200 AAs. Hemopexin is required for interactions with other MMPs and TIMP. The exceptions include MMP-7 (matrilysin-1), MMP-26 (matrilysin-2), and MMP-23; they do not include hinge region and hemopexin domain, and MMP-23 has a unique cysteine-rich domain and immunoglobulin domain. For their activity typical MMPs require both zinc ion in catalytic site and proteolytical activation, because they are synthetized as inactive zymogens[10].

MMPs family

On the basis of structure and in terms of substrate specificity, MMPs were divided into six groups: collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and other non-classified MMPs. Selected MMP classification is shown in Table 1.

MMPs and cancer

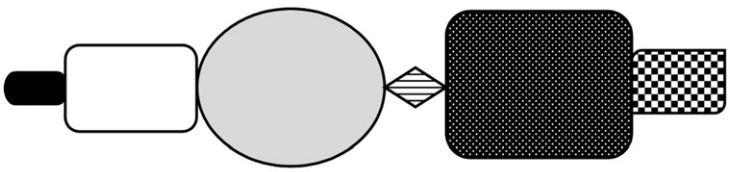
Interactions of cells with the ECM are important for the pathological changes occurring during cell transformation and carcinogenesis. Some ECM proteins affect the phenotype of the tumor through their effect on cell migration or angiogenesis. These include: fibronectin, thrombospondin-1, laminin, and osteopontin. MMPs were traditionally associated with metastasis facilitation by ECM physical barriers breakdown. However, now it's confirmed that they have multiple biological functions in all stages of cancer, from initiation to outgrowth of clinically relevant metastases[13,14].

Although MMPs are connected with cancer cells survival and expansion, they are synthetized by cancer cell in a very small amount. Cancer cells in a paracrine manner, by secreting interleukin, interferon, growth factors, and extracellular MMP inductor, stimulate surrounding host cells to produce required MMPs. MMPs secreted by normal cells can be bounded on the cancer cell surface and used by the tumor cells. They are involved in all steps during carcinogenesis[15].

MMPs influence on tumor growth

Several different mechanisms can be distinguished, by which MMPs regulate the growth of cancer cells, e.g. releasing of cell membrane bound precursors of some growth factors, modulation of bioavailability of growth factors and indirect regulation of proliferative signals by integrins. MMPs may also inhibit tumor growth by different mechanisms, e.g. TGF-β activation or the stimulation of the production of proapoptotic molecules (TNF-α, Fas ligand)[16,17].

Figure 1. Typical MMP structure.



Predomain	Propeptide domain	Catalytic domain	Hinge region	Hemopexin domain	Transmembrane domain

Table 1. Classification of the main members of MMP family with their biological effect, chromosomal location and the group of substrates[6,11,12].

Traditional classification (common name)	Numerical classification	Biological effect	Chromosomal location	Group of substrates for enzymes
MMP classification				
Collagenases				
Collagenase-1	MMP-1	The migration of keratinocytes, reepithelialization, cell migration, platelet aggregation, increase in the bioavailability of IGF-1, cell proliferation, pro-inflammatory effect, and PARP1 activation; in cancer progression – proteolytic activity, degrade physical barriers	11q22-q23	Collagen (I, II, III, VII, VIII, X), casein, entactin, laminin, pro-MMP-1, -2, -9, and serpins
Collagenase-2	MMP-8	The activation of osteoclasts, the enhancement of collagen affinity, β-FGF release, anti-inflammatory activity; in cancer progression – cleavage of α- and β-chemokines and regulation of their mobilization	11q21-q22	Collagen (I–III, V, VII, VIII, X), gelatin, aggrecan, fibronectin
Collagenase-3	MMP-13	In cancer progression- induction of EMT; cell migration	11q22.3	
Gelatinases				
Gelatinase A	MMP-2	The growth of axons, cell migration, the differentiation of mesenchymal cell with inflammation phenotype, enhancement of collagen affinity, cell proliferation, migration of epithelial cells, anti-inflammatory, an increase in the bioavailability of TGF-β, neuronal apoptosis leading to neurodegeneration; in cancer progression – cleavage of IGF-1 binding proteins, proliferation	16q13	Gelatin, collagen (IV–VI, X), elastin, fibronectin
Gelatinase B	MMP-9	Collagen affinity enhancing, pro-inflammatory and anti-inflammatory activity, tumor cell resistance, IL-2 response reduction, hypertrophic chondrocyte apoptosis and the subsequent incorporation of new units of functional osteoblasts; in cancer progression–activation of TGF-β	20q11.2-q13.1	Gelatin, collagens (IV, V, VII, X, XIV), elastin, fibrillin, osteonectin
Stromelysins				
Stromelysin-1	MMP-3	Migration of cells, epithelial cells apoptosis, the formation of epithelial bubbles, epithelial–mesenchymal conversion, angiostatin-like elements generation, the collagen affinity enhancement, release of bFGF, increase in the bioavailability of IGF-1, cell proliferation, pro-inflammatory and anti-inflammatory activity, increase the bioavailability of TGF-β, disorder in cells aggregation, increase in cell invasiveness; in cancer progression–degradation of COL-IV, perlecan; release of VEGF and bFGF, upregulation of angiogenesis	11q23	Laminin, aggregan, gelatin, fibronectin
Stromelysin-2	MMP-10	In cancer progression–degradation of COL-IV, COL-XVIII, perlecan; generation of tumstatin, endostatin, angiostatin, and endorepellin	11q22.3-q23	Collagens (III–V), gelatin, casein, aggregan, elastin, MMP-1,8
Stromelysin-3	MMP-11	In cancer progression – release of α1-proteinase inhibitor, decrease cancer cell sensitivity to NK cells	22q11.2	Fibronectin, laminin, aggregan, gelatin
Matrilysin	MMP-7	Adipocyte differentiation, collagen affinity enhancement, an increase in the bioavailability of IGF 1 and TGF-β, cell differentiation, abnormal cell aggregation and increase in cells invasiveness, apoptosis induced by Fas receptor activation, the effect of pro-inflammatory activation of osteoclasts, vasoconstriction and cell growth	11q21-q22	Collagen (IV–X), fibronectin, laminin, gelatin, aggregan, pro-MMP-9
Metalloelastase	MMP-12		11q22.2-q22.3	Elastin, gelatin, collagen I, IV, fibronectin, laminin, vitronectin, proteoglycan
Matrilysin-2	MMP-26		11p15	Gelatin, collagen IV, pro-MMP-9
Membrane-type MMPs (*MT-MMP*)				
MT-MMP-1	MMP-14	Anti-inflammatory, cell migration, the formation of renal tubules, epithelial cell migration, adhesion reduction, flattening of the cells reduction, trailers embryo to the uterine epithelium	14q11-q12	Collagen (I, II, III), gelatin, fibronectin, laminin aggrecan, tenascin
MT-MMP-2	MMP-15	Adhesion and cell flattering reduction	15q13-q21	Fibronectin, laminin, aggrecan, perlecan
MT-MMP-3	MMP-16	Adhesion and cell flattering reduction	8q21	Collagen III, gelatin, casein
MT-MMP-4	MMP-17		12q24.3	Fibrinogen, TNF precursor
MT-MMP-5	MMP-24		20q11.2	Proteoglycans

The degradation of ECM by different members of MMP family not only removes the physical barriers for a growing tumor, but also releases a lot of biologically active molecules, and reveals the hidden sites in the ECM, where various cell receptors can be bound to. Especially in invasive cancer cell can be found the actin-rich protrusions of the plasma membrane associated with ECM degradation, called invadopodia. F-actin and other cytoskeletal proteins aggregation causes MT-1MMP accumulation,

which occurs in invadopodia. Soluble MMPs attach to adhesive molecules such as integrins and CD44 located on the surface of invadopodia. MMPs degrade different ECM ingredients, releasing a number of various types of molecules affecting cells behavior[18].

One of the major factors connected with tumor growth is TGF-β. Fibronectin degradation by MMP-9 bound to CD44, leads to the releasing of active form of TGF-β. Likewise, decorin considered as a reservoir of TGF-β, releases this factor after the degradation by MMP-1, -2, -3, -7, and -9. The operation of TGF-β depends on the stage of cancer development. In normal epithelial, endothelial, and cancer cells at an early stage of tumor growth, TGF-β causes an inhibition of cell proliferation. It was observed, however, that 85% of all human cancers become resistant to the TGF-β inhibitory effect on proliferation. From that moment TGF-β promotes the development of cancer. Literature data indicate that after having become resistant to TGF-β, the tumor cells increased its production, which affects the ECM and cell adhesion molecules, facilitating metastasis, angiogenesis and induce immunosuppression[19].

Many growth factors in their inactive form are connected with the cell surface. MMPs are responsible for their activation. For example, connection of MMP-7 and CD44 causes proteolytic activation of heparin epidermal growth factor (HB-EGF) and its conversion to active form – EGF. MMPs release also TNF-α, one of the most important pro-inflammatory cytokine that is expressed as a membrane bound precursor (pro-TNF-α) on the macrophages and T-cell surface. In many types of cancer, cells produce an excessive TNF-α that promotes the survival of tumor cells in a NF-κB-dependent manner[20,21].

MMPs interact with cadherins, integrins, and other cell adhesion molecules. Cell adhesion molecules belong to a group of cell surface receptors, which specifically interact with the molecules present on the surface of the neighboring cells or in the ECM. Receptors on cell surfaces belong to a five major classes: cadherin, integrin, super family of immunoglobulin (Ig-CAMs), selectins, and CD44 hyaluronic receptors. Inside the cell receptors interact with many molecules involved in signaling pathways. Tumor cells have an increased number of CD44 isoforms. CD44 receptors bind to MMP-9 on their surfaces, and the resulting complex is involved in the degradation of type IV collagen. Activation of MMP-9 with CD44 causes changes in tumor invasiveness and angiogenesis, probably resulting from the activation of TGF-β. The CD44 joins the MMP-7. In contrast, MT1-MMP is involved in the degradation of CD44, thereby promoting cell migration[22,23].

MMPs influence on apoptosis

MMPs exhibit both pro-apoptotic and anti-apoptotic activity. Their anti-apoptotic action include: cleaving the Fas ligand, proteolytic shedding of tumor associated MHC complex class I related protein and activation of serine/threonine kinase AKT/Protein kinase B. The pro-apoptotic activity of MMPs is usually connected with changes in ECM composition. MMPs lead to apoptosis by cleaving adhesion molecules. MMP-3 induces apoptosis in case of its over-expression in epithelial cells, probably by digestion of laminin. MMPs may also contribute to apoptosis of cells in anoikis process. As a result of such phenomena the selection of resistant cells occurs and the activity of MMPs may lead to tumorigenic cell survival with reduced sensitivity to apoptotic stimuli[11,24,25].

MMPs influence on angiogenesis

Angiogenesis is a process which is essential for tumor growth and development and it involves complex mechanisms by which new blood vessels are formed from existing vessels. MMPs, like in other described mechanisms, may stimulate or inhibit this process and the most important role is played by the following enzymes: MMP2, MMP9, and MMP14[26].

One of the mechanisms by which MMP may promote angiogenesis is basement membrane and ECM components degradation. The disruption of the basement membrane allows the migration of endothelial cells from existing vessels to the newly created. Also releasing ECM bound factors and increasing their bioavailability, in which MMP9 plays a key role, are important mechanism in angiogenesis. The main factor that stimulates angiogenesis and which is releasing by MMP is VEGF (vascular endothelial growth factor). It is mitogen factor specific for endothelial cells, that stimulates formation of new blood vessels from preexisting and increasing their permeability. MMP also trigger the integrin intracellular signaling[10]. On the other hand, MMPs can also inhibit the process of angiogenesis by releasing angiostatin caused by plasminogen cleavage and by the influence on endostatin production caused by collagen XVIII cleaving. Especially MMP-2, -7, -9, and 12 are capable of plasminogen digestion and angiostatin releasing. Angiostatin can increase an apoptosis in cancer cells. However, endostatin, which is produced under the influence of MMP-3, -7, -9, 12, -13, -20, creates stable complexes with pro-MMP-9 and -13 and blocs their activation. It also inhibits the formation of capillaries through binding to α5β1 integrin and FAK phosphorylation blocking[27].

As mentioned above, the activity of MMP causes the uncovering of hidden epitopes of ECM proteins. MMP-9 digests type IV collagen revealing at the same time HUIV26 epitope and regulating blood vessels development. The other epitope – HU177 is present in type I and IV collagen. Its removal from cancer blood vessels causes cell cycle inhibitor expression (cyclin-dependent kinase inhibitor)[28,29].

According to the literature, the major role in angiogenesis plays MMP-2, MMP-9, and MT1-MMP. Other MMPs may play a supporting role by complementing the main activity of MMPs. However, in the studies using knockout mice, one of the MMP genes did not cause any negative consequences on the development of the vascular network. The reason for this may be the prevalence of angiogenesis that may occur under physiological conditions in virtually every tissue in the body[30].

MMPs role in invasion and metastasis

The process of metastasis is a multistage mechanism, starting from losing the intercellular connections and releasing of single cells of the tumor through anoikis prevention, ECM degradation and cell migration, penetration into the blood or lymphatic vessels, adhesion to endothelial cells and finally a secondary growth in the new location[31]. Anoikis may occur due to the loss of cell connection to the ECM. In the tumor cells insensitivity to this mechanism was observed. One of the ways by which cancer cells can cope with anoikis is an epithelial to mesenchymal transition (EMT). In this process, epithelial cells change their phenotype from epithelial to mesenchymal and they also lose their integrity. In EMT an increase in migration, invasion, and metastasis is observed. One of the main inducers of EMT is TGF-β, which is proteolytically activated by MMP28. The cells of mesenchymal phenotype produce more MMPs, and therefore are less dependent on the production of these enzymes by the host cells, increasing their ability to metastasize. After moving to the metastatic locations, cancer cells can return to their epithelial phenotype[32,33]. Cancer cell migration leads to new localization for tumor growth and development. Two ways for cancer cell migration in ECM were described: moving of single cell or a group of cells. During cell group movement, cells connections are preserved, however when cells migrate individually, they move in a way that's called

''mesenchymal'' or ''amoeboidal''. Mesenchymal type of migration occurs after phenotype changing form epithelial to mesenchymal. MMP participation in this process is limited to connecting and disconnecting phase in the migration of mesenchymal type. During cells migration MMPs are associated with adhesion molecules on the cell surface. MMPs digest the ECM components and therefore facilitate the movement of cells. ECM degradation and reorganization during mesenchymal invasion leads to the microspaces formation, that can be used and extended by other cells. Cancer cells can change the way of moving depending on conditions. Inhibition of proteases will be conducive to the amoeboidal type, and with the stiffness of the ECM mesenchymal will be the dominant type of moving[20].

MMPs inhibition strategies as an anticancer target

MMPs play a central role in virtually all major stages of tumor progression: the invasiveness and migration of tumor cells, escape from apoptosis and immune surveillance, metastasis, and angiogenesis. In order to produce drugs with better antitumor activity should be developed inhibitors specific only to those members of the MMPs, which has the procancerogenic properties. It appears that the major role they play in the early stages of tumor growth in which suppression of their activity could lead to tumor growth inhibition and degradation. In contrast, in the fully formed and vascularized tumor MMP activity is not critical for survival. This may explain the lack of good results of therapy using MMPI, which have been subjected patients in advanced stages of cancer development. Effect of MMP varies depending on the tumor type or stage of tumor development[34].

The obvious relation between MMPs activity and cancer development suggests the possibility of various strategies connected with blocking of these enzymes activity. According to literature data, there are three main strategies of MMPs inhibition – at the level of transcription, activation, and inhibition. At the transcription level, the inhibition of MMPs can be achieved by interfering with the extracellular factors (MMPs transcription can be inhibited by interferon) and by blocking signal transduction pathways, like MAPK pathway or ERK pathway. The other step which is crucial for MMPs inhibition is influence on nuclear factors of transcription, e.g. NF-κB or AP-1[35,36]. The next important issue in MMPs activity regulation is their activation, because they are secreted as inactive zymogens. That is why anti-MMPs monoclonal antibodies are considered as an effective

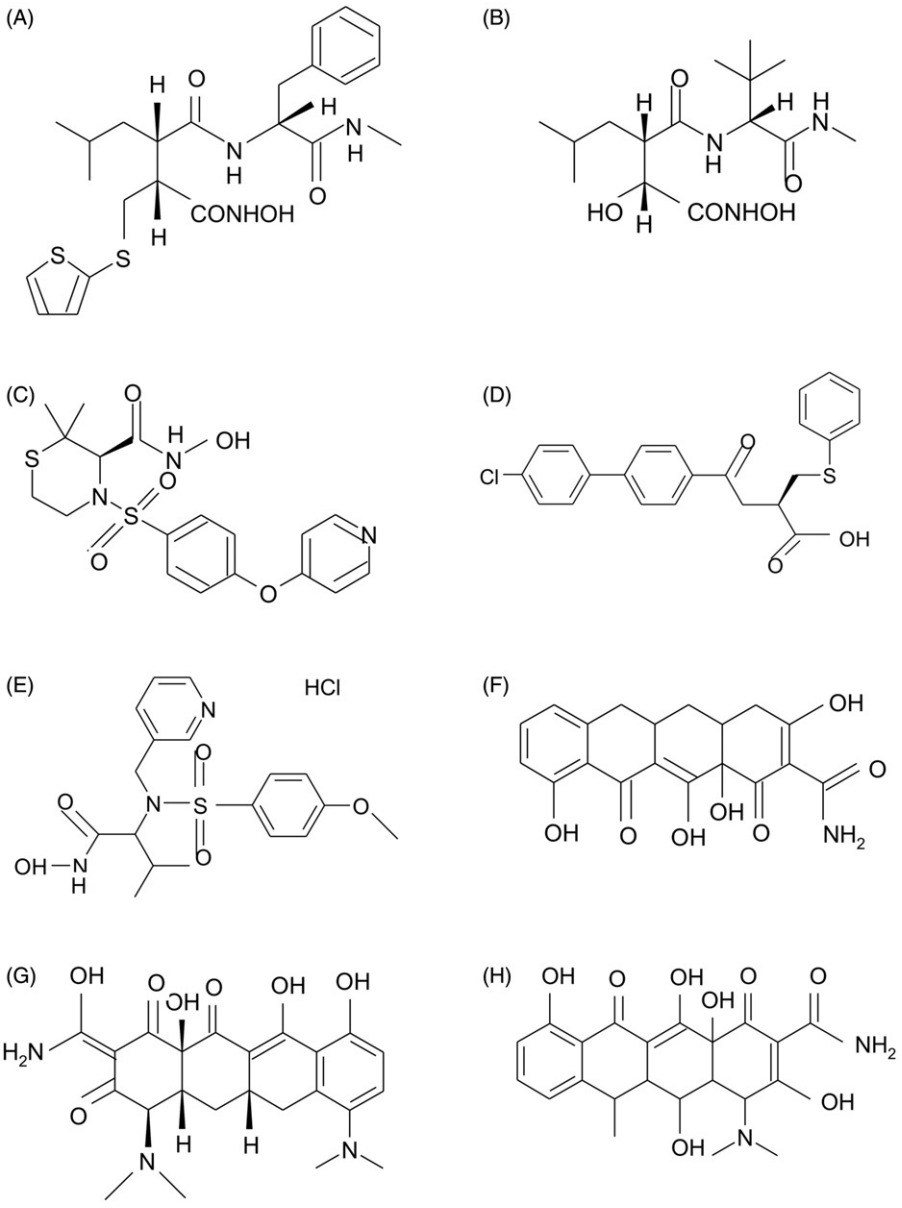


Figure 2. Chemical structure of Batimastat (A) [according to[45]], Marimastat (B) [according to[45]], Prinomastat (C) [according to[46]], Tanomastat (D) [according to[47]], MMI 270B (E) [according to[48]], Metastat (F) [according to[48]], Minocycline (G) [according to[48]], Doxycycline (H) [according to[48]].

method for MMP inhibition. Active MMPs can be inhibited by exogenous and endogenous factors, such as nonspecific α-2 macroglobulin, or specific by TIMP[37].

The MMPI can be divided into two main groups: synthetic and natural inhibitors. Selected synthetic inhibitors are in clinical trials in human, e.g. synthetic peptides, non-peptidic molecules, chemically modified tetracyclines, and bisphosphonates. Peptidomimetic MMPI are pseudopeptide derivatives which act as a competitive inhibitors that inhibit MMP activity mainly by interacting with Zn^{2+} ions located in catalytic sites of enzyme. Hydroxypyrones and hydroxythiopyrones are alternative zinc-binding groups (ZBGs) that, when combined with peptidomimetic backbones, comprise a novel class of MMPI. One of the first drugs that entered clinical trial phase was Batimastat (BB-94) – a hydroxymate derivative with low water solubility and a broad spectrum of inhibition (Figure 2A). To overcome problems with poor solubility, Marimastat (BB-2516) was introduced (Figure 2B). However Marimastat showed side effects, e.g. musculoskeletal pain[11,38].

The second group of MMPI is nonpeptidomimetic MMPIs, that have high specificity, because these agents are based on the 3D conformation of the MMP active site. This category comprises of Prinomastat (AG-3340) (Figure 2C), Tanomastat (BAY12–9566) (Figure 2D), and MMI 270 B (CGS 27023 A) (Figure 2E). Few of them, e.g. BMS, also exhibit musculoskeletal side effects[39]. The other category of MMPI are chemically modified tetracycylins – Metastat (COL-3, CMT-3) (Figure 2F), Minocycline (Figure 2G) and Doxycycline (Figure 2H). In Metastat the dimethyl amino group was removed, that's why it has lower systemic toxicity and lacks antimicrobial activity. It inhibits MMPs by binding to metal ions, such as zinc or calcium. It has entered phase II trials for Kaposi's sarcoma and brain tumors. Doxycycline is currently the only Food and Drug Administration officially approved MMPI for the prevention of periodontitis[40].

In a group of MMPI can be found several drugs that have influence on ECM molecules including MMPs beyond their primary target. For example, bisphosphonates besides the inhibition of the mevalonate pathway, osteoclast activity and bone resorption, also inhibit selected MMPs activity. According to the literature data certain bisphosphonates influence the gene and protein expression of several MMPs and TIMPs, especially in breast cancer. The other agent is letrozole – a reversible nonsteroidal inhibitor of P450 aromatase, which additionally to its main function, inhibits the gelatinases (MMP-2 and -9) released by breast cancer cells and limits metastatic potential of these cells[41,42].

Due to the fairly frequent side effects of above mentioned medicines, the attention was drawn to substances of natural origin, which may also have inhibitory effects on MMPs. The example of such compound is extract from the shark cartilage. It has antiangiogenic and antimetastatic properties, because it inhibits MMP-2, -9, -12, -13, and VEGF. The other natural substance with anticancer properties is genistein, a soy isoflavonoid, that interferes with the expression of several MMPs and TIMPs[43,44].

Considerations for the future

Currently cancer is a leading cause of death worldwide and therefore the research on the new agents with potential anticancer properties are of such importance. MMPs play a crucial role in ECM remodeling and cancer progression, so it seems obvious that they and their inhibitors could be a target for newly synthetized anticancer drugs. Selective inhibition of enzymatic activity in defined localization is also connected with potential anticancer activity. The link of function of the MMPs with the processes of apoptosis, cell migration, angiogenesis, which often lead to the pathological processes, allows to use metalloproteinases as tumor markers. An increased expression and activity of MMPs in both tissues and blood of patients with various types of cancer is observed. This may have potential value as a marker of invasiveness, and the risk of distant metastasis. There are few studies examining the concentration of MMPs *in vivo*, but there is the possibility of MMPs inhibition by synthetic inhibitors of MMPs, what offer the hope to implement new therapeutic strategies for treating cancer patients.

Declaration of interest

The authors confirm that this article content has no conflict of interest.

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