

## MATRIX METALLOPROTEINASES: IMPORTANT PARTICIPANTS IN EVERY STEP OF TUMOR DEVELOPMENT AND PROMISING TARGETS IN MODERN ANTI-TUMOR THERAPIES

*Simonida Stojanović<sup>1</sup>, Sanja Veličković<sup>2</sup>, Ivana Radojević<sup>1</sup>, Simona Stojanović<sup>3</sup>, Ljubinka Janković Veličković<sup>4</sup>*

Matrix metalloproteinases are proteolytic enzymes that are able to cleave almost all components of extracellular matrix as well as many other soluble and membrane attached molecules of very diverse nature. Their proteolytic activity is crucial for embryogenesis, tissue development, remodeling and organisation. As important as in physiological processes, they play crucial role in tumor development, progression, tissue invasion and metastasis.

In this review, we discuss complex involvement of these zinc-dependent endopeptidases in every step of tumor development and progression. We highlight the importance of collaboration between tumor cells and tumor microenvironment at different levels of tumor development and spreading. We also emphasize the importance of inhibition of certain matrix metalloproteinases (depending on tumor type and stage) in order to support cytostatic therapy. *Acta Medica Medianae 2023;62(2): 45-51.*

**Key words:** matrix metalloproteinases, tumor microenvironment, stem cells, angiogenesis, invasion

<sup>1</sup>Milutin Milankovic High Medical College of Vocational Studies, Beograd, Srbija

<sup>2</sup>University Clinical Center Niš, Hematology and Clinical Immunology Clinic, Niš, Serbia

<sup>3</sup>University of Niš, Medical Faculty, Narrow Scientific Field Oral surgery, Niš, Serbia

<sup>4</sup>University of Niš, Medical Faculty, Department of Pathology, Niš, Srbija

Contact: Simonida Stojanović  
Učitelj Milina 20/16, 18000 Niš, Serbia  
E-mail: simonidast78@yahoo.com  
Phone: 062/1803718

### Introduction

Matrix metalloproteinases (MMPs) are family of zinc-dependent endopeptidases (1) that are capable of cleaving almost every component of the extracellular matrix (ECM). According to their substrate specificity and their primary structure, they can be divided into subgroups: collagenases, gelatinases, stromelysins, membrane-associated MMPs (Table 1).

All MMPs possess basic domain structure: 1) signal peptide for extracellular localization; 2) prodomain that inhibits the zymogen form and 3) conserved catalytic domain. Some MMPs possess additional domains that enable localization,

interaction with protein complexes or selectivity for specific proteins (2). They are synthesized as inactive zymogens and can be activated either by other MMPs or by serine proteases.

MMPs are crucial for organ development during embryogenesis (3, 4), healing processes, tissue regeneration, angiogenesis and many other processes that include rearrangement of extracellular matrix (ECM) and modulation of signaling pathways (5). Due to their ability to interact with multiple substrates in a proteolytic manner, MMPs can control cell adhesion, migration and stem cell differentiation (6-8). As important as in physiological processes, they also play crucial role in tumor development, invasiveness and metastases (9). Earlier researches were based on the ability of MMPs to degrade components of ECM (10) and enable invasion and metastases of cancer cells (11). Furthermore, it was established that the role of MMPs in tumor development is much wider and much more complicated. They are also involved in cell proliferation, apoptosis, angiogenesis and epithelial to mesenchymal transition (EMT) (12-14). Due to their ability to cleave different molecules, such as growth factors, cell surface receptors, cell adhesion molecules, cytokines or chemokines, MMPs can also modulate signaling pathways that regulate differentiation and modulate stem cell niches (15).

MMPs can be derived from tumor cells and also from tumor microenvironment (host derived),

**Table 1.** Classification of matrix metalloproteinases

| MMP family    | Name                     | Number |
|---------------|--------------------------|--------|
| Collagenases  | Interstitial collagenase | MMP-1  |
|               | Neutrophil collagenase   | MMP-8  |
|               | Collagenase 3            | MMP-13 |
| Gelatinases   | Gelatinase A             | MMP-2  |
|               | Gelatinase B             | MMP-9  |
| Stromelysins  | Stromelysin-1            | MMP-3  |
|               | Stromelysin-2            | MMP-10 |
|               | Stromelysin-3            | MMP-11 |
|               | Stromelysin-4            | MMP-19 |
| Matrilysins   | Matrilysin-1             | MMP-7  |
| Elastase      | Matrilysin-2             | MMP-26 |
|               | Metalloelastase          | MMP-12 |
| Membrane type | MT1-MMP                  | MMP-14 |
|               | MT2-MMP                  | MMP-15 |
|               | MT3-MMP                  | MMP-16 |
|               | MT4-MMP                  | MMP-17 |
|               | MT5-MMP                  | MMP-24 |
| Unclassified  | MT6-MMP                  | MMP-25 |
|               | Enamelysin               | MMP-20 |
|               |                          | MMP-18 |
|               |                          | MMP-23 |
|               | Epilysin                 | MMP-28 |

such as cancer activated fibroblasts (CAFs) or inflammatory cells. Actually, the interaction between tumor cells and tumor microenvironment is crucial for tumor promotion, invasion and progression (16, 17).

#### The role of MMPs in tumor initiation process

High degree of genetic heterogeneity in tumors suggest that genomic instability is crucial for tumor initiation and development. By cleaving the components of ECM, MMPs can start tumor initiation and progression because the instability of ECM can indirectly activate cellular processes that cause genomic instability and DNA damage (18). MMPs target molecules involved in cell-ECM adhesion or cell-cell adhesion, such as E-cadherin. Some researches showed that loss of cell adhesion reduces expression of p53 in diverse cell types. In keratinocytes, the loss of cell adhesion reduces p53 expression by 80% (19). Adhesion dependent loss of genomic surveillance increases DNA damage and induces genomic instability. Rac1b was identified in breast and colorectal tumors and is involved in accumulation of cyclin D1, cell cycle progression, apoptosis resistance and cellular transformation. Production of Rac1b is also involved in elevating levels of reactive oxygen species (ROS) that can directly damage DNA or DNA repairing mechanisms (20, 21). It was also shown that MMP3 stimulates production of Rac1b

in breast cancer. Sustained expression of MMP3 by breast stromal cells leads to hyperplasia, dysplasia and other changes in stromal components (22).

#### Effects of MMPs on proliferation and apoptosis

MMPs can activate TGF- $\beta$  in a proteolytic manner (by cleaving their precursor) or in a non proteolytic manner (by modifying the ECM or though HPX domain). In normal tissue, TGF- $\beta$  has proapoptotic and cytostatic function, but in cancer tissue, its action is reversed. MMPs can also proteolytically activate growth factors (EGF, HGF, IGF...) and promote tumor expansion (23, 24). On the contrary, they can inactivate Fas receptor and disable proapoptotic pathway, which leads to inhibition of apoptosis and consequent resistance to chemotherapy. MMP-7 plays an important role in activation of EGFR and also cleaves cell surface proteins such as Fas ligand and E-cadherin, which promotes cellular proliferation and disables apoptosis (25).

#### MMP take role in epithelial-to-mesenchymal transition

Epithelial-to-mesenchymal transition (EMT) is a key step in tumor invasion and metastasis. It is a process during which epithelial cells loose cell to cell adhesion and polarity and enhance their motility (26). This process is characterised by

upregulation of mesenchymal markers and N-cadherin and downregulation of E-cadherin. MMP-induced EMT has been studied in many different cancer tissues. MMP-3 directly activates EMT process in breast cancer. MT1-MMP induces EMT in esophageal and oral squamous cell carcinoma, breast carcinoma and prostatic carcinoma (27). Upregulation of MMP-7 leads to acinar-to-ductal metaplasia, a precursor of pancreatic ductal adenocarcinoma through activation of Notch signaling pathway (28). MMP-1 can activate proteinase activated receptor (PAR) by cleaving its extracellular domain. This leads to cancer cell migration and invasive behaviour in breast cancer (29).

### **MMP induced EMT can increase tumorigenicity through induction and regulation of cancer stem cell characteristics.**

Cancer stem cells represent small population of tumor cells responsible for tumor growth, heterogeneity, metastatic potential and resistance to chemotherapy. In previous studies has been established that tumor cells with stem cell like characteristics showed asymmetric division, very slow replication and resistance to chemotherapy and apoptosis (30). Cancer stem cells as well as stem cells in normal tissue are placed in stem cell niche which consists of extracellular matrix, adjacent stromal cells and extracellular soluble factors: cytokines, chemokines, growth factors... The niche provides balance between quiescence and self-renewal of stem cell population and prevents uncontrolled proliferation.

Thanks to their ability to cleave and degrade different components of ECM, MMPs can disturb the balance within the stem cell niche (31). The best-studied influence of MMPs on stem cell niche is the one in the bone marrow: MMP-9, MMP-14, MT1-MMP (32, 33). In human epidermal cells, inhibition of MMP-2 and MMP-14 provides longer cell survival (34, 35). MMP-10 leads to the expansion of bronchoalveolar stem cells in the context of K-ras derived lung carcinoma (36). It was also shown that MMP-10 regulates stemness of ovarian cancer stem-like cells and its overexpression leads to maintenance of cancer stem cells (CSCs) and resistance to platinum reagent (37).

### **MMPs influence tumor angiogenesis**

During angiogenesis, quiescent endothelial cells (ECs) become migratory and invade the surrounding tissue. This process requires enzymes that are able to cleave components of basement membranes (BM) and ECM. Many performed studies proved that MMP-9 is a critical component of angiogenic switch. MMP-9 is able to activate vascular endothelial growth factor (VEGF) and start the cascade of events that lead to endothelial cells proliferation, migration, survival and new

vessels formation. Other studies implicated that MMP-9 can also act as an inhibitor of angiogenesis through activation of angiogenesis inhibitors: angiostatin, tumastatin, endostatin (38). Some authors tried to explain these contradictory findings by the origin of MMP-9 and by the diversity of models. In mouse models of chondrosarcoma cells it was shown that downregulation of MMP-2 resulted in suppression of tumor growth through reduced angiogenesis. There are also studies that highlight the role of membrane type metalloproteinase MT1-MMP in tumor angiogenesis (39, 40).

### **MMPs enable tissue invasion and metastasing**

Degradation of stromal connective tissue and basement membrane are two crucial processes in tumor invasion and metastases. Interstitial collagens are extremely resistant to proteolytic attacks and can be degraded only by MMPs (41). MT1-MMP (MMP14) is well established and most important in pericellular proteolysis. Overexpression of MT1-MMP in squamous cell carcinoma (SCC) of oral cavity and oesophageal SCC leads to higher invasiveness and poor prognosis (42). MMP-9 and MMP-11 were shown to be significantly prognostic for shorter relapse-free survival in breast cancer. Serum levels of MMP-2, MMP-9 and MT1-MMP are significantly higher in patients with bone metastases in prostate cancer (43). MMP-13 can activate proteolytic cascade that enables activation of MMP-9 and cleavage of galectin, a suppressor of osteoclastogenesis. This event promotes osteoclastogenesis, and creates favorable microenvironment for bone metastasis in breast cancer (44).

The most studied MMPs whose overexpression correlates with poor prognosis in different types of carcinoma are shown in Table 2.

### **Possibilities for therapeutic inhibition of MMPs**

There are several MMP inhibitors that take part in different processes: physiological or pathological. There is a circulating general protease inhibitor alpha-2-macroglobulin and four tissue inhibitors of metalloproteinases (TIMPs). In physiological circumstances, these inhibitors provide balance between degradation and production in ECM. They are non-selective and all MMPs can be inhibited by a number of different TIMP proteins (45). So far, attempts for MMP inhibition by TIMPs in order to prevent tumor progression revealed mostly unsuccessful. One of possible explanations is that not all MMPs are related to poor prognosis. For example, MMP-8 was shown to be cancer-protective MMP and its downregulation is associated with poor outcome in breast cancer (46) and melanoma (47).

**Table 2.** The most studied MMPs related to poor prognosis in different types of carcinoma

| Tumor type                          | MMPs related to poor prognosis                        | Reference          |
|-------------------------------------|---|--------------------|
| Lung carcinoma                      | MMP-2, MMP-3, MMP-9, MMP-10                           | 17, 36             |
| Breast cancer                       | MMP-3, MMP-7, MMP-9<br>MMP-11, MT1-MMP, MT2-MMP       | 18, 19, 21, 22, 25 |
| Epithelial ovarian cancer           | MMP-10  | 37, 48             |
| Oral squamous cell carcinoma        | MT1-MMP, MMP-7  | 42                 |
| Oesophageal squamous cell carcinoma | MMP-1, MMP-2, MMP-3, MMP-7,<br>MMP-9, MMP-10, MT1-MMP | 27                 |
| Colorectal carcinoma                | MT1-MMP, MMP-1, MMP-2, MMP-3,<br>MMP-7, MMP-11        | 6, 9               |
| Prostate cancer                     | MMP-2, MMP-9, MT1-MMP                                 | 11, 43, 45         |
| Pancreatic carcinoma                | MMP-7   | 28                 |

Marimastat was the first orally bioavailable MMP inhibitor to enter clinical testing. Trials were conducted in patients with colorectal, ovarian, pancreatic and hormone-refractory prostate cancer. Although phase I and II were promising, there are no precise data about phase III trials to date.

Preclinical studies with batimastat—competitive, reversible, broad-spectrum MMPI were performed in mice and suggested favorable therapeutic effects in ovarian, breast, colon cancer treatment as well as in treatment of melanoma, in combination with standard therapies. The most dramatic effect has been accomplished in ovarian carcinoma concurrent treatment with cisplatin and batimastat (48).

Studies with resveratrol (RSV) in cell lines and mouse models were also successful. RSV is natural product whose spectrum of influence is much wider than only MMP inhibition. Studying its effect in prostatic cancer development it was shown that RSV may inhibit cancer initiation, proliferation and metastases in many levels by targeting tumor microenvironment (TME) (49, 50).

### Conclusion and further perspectives

Tumor development and progression is multi-leveled process that involves the interaction of tumor cells and host microenvironment. Interaction between tumor cells and host components such as immune cells, fibroblasts, endothelial cells, components of ECM is necessary for tumor growth at primary site, invasion and progression as well as metastasing to distant organs.

Matrix metalloproteinases, as powerful proteolytic enzymes, derived from tumor cells and also from host cells, contribute to multiple stages

of tumor progression. Through their ability to degrade basement membrane, components of ECM and nonmatrix substrates enable tumor spreading and help tumor angiogenesis. Their role in maintenance of cancer stem cells is also important and contributes to resistance to chemotherapy and apoptosis.

As important as destruction of tumor cells by chemo and radiotherapy, it is also necessary to block the interaction between tumor cells and tumor microenvironment, because tumor microenvironment enables maintenance and survival of tumor cells. Compromising the expression of wide range of MMPs is a logical and promising step in anti-cancer therapy to support standard therapies.

Trials with TIMPs were not so successful and differed in cell culture and animal models. The reason might be in non-selectivity of these inhibitors. Nowadays, the understanding of how each MMP acts in different cancers and different stages of cancer development and progression is much more sophisticated. In combination with newly developed methods for discovering highly selective inhibitors of MMPs it can be a promising step forward in attempts to disable communication between cancer cells and their microenvironment. Targeting multiple proteases may be an effective strategy for stopping tumor growth and progression. All of this could lead to much more successful, combined anticancer therapies.

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## MATRIKS METALOPROTEINAZE – VAŽNI UČESNICI U SVAKOM KORAKU RAZVOJA TUMORA I OBEĆAVAJUĆE METE U SAVREMENOJ ANTI TUMORSKOJ TERAPIJI

*Simonida Stojanović<sup>1</sup>, Sanja Veličković<sup>2</sup>, Ivana Radojević<sup>1</sup>, Simona Stojanović<sup>3</sup>, Ljubinka Janković Veličković<sup>4</sup>*

<sup>1</sup>Visoka medicinska škola strukovnih studija „Milutin Milanković“, Beograd, Srbija

<sup>2</sup>Univerzitetski klinički centar Niš, Klinika za hematologiju, alergologiju i kliničku imunologiju, Niš, Srbija

<sup>3</sup>Univerzitet u Nišu, Medicinski fakultet, UNO Oralna hirurgija, Niš, Srbija

<sup>4</sup>Univerzitet u Nišu, Medicinski fakultet, Katedra za patologiju, Niš, Srbija

Kontakt: Simonida Stojanović  
Učitelj Milina 20/16, 18000 Niš, Srbija  
E-mail: simonidast78@yahoo.com  
Telefon: 062/1803718

Matriks metaloproteinaze su proteolitički enzimi koji mogu da razgrađuju skoro sve komponente ekstracelularnog matriksa, kao i mnoge druge solubilne i membranske molekule različite prirode. Njihova proteolitička aktivnost veoma je značajna za embriogenezu, razvoj, remodelovanje i organizaciju tkiva. Osim što su veoma značajne za odvijanje fizioloških procesa, imaju i veoma važnu ulogu u razvoju i progresiji tumorskog procesa, tkivnoj invaziji i metastaziranju tumora.

U ovom preglednom članku razmatramo kompleksno učešće ovih endopeptidaza zavisnih od cinka u svakom koraku razvoja i progresije tumorskog procesa. Posebno ističemo značaj saradnje između tumorskih ćelija i njihove mikrookoline na različitim nivoima razvoja i širenja tumorskog procesa. Takođe, naglašavamo značaj inhibicije pojedinih matriks metaloproteinaza (u zavisnosti od vrste i stadijuma tumora) u cilju podrške citostatskoj terapiji. *Acta Medica Medianae 2023;62(2):45-51.*

**Ključne reči:** matriks metaloproteinaze, tumorska mikrookolina, matične ćelije, angiogeneza, invazija

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