Chapter 6

Metalloproteinases in Brain Tumors

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1. Introduction

Metalloproteinases (MMPs) were first described by Gross more than fifty years ago. They are a family of zinc-dependent endopeptidases. They comprise a group of 25 enzymes. MMPs were first described as proteases degrading extracellular matrix (ECM) proteins such as collagens, elastin, proteoglycans and laminins, hence they were named matrix metalloproteinases. MMPs were divided according to their substrate specificity into collagenases, gelatinases, stromolysins and matrilysins. This classification was later replaced by numbering the enzymes according to the chronology of their identification.

Four metalloproteinases (MMP-14, MMP-15, MMP-16 and MMP-24) have a transmembrane and cytosolic domains. They constitute a subgroup of membrane-type metalloproteinases (MT-MMPs). Recently an intracellular, nuclear localization and functions of metalloproteinases have been discovered [1-4].

2. Physiological role of metalloproteinases

MMP-1 (collagenase 1) hydrolyzes collagen types I, II, III, VII, VIII, X and XI, as well as gelatin, fibronectin, vitronectin, laminin, tenascin, aggrecan, links protein, myelin basic protein and versican. MMP-2 (gellatinase) degrades collagen types I, II, III, IV, V, VII, X and XI, gelatin, elastin, fibronectin, vitronectin, laminin, entactin, tenascin, SPARC and aggrecan, links protein, galectin-3, versican, decanin and myelin basic protein. One of the most important differences between these two metalloproteinases is the possibility of the hydrolysis of elastin and collagen type IV by MMP-2, but not by MMP-1. Researchers have also focused their interest

on MMP-9 which can degrade collagen types IV, V, VII, X and XIV, fibronectin, laminin, nidogen, proteoglycan link protein and versican.

For a long time metalloproteinases have been viewed solely as enzymes of matrix proteins breakdown. Results of researches performed in recent years indicate that there is a group of non-matrix proteins which can be substrates for various MMPs. Metalloproteinases are involved in the activation of latent forms of effective proteins. For example, MMP-2, MMP-3 and MMP-9 can activate interleukin 1β (IL-1β). They can also act on active cytokines, IL-1β undergoes subsequent degradation catalyzed by MMP-3. Metalloproteinases can alter cell surface proteins such as receptors and act on microbial peptides.

Metalloproteinases are not indiscriminately released by cells. They are secreted to or anchored to cell membrane. MT-MMPs have a specific transmembrane domain placing them in a certain position. Other metalloproteinases can be bound by specific cell-MMP interactions. This phenomenon allows an exact localization of their proteolytic activity [1-3].

3. Activation of metalloproteinases

Metalloproteinases are encoded as inactive proenzymes, zymogens. They undergo proteolytic activation. This process can take place either intracellulary or extracellulary. One third of MMPs are activated by intracellular serine protease, furin. This process takes place in trans-Golgi network. A number of MMPs has a cleavage site for other metalloproteinases. MMP-3 activates proMMP-1 and pro-MMP-7. Some metalloproteinases have been described to be activated by kallikrein or plasmin.

In vivo studies indicate that reactive oxygen species (ROS) generated by neutrophils can both activate and subsequently inactivate MMPs. Hypochlorus acid (HClO) generated by neutrophil myeloperoxidase and hydroxyl radicals can activate proMMP-1, proMMP-7 and proMMP-9, whereas peroxynitrate can activate proenzymes of MMP-1, MMP-2 and MMP-9. This process enables a control of burst of proteolytic activity within an inflammatory setting.

Like some other proteases, activity of MMPs is controlled also by two other mechanisms, regulation of gene expression and specific inhibitors. MMP-2 is constitutively expressed and regulation of its activity occurs by either activation or inhibition. Expression of a number of metalloproteinases is up-regulated during various pathological conditions. Among them inflammation is the most studied setting. MMPs are inhibited by α-2 macroglobulin and tissue inhibitors of metalloproteinases (TIMPs). There are four TIMPs. Their secretion is also regulated and represents another point in a network of control of the activity of metalloproteinases. TIMP-3 is primarily bond to ECM and allows a regulation of MMPs' activity in the very site of their action. The network of the control of the activity of metalloproteinases is complex and very precise. Sometimes TIMP interacts with proMMP and inactivate other MMP, e.g. a complex of TIMP-1 and proMMP-9 inactivates MMP-3.

Protection from MMP degradation represents the next step in this sophisticated network of diverse interactions. Neutrophil gelatinase-associated lipocalin (NGAL) bounds to MMP-9 protecting this metalloproteinase from its degradation [1-3].

4. Metalloproteinases in central nervous system

Metalloproteinases in central nervous system can be produced by cells constituting it, by cells of blood vessels' wall or by blood cells. The production of MMPs in central nervous system under normal conditions is low, however it can be augmented in several neoplastic and non-neoplastic conditions. The expression of MMP-14 (MT1-MMP) in microglia is very low under physiological conditions. It can be increased in neurodegenerative and neuroinflammatory pathologies, e.g. Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS) or even in a stroke. Astrocytes were reported to secrete MMP-2 and MMP-9 [5,6].

For a long time MMPs were thought to be enzymes acting exclusively in extracellular compartment. Studies carried in last few years have revealed nontraditional roles for MMPs in extracellular space as well as in the cytosol and nucleus. MMP-2 and MMP-9 which were largely studied in central nervous system have been shown to present an increased activity in cortex neuronal nuclei after focal cerebral ischemia. These two MMPs, MMP-2 and MMP-9, are also termed gelatinase A and gelatinase B. The increased gelanolytic activity in nucleus occurs to be linked with MMP-dependent cell death triggering neuroinflammatory reactions. MMP-13, named also collagenase-3, was found to be activated mostly in neurons and oligodendrocytes. Its function in cell nucleus may be linked to the apoptosis cascade following ischemic stimulus. MMPs localized in cell nucleus can have a different set of target proteins than MMPs acting in extracellular space. Poly-ADP-ribose polymerase-1 (PARP-1) and X-ray cross-complementary factor-1 (XRCC-1) can be the substrates for MMP-dependent cleavage [4].

5. Metalloproteinases in brain tumors

Gliomas are the most common malignant tumors in the brain, and the overall prognosis for patients suffering from this neoplasm is poor. Glioblastoma multiforme (GBM) is the most aggressive type of glioma. Molecular mechanisms of invasiveness of this neoplasm have been most widely studied. Many factors are involved in the migration and invasiveness of GBM. MMPs have gained a large interest of researchers. The role of MMPs is significant in the degradation of ECM, thereby facilitating tumor cell invasion into surrounding stroma. Neoplastic cell invades in three steps. The first one is the attachment of tumor cell to the basement membrane through binding of neoplastic cell receptors to the basement membrane receptors. The next one is the secretion of hydrolytic enzymes, MMPs, which locally degrade ECM by extracellular proteolysis. The third step comprises the movement of the tumor cell to the free space obtained by degradation of ECM. MMP-13 is involved in the initiation of progression of invasion due to its proteolytic activity. Expression of MMP-13 is higher in glioma than in the surrounding normal brain tissue. High expression of this MMP is more often detected in advanced grades of glioma. Some researchers suggest that MMP-13 can be used as a biomarker of GBM progression. A study of Hsieh *et al.* revealed that GBM cells express higher amount of endothelin-1 receptors ET_A and ET_B. The stimulation of one of the most invasive glioma cell lines *in vivo*, U251, with endothelin resulted in an increased expres-

sion of MMP-13, MMP-9 and increased cell migration. The addition of MMP-13 and MMP-9 inhibitors attenuated this increased cell migration [7-9].

Other scientists have shown that GBM cells can present an increased expression of other metalloproteinases: MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-14. Some researchers tried to reveal the molecular markers of invasiveness in gliomas. In the results of their studies various MMPs can be found. Bakalova *et al.* found that patients in terminal stages of brain tumors had elevated plasma levels of MMP-2 and MMP-9. Mariani *et al.* measured levels of MMP-2 and MMP-9 in cerebrospinal fluid (CSF) of dogs with intracranial tumors. Latent, but not active form of MMP-2 was found in all samples. MMP-9 was found in CSF of a minority of studied animals. Xu *et al.* analyzed brain samples obtained from patients undergoing surgery for GBM and non-malignant condition, epilepsy. Overexpression of both MMP-1 and vascular endothelial growth factor-1 (VEGF-1) was an independent poor prognostic factor in gliomas. Wang and co-workers analyzed frozen glioma samples and found out an increased expression of stromal periostin (POSTN) gene. This protein took part in both cell invasion and migration. In glioma cells POSTN signaling led to increased MMP-9 expression. The expression of POSTN correlated with both grade and progression of glioma being a poor prognostic factor [10-13].

MT1-MMP (MMP-14) activates directly proMMP-2 and indirectly MMP-2 and MMP-9. Expression of MMP-14 was shown to correlate with invasiveness of glioma and to increase with glioma grade. MMP-14 expression was also shown to correlate with brain tumor progression. This metalloproteinase, MMP-14, has been proposed as a biomarker to determine the type and grade of specific tumor. MMP-14 has a very interesting set of digested proteins. Apart from ECM proteins it can hydrolyze the most potent central nervous myelin inhibitory proteins, including BN-220. MMP-14 can also digest some proteins having adhesion functions. MMP-14 can also be involved in some intracellular processes. It can be trafficked along the tubulin cytoskeleton and be involved in intracellular recycling pathway. MMP-14 expression abnormalities were linked to mitotic spindle aberrations and chromosome instability leading to malignant transformation of neoplastic cells. MMP-14 may also be involved in regulation of VEGF-A expression. VEGF-A induces angiogenesis and inhibits apoptosis. MMP-14 seems to promote malignant glioma transformation, invasion and metastasis through intracellular signaling pathways [14].

6. Metalloproteinases and intracellular signaling pathways

Increased expression of various MMPs observed in brain tumors is a result of multiple intracellular events which may be termed as dysregulated pathways. These intracellular molecular mechanisms leading to increased invasion of neoplasmatic cells have focused scientists' interest. Understanding these complex mechanisms may be a key to design a molecular targeted therapy for patients with brain tumors. Signaling pathways leading to increased expression of MMPs are of special interest.

Tsai *et al.* observed that inhibition of focal adhesion kinase (FAK) phosporylation by osthole reduced MMP-13 expression in human glioma cells. This inhibition led to a reduction of cells migration even in a subgroup of glioma cells selected for high migratory ability. Lee *et al.* observed GMB U251 cell line presented increased FAK activation which led to an augmented expression of MMP-2. This study also revealed that examined GBM cells had an increased Bcl-w (B-cell lymphoma-w) expression. This protein is a prosurvival member of Bcl-2 family. The augmented expression of this protein is associated with infiltration properties and aggressiveness of various cancers. Bcl-w promotes the mesenchymal traits of glioblastoma cells by inducing vimentin expression of transcription factors, β-catenin, Twist1 and Snail. The increased expression of MMP-2 is accompanied by and results from the FAK activation, i.e. phosphorylation, via the PI3K-p-Akt-p-GSK3β-β-catenin pathway. The role of Bcl-w in promoting invasiveness of GBM by increasing MMP-2 activation was also confirmed in another study of this researchers team which proposed Bcl-w induced activation of β-catenin, also termed specificity protein-1 (Sp1), as a putative marker for aggressiveness of GBM. Nuclear factor of activated T cell (NFAT) family has been identified as a group of regulators of oncogenic transformation in several human malignancies. NFAT1 (NFATc2) is the prevalent family member expressed in peripheral T lymphocytes and many other cells outside the immune system. It is associated with tumor cell survival, apoptosis, migration and invasion. Clustering analysis of microarray data revealed that in glioma cells the expression of invasion related genes, cyclooxygenase-2 (COX-2), MMP-7 and MMP-9, was correlated with the expression of NFAT1. In vitro analysis confirmed the role of NFAT1, as in a specific NFAT1 knock down in U87 glioma cell line led to a marked reduction of COX-2, MMP-7 and MMP-9 expression [7,15-17].

MMP-2 has been discovered to posses intracellular activity and play some role in cell nucleus. A study by Kesanakurti *et al.* put new light on a role of MMP-2 in molecular mechanisms engaged in aggressiveness of glioma cells. p21 activated kinase 4 (PAK4) is one of down stream effectors of small GTPases Rac1 and Cdc42 which have diverse cellular functions by regulating cytoskeletal reorganization, cell survival and angiogenesis. Abberant PAK4 expression was found to be associated with enhanced tumor progression in various carcinomas. MMP-2 directly interacts with PAK-4 and augments the activation of $\alpha v\beta 3$-mediated phospho-epidermal growth factor receptor (phospho-EGFR) in GBM. MMP-2 is supposed to bind to PAK4 and the complex PAK4/MMP-2 is supposed to regulate integrin mediated pathways in gliomas. Earlier study of Kesanakurti study group revealed that MMP-2 knock down glioma cells entered on apoptosis pathway [18-20].

Understanding the molecular pathways enhancing aggressiveness of glioma cells may lead to introducing a complex therapy focused on several targets which may give a better effectiveness.

7. Metalloproteinases in other cells supporting tumor and metastasis development

In last few years scientists have paid more attention to interactions between glioma cells and microglia as well as on inreactions between metastatic cancer cells and astrocytes. Ellert-

Miklaszewska *et al.* observed that glioma attracted microglia and polarized them into tumor-supporting cells that participated in matrix-remodeling, invasion, angiogenesis and suppression of adaptative immunity. In her experiment rat microglial cultures exposed to glioma conditioned medium polarized into pro-inflammatory or alternatively activated cells. Glioma derived factors increased cell motility, phagocytosis and sustained proliferation. Glioma induced activation of microglia was associated with induction of expression of several genes. One of them was MT1-MMP. Vinnakota *et al.* also observed that microglia promoted glioma through upregulation of MT1-MMP. This conversion of microglia into glioma supportive phenotype was dependent on activation of Toll-like receptor 2 (TLR 2) along with TLR 1 and or TLR 6 signaling [21, 22].

Brain metastasis is a defining component of tumor pathophysiology and underlying mechanisms urgently need deeper elucidation. The relationship between metastatic cells and astrocytes is crucial for tumor cell sustenance in brain. Some researchers postulate that tumor cell metastasis to the brain are influenced by astrocyte secretome and astrocytes play a direct role in tumor metastasis. Wang *et al.* revealed that astrocyte conditioned tumor cells displayed highly invasive and metastatic behavior both *in vitro* and *in vivo* as well. MMP-2 and MMP-9 were two factors in the astrocyte secretome that were responsible for that response. Blocking these MMPs proteins partially prevented the invasion and metastasis of tumor cells both *in vitro* and *in vivo* as well. A very important question arises. What are the mechanisms by which MMPs secreted by astrocytes trigger invasion of tumor cells? MMP-2 and MMP-9 may increase the permeability of blood-brain barrier and allow the transfer of metastatic cells reaching brain via blood stream. The alternative hypothesis is that latent MMPs substrates on tumor cells or cells of tumor microenvironment may be activated upon cleavage by astrocyte secreted MMP-2 and MMP-9 leading to an invasive phenotype. The precise elucidation of these interactions is urgent as astrocytes may be a novel target for therapy aimed at prevention of brain metastases in patients with various cancers [21-23].

8. Blocking MMPs expression and/or activity

Scientists have widely studied the possibilities of attenuating MMPs expression and activity in order to reduce the invasiveness of gliomas. They efforts have combined various directions.

Atorvastatin is a well known statin, an inhibitor of β-hydroxy-β-methylglutaryl-CoA reductase. By inhibiting the key enzyme in a mevalonate synthesis pathway atorvastatin has pleiotropic effects. The main mode of action of this drug is the inhibition of *de novo* cholesterol synthesis. However, this drug has some other advantages resulting in its pleiotropic antiatherogenic properties due to the inhibition of synthesis of other biologically important mevalonate pathway derivates: dolichol, ubichinon, farnesyl and geranyl residues. This inhibition leads to disturbances in some signaling pathways. The possible anticancer properties of statins have been postulated since a long time.

Yongjun and co-workers have observed that atorvastatin reduced pro-tumorigenic effects of microglia on glioma migration and invasion by reducing microglial expression of MT1-MMP

(MMP-14). Mohebbi *et al.* observed that atorvastatin 40 mg administered twice daily seven from days before till three weeks after the neurosurgical procedure led to better outcome after the neurosurgical treatment of brain tumors and raised significantly Karnofsky score. The biochemical analysis showed that two weeks after the surgical treatment patients on atorvastatin therapy had significantly reduced plasma level of MMP-9 compared to patients receiving placebo [24,25].

Locatelli *et al.* evaluated a composition of polymeric nanoparticles containing a composition of two cytotoxic agents, drug alisertib and nanosilver conjugated with chlorotoxin, a peptide binding specifically to MMP-2. Their experimental *in vitro* and *in vivo* studies showed the tumor reduction [26].

Researchers are trying to investigate drugs aimed at inhibiting MT1-MMP (MMP-14). DX-2400, a fully human antibody was shown to reduce MMP-14 activity, retard tumor progression, metastasis, migration and invasion. Two natural isoflavonoid phytoestrogens, genistein and biochain A, were shown to reduce MMP-14 activity in a dose dependent manner in U87MG cell line. The green tea polyphenol, (Q)-epigallocatechin gallate (EGCg), has been found to inhibit MMP-14 mediated cell migration. This compound also disrupted proMMP-2 activation via downregulation of MMP-14 gene expression. Marimastat, an orally administered MMP inhibitor, was tested in two clinical trials in GBM patients after neurosurgery or irradiation. Marimastat alone did not improve survival, but in conjunction with cytotoxic chemotherapy gave promising results [27-30].

The next point of scientists interest are microRNAs (miRNAs). These small, non-coding RNA molecules containing 18-25 nucleotides in length can inhibit gene expression by binding to the 3′ untranslated region of their target genes and suppress translation. Several studies have shown that various miRNAs can inhibit expression of MMP-14, MMP-2 and inhibit tumor cell adhesion, migration, invasion and angiogenesis [31-35].

Lei *et al.* proposed a new strategy combining a cytotoxic drug paclitaxel and RNA interference suppressing MMP-2 expression. This conception was aimed at blocking tumor growth and proliferation by Paclitaxel and blocking tumor angiogenesis and invasion by inhibiting MMP-2 expression [36].

9. Conclusions

In last few years MMPs have been shown to exert new biochemical properties. Their extracellular mode of action as well as intracellular, intranuclear activities were shown to be involved in invasiveness of brain tumors, especially gliomas. Inhibiting their expression may be a new therapeutical approach. So far some drugs being MMPs inhibitors have some serious adverse effects. Inhibiting MMPs expression and activity seems to be rather a supplement to chemotherapy, radiotherapy or neurosurgical procedures than a new single method of treatment of brain tumors.

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Sections 1-3 contain text originally published in [3].

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