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Review

The emerging role of MMP14 in brain tumorigenesis and future therapeutics

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ABSTRACT

Glioblastoma is a malignant brain tumor of glial origin. These tumors are thought to be derived from astrocytic cells that undergo malignant transformation. A growing body of evidence suggests that upregulation of MMP expression plays a significant role in promoting glioma pathogenesis. Elevated expression of MMP14 not only promotes glioma invasion and tumor cell proliferation but also plays a role in angiogenesis. Despite the fact that levels of MMP14 correlate with breast cancer progression, the controversial role of MMP14 in gliomagenesis needs to be elucidated. In the present review, we discuss the role of MMP14 in glioma progression as well as the mechanisms of MMP14 regulation in the context of future therapeutic manipulations.

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Contents

1. Introduction . . . 0
1.1. The invasive nature of glioblastoma multiforme . . . 0
2. Matrix metalloproteinases and brain tumor . . . 0
3. MMP14 and glioblastoma multiforme: a party of two . . . 0
3.1. MMP-14 in glioma invasion and migration . . . 0
3.2. Role of MMP-14 in glioma angiogenesis . . . 0
4. Therapeutic targeting of MMP-14 . . . 0
4.1. Biological inhibitors of MMPs . . . 0
4.2. In vitro studies . . . 0
4.3. Xenograft models . . . 0
4.4. Clinical trials with inhibitor against MMP . . . 0
5. Concluding remarks/future directions . . . 0
Acknowledgments . . . 0
References . . . 0

1. Introduction

Each year, approximately 35,000 people are diagnosed with primary brain tumors. Among them, 47% are diagnosed with glioblastoma multiforme (GBM), the most aggressive of all primary brain tumors [1]. GBM is also the most prevalent brain tumor, accounting for approximately 50% of all functional brain tumors and 20% of intracranial tumors [2]. Despite recent advances in treatment for many other cancers, the prognosis for GBM remains extremely poor. GBM prognosis has not improved in decades, and patients treated through multiple therapies including aggressive surgery, radiation, and chemotherapy, have a median survival rate of less than 16 months [2]. The two year survival rate for patients diagnosed with GBM nears 30%, at most, for

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patients younger than 20 years, less than 10% for patients aged 20–44, and drops to 2% for patients older than 65 years [1]. Thus, it is clear that novel therapies for the treatment of GBM are urgently needed. (See Table 1.)

Glioblastoma multiforme, the most common malignant brain tumor in adults [3], falls under a larger class of tumors known as glioma, tumors which arise from the astrocytic glial cells [4,5]. The World Health Organization has divided astrocytic tumors (astrocytoma) into four grades based on cell's ability to infiltrate the surrounding brain. Grade I astrocytomas consist of benign pilocytic tumors and other noninfiltrating tumors, while Grades II, III, and IV consist of infiltrating astrocytomas of various malignancy. Glioblastoma multiforme is WHO Grade IV astrocytoma, the most malignant form of astrocytoma.

1.1. The invasive nature of glioblastoma multiforme

The poor prognosis of GBM is largely the result of its highly invasive nature. This diffusely infiltrative nature of glioblastoma multiforme makes surgical intervention extremely difficult. Also surgical resection of the tumor alone is not curative [2]. It has been observed that GBM cells migrate in the brain in various directions such as through the normal parenchyma, the white matter tracks in the corpus callosum and contralateral cerebral hemisphere, ventricular ependymal areas, and cerebral spinal fluid (CSF) pathways. This pattern of invasion often results in aggressive infiltration of the adjacent brain and vital areas of brain necessary for survival [2].Therefore, the infiltrative nature of glioblastoma multiforme severely impairs the efficacy of surgery and eventually leads to tumor recurrence [6]. Almost 80% of recurrences occur within 2 to 3 cm of the original tumor location, showing that cells of the primary tumor have already invaded the adjacent brain by the time of surgery [7].

It is important to design treatment strategies that will minimize the chance of relapse in these patients. In order for glioma cells to invade the surrounding normal tissue, the tumor cells must be able to degrade the extracellular matrix (ECM). Normally, existence of ECM does not allow for cell movement except during processes such as tissue healing and remodeling, inflammation, and neoplasia. It has been suggested that tumor cells invade in three main steps: first, neoplastic cells attach to the basement membrane through binding of cell surface receptors to the ECM, second, tumor cells secrete hydrolytic enzymes which locally degrade the basement membrane; and finally, cells move into the region of the ECM degraded by proteolysis [8]. In order to invade, glioma cells must secrete proteolytic enzymes, or proteases, which degrade this extracellular matrix and mediate the invasion process. Several of proteases have been implicated in this invasion process including cysteine proteases, serine proteases, and matrix metalloproteinases.

Recent studies have suggested that matrix metalloproteinases in particular are responsible for the degradation of the ECM in tumor invasion. It has been shown that specific members of the matrix metalloproteinase (MMP) not only promote glioma cell invasion but also alter tumor cell behavior and stimulate cancer progression. As the invasive nature of GBM largely contributes to high mortality and poor prognosis of the disease, targeting MMPs could provide a novel therapeutic approach for GBM treatment. This review discusses the function of a specific matrix metalloproteinase, MMP14, in GBM and its potential as a therapeutic target in the treatment of glioblastoma.

2. Matrix metalloproteinases and brain tumor

Matrix metalloproteinases are a family of zinc-dependent endopeptidases, members of the metalloproteinase class and "metzincin" superfamily of endopeptidases [9]. The metalloproteinase class can be distinguished from other endopeptidases, which include "serine," "cysteine," and "aspartic" proteinases, by their shared catalytic domain containing three conserved histidines in a zinc-binding HexxHxxGxxH motif [10]. Most MMPs are secreted with the exception of the six membrane-type MMPs (MT-MMPs) which are anchored by either a glycosyl-phosphatidylinositol (GPI) link or a transmembrane domain. The majority of MMPs contain four domain structures: a highly conserved N-terminal propeptide, a catalytic linker region, and C-terminal hemopexin-like domains. The 23 known human MMPs are traditionally classified into five subclasses based on substrate specificity, protein domain structure, and sequence homology: collagenases, gelatinases, stromelysins, membrane-type MMPs, and other MMPs. The currently known MMPs are numbered based on their order of discovery. The collagenases consist of MMP1, MMP8, and MMP13; the stromelysin subclass include MMP3, MMP10, MMP11, MMP7, and MMP26; the gelatinases are MMP2 and MMP9; the six membrane-type MMPs comprise MMP14, MMP15, MMP16, MMP17, MMP24, and MMP25. The membrane-type MMPs (MT-MMPs) are often numbered one through six and are referred to as MT1-MMP through MT6-MMP. Though MMPs are primarily classified based on their substrate specificity, substrates for which they show as a function of time, there is a considerable overlap in substrate preference between subclasses. Therefore, multiple MMPs could fulfill the same or similar roles during pathogenic processes.

MMPs degrade most, if not all, proteins of the extracellular matrix and basement membranes, including fibrillar and nonfibrillar collagens, fibronectin, laminin, and basement membrane proteoglycans [3]. Regulation of the ECM and basement membrane (BM) is vital for many functions and mediates interactions between individual cells and their environment. Thus, MMPs are involved in diverse physiological processes including tissue growth and regeneration, wound healing,

Table 1
MMP14 targets.

MMP14 targets				
Extracellular effect			Type of study	REF
CD44	Cleaves CD44 extracellular domain	Decreases cell surface adhesion	Experiment research	43, 44
Transglutaminase	Proteolytically degrades transglutaminase into three fragments	Promotes matrix proteolysis	Experiment research	50,51
Low-density lipoprotein receptor related protein	Regulates the expression and uptake of LRP	Promotes matrix proteolysis	Experiment research	52, 53
Syndecan-1	Cleaves Syndecan-1	Promotes cell migration by promoting shedding	Experiment research	55-57
Collagens	Cleaves collagen into specific collagenase fragments	Disrupts tissue architecture	Experiment research	41,42
Extracellular signal regulated kinase (ERK)	Induces ERK activation	Induction of migration	Experiment research	58, 59
Intracellular effect				
Pericentrin	Disrupts mitotic spindle formation	Causes chromosome instability and malignant transformation	Experiment research	60
VEGF	Complex VEGFR with Src	Promotes angiogenesis and vasculogenesis inhibits apoptosis	Experiment research	61, 62

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embryonic growth and development, implantation, angiogenesis, apoptosis, and nerve growth [10,11]. In recent years, it has been discovered that MMP substrates are not limited to extracellular matrix proteins but also include an ever-expanding group of proteins involved in a variety of signaling and homeostatic systems [9]. In the brain, MMPs are known to cleave proteins involved in synaptogenesis, synaptic plasticity, and long-term potentiation [10].

Many of the known MMPs are implicated in cancer. MMP-mediated ECM degradation not only promotes tumor invasion, but also advances tumor progression and has been implicated in angiogenesis and metastasis. It should be noted that other classes of endoproteases, such as the serine, cysteine, and aspartic classes also degrade the ECM, and thus may play roles in ECM-related tumor progression. While studies have identified several pathways for extracellular matrix degradation involving various proteases, one of the universal pathways require the matrix metalloproteinases. Gliomas, for instance, express a variety of proteases, but MMPs appear to play a particularly significant role in tumor invasion and progression [12]. Studies show elevated levels of MMP-2, MMP-9, and MT1-MMP expression in gliomas in comparison with normal brain tissue. This review will focus on the function of MT1-MMP (MMP-14) in glioblastoma and its potential as a novel therapeutic target in GBM.

3. MMP14 and glioblastoma multiforme: a party of two

Matrix metalloproteinase 14 (MMP-14) was the first membrane type matrix metalloproteinase discovered, and hence is also referred to as membrane type 1-matrix metalloproteinase (MT1-MMP). Like other matrix metalloproteinases, MMP-14 has a pre-propeptide, a catalytic domain, a hinge region, a hemopexin (Hpx) domain, a stalk (linker-2) region, a transmembrane domain, and a cytoplasmic tail [13]. Its carboxyl-terminal cytoplasmic domain and amino-terminal furin recognition site are characteristic of membrane type MMPs [14,15]. MMP-14 is produced and secreted by cells as inactive zymogen, also known as pro-MMP. The zinc ion of its catalytic region is essential for MMP activity, and blocks its active site. Hence an activation step is needed to expose the catalytic site. This activation process begins with the disruption of the cysteine–zinc interaction and involves many proteinases and non-proteolytic agents [16]. The activation process occurs during secretion in the Golgi, and when the enzyme reaches the cell surface, it is in its active form [13].

MMP-14 is vital in glioma cell growth, invasion, migration and angiogenesis. Although overexpression of MMP-14 leads to excessive ECM degradation and other problems, MMP-14 is required in the body. MMP-14 mediates normal physiological processes like pericellular proteolysis and extracellular matrix and hence it modulates cellular remolding, which is essential for normal functioning of the body. Holmbeck et al. and Zhou et al. demonstrated using MMP-14 deficient mice that the loss of MMP14 leads to dysmorphism, arthritis, dwarfism and other kinds of severe defects in skeletal development and soft connective tissues and hard tissues [17,18]. It has been shown that MMP-14 is essential for tissue remodeling, embryonic development as well as reproduction [11,19–23].

The MMP-14 expression level is high in gliomas and particularly high in GBM both *in vivo* and *in vitro* [12,24]. The MMP-14 level is also elevated in the glioma-derived cells in comparison with other cancer-derived cell types [12]. Many studies have used different methods in demonstrating that MMP-14 expression correlates with glioma grades, and expression level increases with histological grade of malignancy. For e.g., Lampert et al. demonstrated using immunostaining that the MMP-14 level increases with glioma grade [25]. VanMeter et al. showed the same pattern using immunoblotting [16]. Moreover, our group confirmed that the level of MM14 is correlated with brain tumor progression and affects patient survival [26]. Fillmore et al. again confirmed this with Northern blot and real time PCR, demonstrating that MMP-14 expression is significantly higher in malignant glioblastoma than low grade gliomas [27]. Also using real time PCR, Yamamoto et al. and then Nakada et al. detected MMP-14 mRNA in 100% of the glioblastomas, but only 22% in anaplastic astrocytomas and 0% in the low-grade astrocytomas and normal brain [13,28]. When surgical specimens of gliomas were analyzed, the RNA levels of MMP-14 increased with gliomas grade [29]. All these studies suggest the possibility of using the level of MMP-14 as a biomarker to determine the type and grade of a specific tumor.

3.1. MMP-14 in glioma invasion and migration

Many studies have demonstrated that overexpression of MMP-14 enhances glioma cellular invasion and migration. Sato et al. demonstrated with reconstituted basement membrane (Matrigel) that cellular invasiveness increased with higher MMP-14 expression [30]. Abe et al. demonstrated that one of the most invasive glioma cell lines *in vivo*, U251, has a higher level of MMP-14 expression than the other cell lines [31]. This confirmed that the correlation between MMP-14 expression level and invasiveness of the glioma cells is bidirectional. This relationship between MMP-14 and tumor cells invasion was also confirmed by Van Meter, who showed that the inhibition of MMP-14 could decrease *in vitro* invasion [16]. Interestingly, the same kind of correlation exists between MMP-14 expression and tumor migration, or metastasis [32,33].

One of the mechanisms of glioma invasion is the activation of downstream targets. It has been noted that MMP-14 activates proMMP-2 and indirectly MMP-2 (also known as gelatinase A and 72 kDa type IV collagenase) and MMP-9 (also known as gelatinase B and 92 kDa type IV collagenase) [13,32,34,35]. Deryugina et al. demonstrated that transfection of glioma cells with MMP-14 cDNA increases proMMP-2 activity [36]. This data corroborates with results published by Hur et al. in which the expression level of MMP-14 closely correlates with the expression level of MMP-2 [37]. MMP-2 along with MMP-9 is widely considered critical in the context of brain tumor invasion [13].

MMP-14 participates in mediating pericellular proteolysis of extracellular matrix (ECM) macromolecules [17,38,39]. More specifically, MMP-14 could degrade ECM macromolecules including collagens I, II, and III, gelatin, laminins 1 and 5, fibronectin, vitronectin, aggrecan, fibrin, tenascin, nidogen, perlecan and lumican [40,41]. Of all these macromolecules, collagen is one of the most crucial ones. Collagens are a group of extracellular, closely related proteins that are the main component of connective tissues including extracellular matrix. Collagens play a vital role in maintaining tissue architecture and in forming a stable scaffold for cells [40]. In a tumor spheroid outgrowth assay, MMP-14 degrades collagen [36]. MMP-14 cleaves native type-I and type-III collagens into the typical ¾–¼ specific collagenases fragments [41]. Due to its role of remodeling the ECM in both normal physiology and cancer, MMP-14 expression is considered essential in tumor invasion and migration [40].

Besides its ability to degrade ECM macromolecules, MMP-14 promotes cell invasion and migration by its interaction with several cell surface proteins. For instance, it is shown that MMP-14-transfected fibroblasts and glioma cells could digest the most potent CNS myelin inhibitory proteins including BN-220 [42]. Through this we could see the huge role MMP-14 plays in GBM cell migration.

MMP-14 is engaged in the cleavage and proteolysis of several proteins that have adhesion functions. Some of these proteins are the following:

CD44:

Invasive tumor cells often express CD44, which is a cell-surface glycoprotein. It is involved in interactions between cells, cell adhesion and migration [43–46]. Shedding of CD44 is important in the CD44 dependent migration of tumors, and the cleavage by MMP-14 is important in this underlying mechanism [45]. Using fluorescence resonance energy transfer (FRET) microscopy, Marerro-Diaz et al. demonstrated that MMP-14 interacts with CD44 at the trailing edge of the invading

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tumor cells and on membrane fragments released during invasion. Also, MMP-14 cleaves CD44 extracellular domain and promotes cell migration [47,48].

(1) Transglutaminase:

Belkin et al. demonstrated that MMP-14 could cause proteolytic degradation of cell surface tissue transglutaminase (tTG) into three fragments *in vitro* [49,50]. They also showed that Fn could protect transglutaminase from MMP-14 proteolysis and support cell adhesion.

(2) Low-density lipoprotein receptor related protein:

Low-density lipoprotein receptor related protein (LRP) has six members within its family. All of them function as cell surface endocytic receptors, which could bind and internalize extracellular ligands for degradation in lysosomes, as well as signaling molecules [51]. Most importantly in glioma cell invasion, LRP is involved in the regulation of matrix proteolysis [52]. The expression and uptake of LRP by malignant cells are regulated by MMP-14 [15,52,53].

(3) Syndecan-1

Syndecan-1 shedding has been implicated in the invasion and progression of gliomas. Using a sample size of 117 patients, Xu et al. demonstrated using immunohistochemistry assay, quantitative real-time PCR and western blot that the Syndecan-1 level is higher in invasive glioblastoma [54]. Endo et al. and Su et al. showed that MMP-14 is able to cleave Syndecan-1 and promote its shedding, thereby stimulating cell migration [55,56].

Cell migration is also promoted through MMP-14's interaction with extracellular signal-regulated kinase (ERK). MMP-14 expression level and the level of ERK are correlated with the increasing pathological grades of glioma tissues [57]. MMP-14 induces ERK activation through c-Src and paxillin in cancer cells, and inhibition of MMP-14 suppresses ERK activation [58]. ERK is involved in the induction of migration, and overexpression of MMP-14 triggers ERK activation which leads to cell migration [33].

Normally, MMP-14 is transported to cell surface upon activation and there processes mostly extracellular substances and functions in extracellular signaling pathways. However, it should be noted that studies in recent years have shown that MMP-14 is also trafficked along the tubulin cytoskeleton and involved in the intracellular recycling pathway [15]. A fraction of MMP-14 is accumulated in the centrosomal compartment via this pathway, where it targets pericentrin, a centrosomal protein vital for normal functioning of centrosomes during the formation of mitotic spindle [59]. MMP-14 level abnormality has been linked to mitotic spindle aberrations, chromosome instability and malignant transformation of cancer cells [60]. In addition, MMP-14 could regulate VEGF-A expression intracellularly through forming a complex with VEGFR-2 and Src [61]. Since VEGF-A induces angiogenesis, vasculogenesis and inhibits apoptosis, MMP-14 likely promotes tumor cell migration and growth via this intracellular pathway as well. In conclusion, MMP-14 appears to promote malignant glioma transformation, invasion and metastasis through intracellular signaling pathways.

3.2. Role of MMP-14 in glioma angiogenesis

Angiogenesis is the formation of new blood vessels and it is crucial for the progression of malignant tumor to constantly nourish growing cancer cells with blood supply. Due to its importance in tumor progression, tumor angiogenesis is a major target for antiglioma intervention. Since, some of these inhibitors stimulate glioma invasion [62] it is important to find a tool that is able to reduce angiogenesis along with decreasing cell invasion and migration at the same time.

MMP-14 has been shown to be a key factor in tumor angiogenesis [32]. In the absence of MMP-14, Zhou et al. observed a defective vascularizaton both in the cartilage of growth plates as well as in a corneal angiogenesis assay, which reinforces MMP-14's role in initiating angiogenesis [18]. Whereas, it is shown that MMP-14 could promote blood vessels sprouting in the rat aortic ring, and this angiogenic phenotype of MMP-14 is associated with an up-regulation of VEGF expression [14,63,64], other studies argue that MMP-14 affects angiogenesis through influencing the bioavailability of growth factors and through functioning as a fibrinolytic enzyme that mediates pericellular proteolysis [38]. Despite these controversies, it has been established that MMP-14 promotes angiogenesis through activation of MMP-2 and MMP-9, which play key roles in angiogenesis [65].

4. Therapeutic targeting of MMP-14

Since MMP-14 is crucial for the progression, invasion, migration and angiogenesis of brain tumor cells, attenuation of MMP-14 could significantly improve patient prognosis and help to prevent recurrence following surgery, radiation, and chemotherapy. There have been many studies which demonstrate the therapeutic potential of inhibiting MMP-14, or MT1-MMP in glioblastoma cell lines, mouse models, and clinical trials.

4.1. Biological inhibitors of MMPs

The tissue inhibitors of metalloproteinases (TIMPs) are a family of homologous inhibitors of MMPs that regulate the degradation of the extracellular matrix by inhibiting MMPs. The TIMP family has four members, TIMP-1, TIMP-2, TIMP-3 and TIMP-4 which play potential therapeutic roles in glioma treatment or diagnostic marker during cancer progression.

1) TIMP-1

There seems to be conflicting results in terms of the expression of TIMP-1 in gliomas. According to Lampert et al. [25], overexpression of MMP is accompanied by simultaneous increase of the TIMP-1 level. Since the MMP-14 expression level is high in GBM, then up-regulation of TIMP-1 should also be seen in glioblastomas. Interestingly, Groft et al. [66] demonstrated that the expression level of TIMP-1 is barely detectable by RT-PCR in normal brain tissue and low grade tumors, but increases dramatically for GBM. Also, another study demonstrated a positive correlation between gliomas grades and TIMP-1 level [29]. In contrast, Mohanam et al. showed higher expression of TIMP-1 in normal brain tissues, meningioma and other metastatic tumors than the highly invasive glioblastoma tumors [67].

Besides its function as a biomarker, TIMP-1, as a tissue inhibitor of metalloproteinases, has also been indicated to have potential therapeutic function by exerting effect on MMP-14. Whereas, some literature suggests that overexpression of TIMP-1 reduces invasion, and prolongs the survival time for glioblastoma patients via repressing MMP-14 [68,69], other researches have reported that TIMP-1 is unable to prevent MT1-MMP from activating MMP-2 [34,70].

2) TIMP-2

Similar to TIMP-1, contrasting data exist for the expression of TIMP-2 in gliomas. Some studies suggest that the TIMP-2 level correlates with MMP-14 level and glioma grade using immunohistochemistry and other methods [25,29], while others show inverse correlation between MMP-14 and glioma grade [67]. TIMP-2 is able to bind with the active site MMP-14 and form a heteromolecular complex (MMP-14/TIMP-2 complex), which is essential for the subsequent formation of a complex with proMMP-2 (progelatinase A). A model of the subsequent binding with proMMP-2 proposes that the catalytic domain of MMP-14 binds with the N-terminal portion of TIMP-2, and the negatively charged C-terminal of TIMP-2 could bind with the hemopexin-like domain of proMMP-2 [32,71]. This trimeric complex is required for the activation of proMMP-2 by MMP-14 and the accumulation of MMP-14 on the cell surface [25,32,72,73]. Additionally, it has also been shown by Will et al., that TIMP-2 is an excellent inhibitor, binding

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to the catalytic domain of MMP-14 and preventing its overexpression [70].

3) TIMP-3

Lampert et al. demonstrated that TIMP-3 has very low expression in gliomas as well as normal brain, hence suggesting that TIMP-3 has a little role in the regulation of MMP-14 [25]. However, Will et al. demonstrated TIMP-3 to be good inhibitor of MMP-14 [70]. Consistent to their study, Butler et al. demonstrated that TIMP-3 has a similar function as TIMP-2, and mechanistically could interact with both the N-terminal of MMP-2 and the C-terminal of MMP-9, both MMPs directly activated by MMP-14 [74].

4) TIMP-4

TIMP-4 is a close homologue of TIMP-2, and like TIMP-2, could bind to proMMP-2 and participate in the activation process. However, unlike TIMP-2, TIMP-4, when binding to MMP-14, inhibits its autocatalytic processing, and greatly reduces pro-MMP-2 activation by MMP-14 [64,75]. TIMP-4 is an excellent inhibitor of MMP-14 and blocks the concavalin A-induced cellular activation of proMMP-2 [32,34,64], hence is a great tumor progression resistance factor. The balance between TIMP-4 and TIMP-2 is crucial in determining the potential of cells both in normal and pathological conditions. Since it is capable of blocking MMP-14, TIMP-4 could inhibit angiogenesis as well as prevent reabsorption of vessels following angiogenesis [64].

5) RECK

Reversion-inducing-cysteine rich protein with Kazal motifs (RECK) is another kind of MMP-14 inhibitor [76]. Using immunohistochemistry and qPCR, two studies demonstrated that RECK protein expression correlates with MMP-14 negatively in glioma cells [77,78]. Also, Golan et al. confirmed that RECK could function to hinder tumor migration and invasion by inhibiting MMP-14 [79].

6) $\alpha v\beta 3$ integrin inhibitor

Deryugina et al. demonstrated that the presence of $\alpha v\beta 3$ integrin may be required to catalyze MT1-MMP mediated activation of progelatinaseA (MMP-2) [80]. Although this study was done in breast carcinoma cells, it points to the potential of this integrin as an inhibitor of MMP-14 in brain tumor as well, though further studies need to be done.

7) DX-2400

Many broad-spectrum MMP inhibitors have limited clinical success due to their poor selectivity and severe toxicities which causes musculoskeletal pain and inflammation. Therefore, it would be useful to find an inhibitor specific to MMP-14, and Devy et al. have identified DX-2400, a fully human antibody, to be such an inhibitor. DX-2400 significantly decreases MMP-14 activity and thereby retards tumor progression, metastasis, migration and invasion.

4.2. In vitro studies

Several anti-cancer approaches were proposed for targeting MMP-14/MT1-MMP *in vitro*. Whereas Atobe et al. developed an immunoliposome based therapeutic tool for targeting of MT1-MMP positive tumor cells [81], other studies tested synthetic targets which directly inhibit MMP-14 expression or function. For instance, Fortier et al. have identified glycocluster constructions which could be used in carbohydrate-based anticancer therapies to specifically target and inhibit MMP-14 functions [82]. Later, Zarrabi et al. designed synthetic peptides which specifically targeted the hemopexin domain found to be responsible for initiating MMP-14 catalytic function in cell migration and invasion [83]. In this study, by evaluating a series of substitution mutations located at the conserved domains, the N terminus, a signal peptide, a propeptide, a catalytic domain, a hinge region, and a hemopexin-like (PEX) domain, Zarrabi et al. found that the PEX domain was responsible for MMP-14 association with CD44 that initiates the cytoskeleton rearrangement and the beginning of various migration and invasion processes, including activation of proMMP-2 [83]. Although, targeting the PEX domain of MMP-14 using specifically designed synthetic peptides inhibited MMP-14-mediated cell migration, invasion, and metastasis both *in vitro* and *in vivo*, these results warrant future validation using other glioma models.

Another strategy to inhibit glioma migration is to use drugs or chemical inhibitors of MMP-14. Two natural isoflavonoid phytoestrogens, genistein and biochanin A, reduced *in vitro* invasion of U87MG cells, and subsequently decreased MT1-MMP protein levels in a dose-dependent manner. Moreover, attenuation of MT1-MMP in U87MG cells correlated with the level exhibited by MMP-2, suggesting that MT1-MMP regulation of MMP-2 activity could be specifically targeted to inhibit tumor cell invasion [84]. Distinct from the first study, Sena et al. noticed that that MT1-MMP activation of MMP-2 could be specifically targeted by the aminopeptidase N/CD-13 inhibitor actinonin [85]. Actinonin was observed to directly inhibit MT1-MMP-mediated conanavalin-A-induced pro-MMP-2 activation in U87 glioma cells. However, while actinonin inhibited MMP-14 proteolytic processing, it was unable to downregulate MMP-14 expression levels, suggesting that actinonin regulates MT1-MMP function at the cell surface rather than its gene expression [85]. Besides actinonin, the green tea polyphenol (Q)-epigallocatechin gallate (EGCg) has also been found to inhibit MT1-MMP mediated cell migration and disrupt proMMP-2 activation via downregulation of MT1-MMP gene expression. EGCg was also found to inhibit proMMP-2 protein secretion and disrupt the secretion of other soluble proteins such as TIMP-2 [86]. These results suggest that EGCg not only regulates MMP-14 transcription, but it also interferes with MMP-14 proteolytic processing by disrupting the formation of the pro-MMP-2/TIMP-2/MT1-MMP tri-molecular complex that leads to MMP-2 activation [87]. Most recently, Zhang et al. demonstrated that microRNA-9 (miR-9) reduces expression of MMP-14 by posttranscriptional targeting of the MMP-14 3′-untranslated region or 3′-UTR [88]. Overexpression of miR-9 in neuroblastoma cells notably inhibited tumor cell adhesion, migration, invasion, and angiogenesis *in vitro* [88].

4.3. Xenograft models

Various *in vivo* studies also support the results that are obtained from the *in vitro* studies. Zhang et al. showed that overexpression of miR-9 also impaired tumor growth, metastasis, and angiogenesis of neuroblastoma cells *in vivo,* supporting the *in vitro* data [88]. Transfection of miR-9 into SH-SY5Y cells resulted in decreased tumor growth and tumor weight compared to cells transfected with an empty vector, lower vessel density within the tumors, and fewer metastatic colonies to the lung [88]. Minocycline hydrochloride has also been identified as a potent inhibitor of MMP-14 and was found to significantly improve prognosis in an experimental mouse model [89]. Minocycline was observed to reduce glioma invasiveness and growth by downregulating MMP-14 expression in microglial cells [89].

In studies of other cancer cell lines, the DNA enzyme Dz13, which targets oncogene c-Jun, was found to downregulate MMP-14 expression, inhibit primary-site tumor growth, and limit metastasis [90]. The DNA enzymes are single-stranded DNA-based catalysts which can be engineered to inhibit gene expression by binding to a complementary sequence in target messenger RNA and cleaving the mRNA at specific phosphodiester linkages [90]. In both cultured tumor cells and sections of ectopic tumor treated with Dz13, the DNA enzyme was found to downregulate expression of MT1-MMP [90]. In mouse models, Dz13 was found to directly inhibit both local and distal tumor metastasis and reduce growth of ectopic osteosarcoma, prostate, and breast cancer tumors [90]. Devy et al., meanwhile, identified DX-2400 as a highly selective human MMP-14 inhibitory antibody using the human

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Fab-phage library FAB310 and MMP-14-CD as the target [91]. *In vivo* studies showed that DX-2400 prevents proMMP-2 processes on tumor and endothelial cells, inhibits angiogenesis, and significantly delays tumor progression and metastasis in MDA-MB-231 and BT-474 tumors [91]. However, treatment of MMP-14 negative tumor MCF-7 showed no difference. DX-2400 was shown to be a potent, selective and robust *in vivo* inhibitor of MMP-14 in the treatment of tumors [91].

Another study designed a synthetic peptide to target and inhibit MMP-14 phosphorylation on its unique cytoplasmic tyrosine residue [92]. The peptide, known as antennapedia-coupled cytoplasmic MMP-14 (ACM-14), consisted of a mutated non-phosphorylable copy of the cytoplasmic domain of MT1-MMP coupled to the cell-penetrating third helix of the homeodomain of the *drosophila* transcript factor antennapedia [92]. While the function of MMP-14 tyrosine phosphorylation in tumor progression is unknown, treating mice with the synthetic peptide significantly inhibited tumor progression and improved survival [92]. It is hypothesized that AMC-14 inhibition of tyrosine phosphorylation improved prognosis by inducing extensive tumor necrosis [92]. Additional studies are needed to elucidate the role of tyrosine phosphorylation in tumor progression, though it appears that inhibition of this process may be a novel method to improve prognosis. However, further studies are needed in glioma models to assess their efficacy in treating GBM.

4.4. Clinical trials with inhibitor against MMP

Two clinical trials of matrix metalloproteinase inhibitors have been conducted with GBM patients. In a placebo-controlled trial, patients with GBM or gliosarcoma were treated with marimastat, an orally-active MMP-inhibitor, following surgery and irradiation [93]. In this double-blind study, despite improvement of the median survival of marimastat treated group vs. placebo received (42.9 vs. 37.9 weeks), there was no statistical difference observed. These findings concluded that marimastat alone does not improve survival, but treatment with marimastat in conjunction with cytotoxic chemotherapy may be beneficial for the patient survival.

A subsequent phase II clinical trial was performed testing marimastat in conjunction with an additional cytotoxic agent. Patients with recurrent and progressive GBM were treated with temolozomide (TMZ) plus marimastat following standard radiotherapy [94]. During that study, joint and tendon pain was detected as the most significant therapy-related toxicity, affecting 47% of patients [94]. Overall, treatment with TMZ and marimastat resulted in a 6-month progression free survival (PFS), 29% higher than predicted by the literature [94].

5. Concluding remarks/future directions

MMP14 mediated signaling is certainly complex. It appears that MMP function is not restricted to only migration and invasion. Emerging evidence indicates that some of the MMPs contribute to angiogenesis. Therefore not surprisingly, targeting of MMP14 results in multiple therapeutic interventions. Given the fact that in normal conditions cells require upregulation of MMP14, selective attenuation of the progression of malignant cells mediated by MMP14 represents a challenge. In addition, a crucial role of MMP14 for the glioma progression is controversial due to: 1) differential role of TIMP in regulation of MMP14 expression, with low concentration that promotes MMP14 expression as well as tumor growth; 2) the elevated level of MMP14 expression mediated by temozolomide and radiation; and 3) the unknown relationship between MMP14 expression and angiogenic, neural subtype of gliomas. Although all of the above options require experimental validation, modulation of MMP14 might serve as an anti-glioma therapeutic option because of its effects on cell proliferation and angiogenesis along with prolonged survival of glioma bearing mice with the inhibition of MMP14. The emerging therapeutic evidence from the breast cancer field also suggests that inhibition of MMP14 mediated signaling has potential to repress tumor growth. Since brain microenvironment constantly contributes to glioma progression via secretion of chemokines and growth factors, regulating glioma progression and invasion via secreting of exosomes packed with proteins, lipids and microRNAs [95–99] it is important to design the anti-glioma approach with simultaneously targeting cancer cells and decreasing the effect of brain environment to prevent glioma recovery.

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