Mini-Review

# Metzincin Proteases and Their Inhibitors: Foes or Friends in Nervous System Physiology?

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**Members of the metzincin family of metalloproteinases have long been considered merely degradative enzymes for extracellular matrix molecules. Recently, however, there has been growing appreciation for these proteinases and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), as fine modulators of nervous system physiology and pathology. Present all along the phylogenetic tree, in all neural cell types, from the nucleus to the synapse and in the extracellular space, metalloproteinases exhibit a complex spatiotemporal profile of expression in the nervous parenchyma and at the neurovascular interface. The irreversibility of their proteolytic activity on numerous biofactors (e.g., growth factors, cytokines, receptors, DNA repair enzymes, matrix proteins) is ideally suited to sustain structural changes that are involved in physiological or postlesion remodeling of neural networks, learning consolidation or impairment, neurodegenerative and neuroinflammatory processes, or progression of malignant gliomas. The present review provides a state of the art overview of the involvement of the metzincin/TIMP system in these processes and the prospects of new therapeutic strategies based on the control of metalloproteinase activity.**

The importance of proteolysis in tissue structure/function is reflected not only in the evolutionary conservation of protease genes in all kingdoms (e.g., from archaea and eubacteria to plants and animals) but also the genomic complexity of this protein class. The "degradome," the repertoire of proteases produced by cells, consists of at least 569 human, 629 rat, and 644 mouse proteases or protease-like proteins and homologs, whereas 156 human protease inhibitor genes have been identified (Puente et al., 2003). The proteases are classified into five major catalytic classes, including metalloproteinases and serine, cysteine, threonine, and aspartic proteinases, with the metalloproteinases representing the largest class (Fig. 1*A*). The metzincin family of metalloproteinases is so named for the conserved Met residue at the active site and the use of a zinc ion in the enzymatic reaction. This family comprises matrix metalloproteinases (MMPs), a disintegrin and metalloproteinases (ADAMs), and ADAM proteases with thrombospondin motifs (ADAMTSs). Interest in MMPs began with the identification of an enzyme that contributes to tail resorption during tadpole metamorphosis (collagenase-1, MMP-1) (Gross and Lapiere, 1962) and increased on the discovery that these enzymes not only play a role in normal tissue remodeling but were upregulated in diverse human diseases, including chronic inflammatory disorders and cancer.

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## MMPs

MMPs, encoded by 24 human and 23 mouse genes, include secreted and membrane-associated members divided into four main subgroups according to their domain structure, including collagenases, stromelysins, gelatinases, and membrane-type MMPs (MT–MMPs) (Fig. 1*B*) (Fanjul-Fernández et al., 2010; Ugalde et al., 2010). MMPs contain a signal peptide because most are secreted, likely in vesicles as reported recently in neurons and astrocytes (Sbai et al., 2008, 2010), and function extracellularly. However, intracellular MMP functions have also been reported (Y. S. Kim et al., 2005; Schulz, 2007), as well as active forms of MMP-2, MMP-9, and MMP-13 in the nuclei of neurons and glial cells (Cuadrado et al., 2009; Sbai et al., 2010; Yang et al., 2010). The prodomain contains a cysteine residue that binds zinc in the active site and maintains the MMP in an inactive state. Thus, metzincin proteases are constitutively expressed but remain in a latent state until activated by enzymes that cleave the prodomain or free the cysteine bond. An exception is MT–MMPs, which are activated intracellularly in the Golgi network by the proprotein convertase furin or the serine protease plasmin and, thus, are active during exposure to the extracellular space. Following the catalytic domain is a C-terminal hemopexin (PEX) domain important for determining substrate specificity and interactions

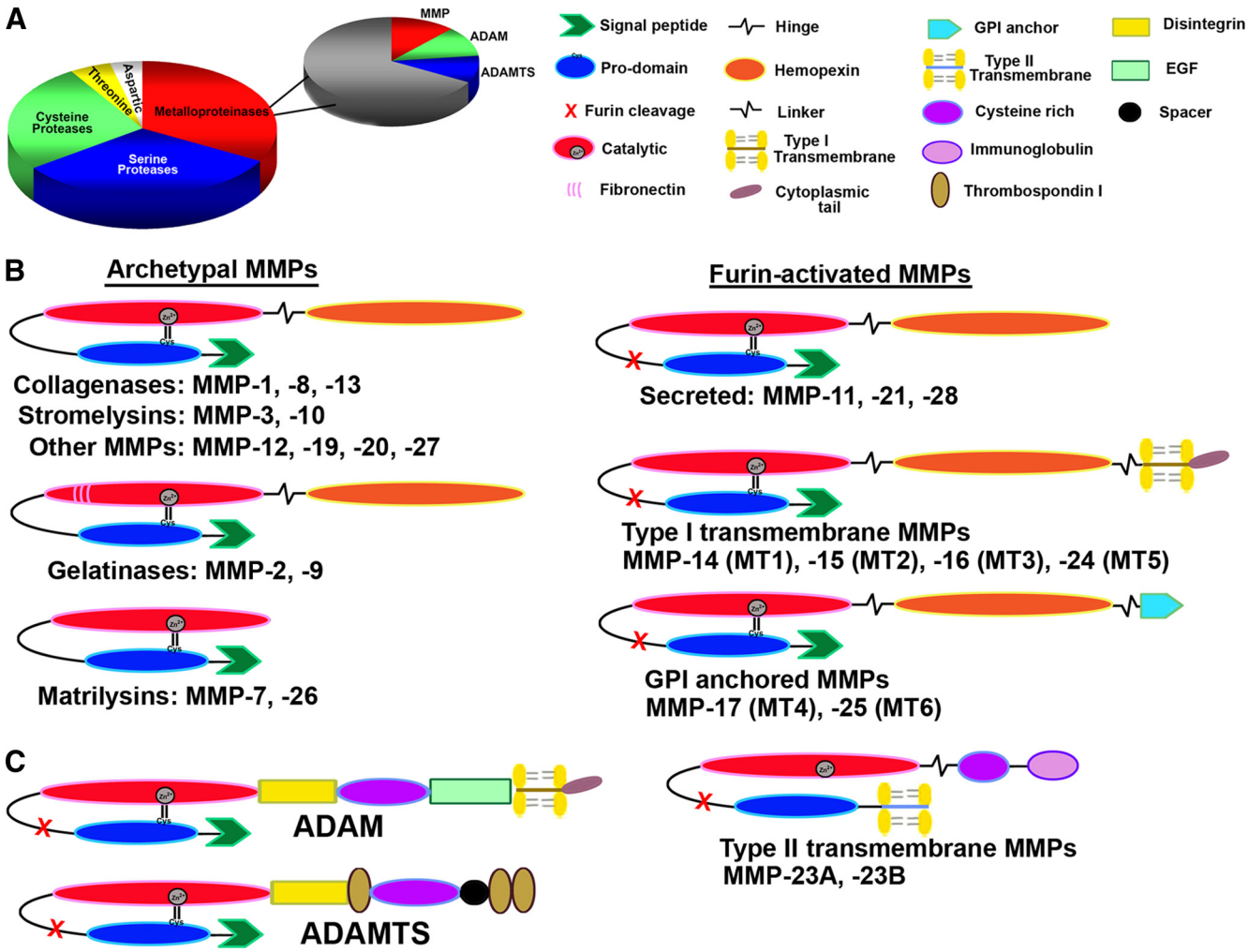


**Figure 1.** Protease classification and structure. ***A***, The human degradome, the repertoire of proteases produced by cells, consists of at least 569 proteases and homologs subdivided into five classes: 21 aspartic, 28 threonine, 150 cysteine, and 176 serine proteases and 194 metalloproteases, including MMP, ADAM, and ADAMTS family members. ***B***, Structural classification of MMPs based on domain composition, including secreted and membrane-associated MMPs, and MMPs that are activated intracellularly via furin-mediated cleavage. ***C***, Most ADAMs are type I transmembrane protein that possess disintegrin, cysteine-rich, and EGF domains in lieu of the MMP hemopexin domain. ADAMTSs are secreted proteins that contain thrombospondin I motifs in lieu of the EGF domain.

with tissue inhibitors of metalloproteinases (TIMPs), native MMP inhibitors. Matrilysins lack the PEX domain, whereas gelatinases possess three fibronectin II modules within the catalytic domain that improve collagen and gelatin degradation. In keeping with their role in physiological as well as pathological tissue remodeling (Yong, 2005; Page-McCaw et al., 2007; Agrawal et al., 2008; Rosenberg, 2009a), MMP expression is regulated at the level of transcription by a variety of growth factors, cytokines, and chemokines, although posttranscriptional and epigenetic modification may also contribute (Clark et al., 2008). It is now well accepted that MMPs not only degrade extracellular matrix (ECM) proteins of relevance to nervous system physiology [e.g., laminin, the chondroitin sulfate proteoglycan (CSPG) brevican, and the glycoprotein tenascin-R] but also activate growth factors (e.g., proNGF and proBDNF) and their receptors (e.g., trkA, trkC, and p75), cytokines [e.g., pro-tumor necrosis factor-$\alpha$ (proTNF-$\alpha$), pro-interleukin-1$\beta$ (proIL-1$\beta$)], and "shed" ECM receptors (e.g., N-cadherin, $\beta$-dystroglycan, and Ephrin-B2) (Schönbeck et al., 1998; Díaz-Rodríguez et al., 1999; McCawley and Matrisian, 2001; Jung et al., 2003; Mateos et al., 2003; Bruno and Cuello, 2006; Ethell and Ethell, 2007; Michaluk et al., 2007; Rodríguez et al., 2010). Because MMP-2, MMP-3, and MMP-9 are the most abundantly expressed MMPs within the brain, antibody reagents are readily available, and MMP-2 and MMP-9 can be easily identified by gelatin zymography, their role in the nervous system has been best characterized.

### ADAMs

ADAMs were first characterized for their involvement in sperm–egg fusion (Blobel et al., 1992), and, of the 21 human and 37 mouse ADAM genes, seven are primarily expressed in the testis; nonetheless, ADAMs play key roles in neuronal development and function. Several features distinguish ADAMs from MMPs (Fig. 1*C*) (Edwards et al., 2008). With the exception of the related snake venom metalloproteinases that are secreted, ADAMs are type I transmembrane proteins whose prodomain is generally removed intracellularly. Thus, ADAMs are specialized for juxtamembrane cleavage of other membrane-associated proteins and, hence, are often referred to as "sheddases." The ectodomain shedding either liberates an active extracellular peptide (e.g., TNF-$\alpha$) or is essential for subsequent "regulated intramembrane proteolysis" that generates an intracellular domain that translocates to the nucleus and regulates gene expression (e.g., Notch). However, only 13 of the human ADAMs possess proteolytic ac-

tivity, suggesting that other domains contribute to ADAM biological functions. ADAMs and ADAMTSs possess a disintegrin-like domain that is implicated in interactions with integrins (Bridges and Bowditch, 2005). With the exception of ADAM15, ADAMs lack the classical RGD integrin binding motif but possess a (D/E)ECD motif that contributes to integrin binding specificity and can influence cell adhesion positively (e.g., ADAM-12-mediated integrin $\alpha_6\beta_1$ sperm–egg fusion) (Gupta et al., 2000) or negatively (e.g., snake venom-mediated blockade of platelet aggregation via integrin $\alpha_{IIb}\beta_{IIIa}$) (Niewiarowski et al., 1994). In contrast, the cysteine-rich domain of ADAMs and ADAMTSs promotes cell adhesion via interaction with syndecans, fibronectin, and other ADAMs (Iba et al., 2000; Gaultier et al., 2002). Most ADAMs, except ADAM-10 and ADAM-17, also have an epidermal growth factor (EGF)-like domain adjacent to the membrane-spanning domain. The cytoplasmic tail of ADAMs is of varying length, with some potentially interacting with Src homology 3 domain-containing signaling molecules (e.g., src, grb), yet a role of ADAMs in signal transduction is not well characterized. At least 17 ADAMs are expressed in the nervous system (for review, see Yang et al., 2006), with ADAM-22, which lacks metalloproteinase activity, and ADAM-23 predominantly present in the nervous system (Sagane et al., 1999). However, ADAM-22 deficient [knock-out (KO)] (Sagane et al., 2005) and ADAM-23 KO (Mitchell et al., 2001) mice exhibit relatively minor phenotypes (e.g., ataxia, gait disturbances, tremor). In contrast, ADAM-10 KO (Hartmann et al., 2002) and ADAM-17 KO (Zhao et al., 2001) mice are embryonic or perinatal lethal. Even conditional knock-out of ADAM-10 in neural progenitor cells results in perinatal lethality (Jorissen et al., 2010). Although ADAM-10 and ADAM-17 get a bad rap for promoting proinflammatory signaling events (e.g., shedding of TNF-$\alpha$, IL-6, and IL-15 receptors), they also exert protective effects in neuronal differentiation, regeneration, and neurodegeneration (e.g., processing of amyloid precursor protein, N-cadherin, Ephrins) (Pruessmeyer and Ludwig, 2009).

**ADAMTSs**

Considerable attention has been focused on this family based on their role in thrombotic thrombocytopenic purpura, a form of microangiopathic hemolytic anemia, attributable to autoimmune inhibition of ADAMTS-13-mediated cleavage of von Willebrand factor (Zhou et al., 2010) and arthritis and other connective tissue disorders (e.g., Ehlers–Danlos syndrome attributable to ADAMTS-2 mutation and Weill–Marchesani syndrome attributable to ADAMTS-10 mutation) (Jones and Riley, 2005). Like ADAMs, ADAMTSs are activated intracellularly and secreted in active form. However, unlike ADAMs, ADAMTSs lack a transmembrane domain. Instead, ADAMTSs possess a conserved thrombospondin type 1-like repeat that is believed to function as a binding domain for sulfated glycosaminoglycans present on proteoglycans (Fig. 1*C*) (Porter et al., 2005). Since the discovery of the first family member (Kuno et al., 1997) and characterization of ADAMTS-1 as the previously identified "aggrecanase" (Sandy et al., 1991), additional ADAMTS members have been reported to cleave aggrecan (e.g., ADAMTS-1, ADAMTS-4, ADAMTS-5, ADAMTS-8, ADAMTS-9, and ADAMTS-15). However, the more global term "hyalectanase" (Gao et al., 2002) may be more relevant because ADAMTSs, particularly ADAMTS-4 and ADAMTS-5, also cleave the hyaluronan binding lectican proteoglycans versican (Sandy et al., 2001) and brevican (Nakamura et al., 2000). Brevican cleavage is of particular relevance to nervous system physiology because of its involvement in synaptic plasticity (Yuan et al., 2002; Mayer et al., 2005) and glioma invasion (Matthews et al., 2000) (discussed in greater detail later in this review). Although substrates have not been identified, evidence suggests that ADAMTSs contribute to neurodegenerative disorders [i.e., ADAMTS-1 expression is increased in Alzheimer's disease (AD) and Down syndrome] (Miguel et al., 2005) and cerebral ischemia (i.e., increased expression of ADAMTS-1, ADAMTS-4, ADAMTS-8, and ADAMTS-9) (Cross et al., 2006a; Tian et al., 2007b; Reid et al., 2009). Both ADAMTS-1 and ADAMTS-8 exert anti-angiogenic effects but display differential temporal upregulation in ischemia, with peak ADAMTS-1 expression at 24 h after occlusion and peak ADAMTS-8 expression after 3 d (Tian et al., 2007b); thus, each likely subserves different postischemia effects. Although MMPs play a well accepted role in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), the murine MS model (Rosenberg, 2002) (discussed in greater detail below), the contribution of ADAMTSs is less equivocal. ADAMTS-4 expression is decreased in EAE yet increased in MS white matter (Cross et al., 2006b; Haddock et al., 2006). This disparity may be explained, in part, by differential expression (i.e., increased in EAE and decreased in MS) of TIMP-3, the primary ADAMTS inhibitor. Thus, phenotype is driven by the balance between expression of proteases and their endogenous inhibitors.

**Metzincin inhibitors**

Three inhibitors negatively regulate metalloproteinase proteolytic activity: $\alpha$-macroglobulin (primary inhibitor in blood and lymphatic tissue), reversion-inducing cysteine-rich protein with Kazal motifs (RECK), and TIMPs. Thus far, RECK has been reported to inhibit a rather small repertoire of proteases (e.g., MMP-2, MMP-9, and MT1-MMP) and primarily within the context of tumorigenesis (Takahashi et al., 1998; Oh et al., 2001; Liu et al., 2003). Nonetheless, RECK appears to modulate Notch-mediated cortical neurogenesis by regulating ADAM-10 activity (Muraguchi et al., 2007). Hence, TIMPs represent the principal endogenous metalloproteinase inhibitors (Brew and Nagase, 2010). Four highly conserved TIMP genes are present in humans and mice. Among the TIMPs, TIMP-1 has the most restricted inhibitory range because it shows low affinity for MT–MMPs and exhibits adult CNS expression primarily restricted to regions of persistent neuronal plasticity, such as the hippocampus, olfactory bulb, and cerebellum (Rivera et al., 1997; Fager and Jaworski, 2000). The relative restricted tissue distribution of TIMP-4 (e.g., heart, kidney, pancreas, colon, testes, brain, and adipose tissue) suggests that it plays a role in tissue-specific physiological functions (Greene et al., 1996), but little else is known about this molecule (Melendez-Zajgla et al., 2008). TIMP-3 has the broadest inhibition spectrum, inhibiting several ADAM and ADAMTS proteases, and is the only TIMP bound to the ECM (Leco et al., 1994). TIMP-2 is the most abundantly expressed TIMP in the brain (Fager and Jaworski, 2000) and not only inhibits MMP-2 but, paradoxically, also contributes to proMMP-2 activation (Butler et al., 1998). Indeed, TIMP-2 forms a trimolecular complex with MT1-MMP and proMMP-2 and is required for MT1-MMP-mediated activation of proMMP-2. Hence, proMMP-2 activation is impaired in its absence (i.e., TIMP-2 KO mice) (Caterina et al., 2000; Wang et al., 2000). Similar proMMP interactions occur (e.g., TIMP-1 and proMMP-9), but this interaction is not required for proMMP activation. Although other MMPs can activate proMMP-2 independent of TIMP-2 (e.g., MT2-MMP) (Morrison et al., 2001), MT1-MMP is principally responsible for proMMP-2 activation. In addition to their dual roles in MMP

inhibition and MMP activation, TIMPs exert diverse biological functions (e.g., cell cycle, anti-angiogenesis, apoptosis) independent of MMP interaction (Crocker et al., 2004; Chirco et al., 2006; Stetler-Stevenson, 2008b). Inhibitors specifically targeting these MMP-independent functions may be exploited therapeutically without altering tissue integrity.

### Confounding factors in metzincin biology

The development of efficacious analytical tools has supported progress in the metzincin field, but investigating the expression and role of these proteinases still encounters limitations. Perhaps one of the most important is the paucity of selective synthetic metzincin inhibitors, principally because of the high level of structural conservation in their catalytic sites. Some inhibitors have been reported to selectively inhibit MMP-2, MMP-9, MMP-11, MMP-12, MMP-13, and MMP-14, ADAM-17, and ADAMTS-4 and ADAMTS-5, whereas some compounds that broadly inhibit MMPs spare ADAMs (at least ADAM-17). Exhaustive information on current progress in the ability to design specific metzincin inhibitors (including synthetic, antibody-based or endogenous inhibitors) can be found in specialized reviews (Fisher and Mobashery, 2006; Yiotakis and Dive, 2008; Brew and Nagase, 2010; Sela-Paswell et al., 2010). Additional difficulties stem from the use of commercially available antibodies. Most commercial antibodies were initially developed to human antigens for use in clinical studies, but many of these reagents displayed limited cross-reactivity with other species. Thankfully, this limitation is waning as companies develop antibodies to murine antigens. Nonetheless, antibodies may not display sufficient sensitivity to detect the low level of metzincins present in some cell types or subcellular compartments and multiple antibodies often need to be tested. Immunocytochemistry also fails to detect the subcellular localization of the latent versus active forms of the enzymes. Although this may be accomplished by molecular mass on Western blots, it does not provide information about their inhibitor-bound or free state in the cell. The highly sensitive technique of gel zymography detects picogram levels of the zymogen and active forms of gelatinases MMP-2 and MMP-9 on the basis of their ability to cleave gelatin in SDS-PAGE. Nevertheless, gel zymography is hardly useful for other MMPs and reflects the steady-state levels of MMPs rather than their activity in the tissue. *In situ* zymography partially alleviates this problem because the fluorescence resulting from the cleavage of FITC-quenched gelatin added to fresh tissue slices or cells represents the net *in situ* balance between active gelatinases and their endogenous inhibitors. However, this technique reveals the net activity of all gelatinases, not just MMP-2 and MMP-9. Thus, the use of inhibitors (e.g., serine proteinases) is recommended to ascertain the nature of the proteolytic activity. These few examples illustrate the limitations of widely used tools and bring about the opportunity of combining them with molecular tools (small interfering RNA, antisense oligonucleotides, genetically engineered molecules, cells, and mice) to better assess the biology of a specific proteinase.

This brief review of metzincin structure and function has only given the reader a small glimpse into the complexity of this fascinating protein family. The four reviews that follow highlight the contributions of these proteases and their inhibitors in nervous physiology and pathology, with special emphasis on the concept that not all proteolysis has negative consequences.

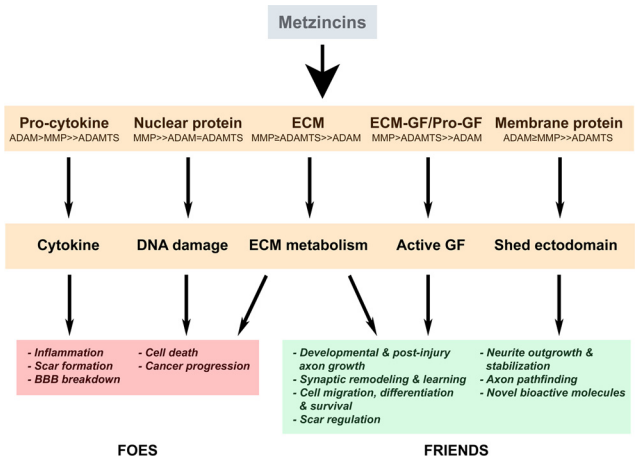


**Figure 2.** Physiopathological consequences of metzincin–substrate interactions. Nonexhaustive representation of interactions between metzincins and putative substrates in the nervous system, leading eventually to detrimental or beneficial effects in different physiological and pathological settings. The hierarchy between proteinase subtypes is established on the basis of current knowledge on metzincin actions and substrate preferences in the nervous system. The substrates include cytokines, soluble or ECM-bound growth factors (GF), and nuclear or membrane proteins. Metzincin-mediated proteolysis may lead to the following: (1) conversion of latent forms of proinflammatory cytokines (e.g., TNF$\alpha$, IL-1$\beta$, etc.) or growth factors (e.g., BDNF, NGF) into their biologically active forms; (2) cleavage of nuclear (e.g., DNA repair enzymes) or ECM proteins (e.g., CSPGs, laminin, tenascin) causing irreversible changes in their structure and function; (3) cleavage of membrane proteins leading to their activation or inactivation or to the release of soluble ectodomains with, in most cases, yet unknown biological activity.

### Metzincins and TIMPs at the crossroads of developmental and postinjury plasticity

Although metzincins and TIMPs have been mostly studied in the context of nervous system disease and injury, the past decade has witnessed a growing interest of neuroscientists for their role in developmental plasticity and repair. The molecular and cellular events that support postlesion repair of the mature CNS recapitulate some of the processes set in motion during development. Strong evidence now indicates that the metzincin/TIMP system plays critical roles in these phenomena (Fig. 2, Table 1).

#### *Metzincins and TIMPs in developmental processes*

The increased interest in metzincin proteinases notwithstanding, the expression of all metzincins and TIMPs has not been evaluated in all cell types or regions of the nervous system. Relatively high mRNA and protein levels of MMP-2, MMP-11, MMP-13, MMP-14, MMP-15, and MMP-24 and TIMP-1 and TIMP-3 are found in the perinatal rodent CNS but generally decline with age (Rivera et al., 1997; Vaillant et al., 1999; Fager and Jaworski, 2000; Jaworski, 2000; Ayoub et al., 2005; Ulrich et al., 2005; Ranasinghe et al., 2009). In contrast, TIMP-2 and TIMP-4 increase with age (Fager and Jaworski, 2000; Ulrich et al., 2005), and MMP-12 levels peak at 4–5 postnatal weeks, coincident with the peak of myelination (Ulrich et al., 2005). Less is known about the developmental regulation of other metzincin family members. ADAMTS-9 expression is restricted to the floor plate of the diencephalon and cerebral cortical ventricular zone (Jungers et al., 2005), yet its function in corticogenesis has not been investigated. These data suggest that each MMP and TIMP likely subserves distinct developmental functions.

The MMP/TIMP system has been shown to influence neural cell differentiation and survival. TIMP-2 acts in synergy with NGF to induce cell cycle arrest of neuronal precursors and promote neuronal differentiation (Pérez-Martínez and Jaworski,

**Table 1. Metzincin functions in the nervous system**

| Metzincin | Physiological function | Postinjury function |
|---|---|---|
| MMP-2 | Neurite outgrowth[c]<br>Astrocyte motility[b]<br>PNS myelination[b] | Axonal regeneration and tissue repair[c] |
| MMP-3 | Neurite outgrowth[c]<br>Neural cell survival[c] | |
| MMP-7 | Neurotrophin convertase[a] | |
| MMP-9 | Neurite outgrowth[c]<br>Neural cell precursor migration[c] and survival[a]<br>Oligodendrocyte maturation and myelination[c]<br>NGF degradation[a] | Excitotoxic neuronal death[c]<br>Scar formation[c]<br>Remyelination[a]<br>Neural cell precursor mobilization[c] |
| MMP-12 | Oligodendrocyte maturation and myelination[c] | Secondary damage in SCI[c] |
| MMP-24 | | Spinal cord axonal sprouting[c] |
| MT–MMPs | Neuroblast migration[b] | |
| ADAM-10 | Axonal extension,[a] guidance,[a] and stabilization[c]<br>Neuronal migration and differentiation[a] | |
| ADAM-17 | | Neurite outgrowth in the presence of myelin ligands[c] |
| ADAMTS-4 | Neurite outgrowth[a] | |
| ADAMTS-5 | Neurite outgrowth[a] | |

Findings have been obtained mostly with [a]molecular, [b]pharmacological, or [c]both molecular and pharmacological approaches. Pharmacological approaches essentially use metzincin inhibitors, whereas molecular approaches include the use of recombinant metzincins or gain–loss-of-function engineered molecules. SCI, Spinal cord injury; NGF, nerve growth factor; PNS, peripheral nervous system.

2005), whereas MMP-9 and MMP-12 regulate oligodendrocyte maturation and myelination possibly through the modulation of insulin-like growth factor bioavailability (Larsen et al., 2006). A role for MMP-2 in peripheral nervous system myelination has also been reported recently in a coculture model of Schwann cells and dorsal root ganglia (DRG) neurons (Lehmann et al., 2009). Moreover, cell culture studies have shown that MMP-3 can promote neural cell survival by suppressing Fas ligand-mediated programmed cell death signaling (Wetzel et al., 2003). *In vivo*, postnatal programmed cell death of cerebellar granule cell precursors is reduced in MMP-9 KO mice (Vaillant et al., 2003). These data underscore the importance of positive roles for MMPs in neuronal survival.

Cell migration is another pivotal developmental function that involves metzincin activities. Migration of cerebellar granule cell precursors correlates with changes in MMP-9 expression, and external granular layer migration is delayed in MMP-9 KO mice or after blockade of MMP-9 activity with neutralizing antibodies in cerebellar explants (Vaillant et al., 2003). Another gelatinase, MMP-2, regulates the motility of cultured nonstimulated astrocytes possibly via an interaction with $\beta$1 integrins and the actin cytoskeleton (Ogier et al., 2006). The migration of individual neuroblasts along the rostral migratory stream (RMS) from the subventricular zone (SVZ) to the olfactory bulb or those migrating radially within the olfactory bulb is perturbed after birth by furin inhibitors thought to inhibit the activation of MT–MMPs (Bovetti et al., 2007). The expression of TIMP-3, a physiological MT–MMP inhibitor, in the SVZ and RMS (Jaworski and Fager, 2000) may negatively regulate neuroblast migration. Besides MMPs, a central role for ADAM-10 in brain development has been demonstrated recently. Conditional KO of ADAM-10 specifically in neural progenitor cells induces aberrant neuronal migration and a disorganized laminar neocortical architecture attributable to precocious neuronal differentiation and consequent early depletion of progenitor cells (Jorissen et al., 2010).

Perhaps the most critical role of metzincins in developmental plasticity is regulation of neurite outgrowth. Metalloproteinase activity is permissive for axonal extension via cleavage of inhibitory ECM proteins (e.g., CSPGs). ADAMTS-4 and ADAMTS-5 promote neurite outgrowth (Hamel et al., 2008) via brevican cleavage (Hamel et al., 2005). ADAMTS-4 also enhances neurite outgrowth via a mechanism that does not require proteolysis but is dependent on activation of mitogen-activated protein (MAP) extracellular signal-regulated kinase 1/2 (ERK1/2) kinase (Hamel et al., 2008). Thus, like TIMPs, metzincin proteases also exert effects that are independent of proteolytic activity. MMPs also mobilize ECM-sequestered trophic factors, such as EGF (Suzuki et al., 1997). In addition, MMP-7 can proteolytically convert the pro-forms of BDNF and NGF into the biological active forms (Lee et al., 2001), and MMP-9 degrades active NGF (Bruno and Cuello, 2006). In turn, NGF and BDNF can stimulate the expression and activity of MMP-2, MMP-9, and MMP-14 (Machida et al., 1991; Muir, 1994; Cazzin et al., 2010). This proteolysis can either activate or inhibit signaling pathways. Broad-spectrum metalloproteinase inhibitors prevent shedding of deleted in colorectal cancer, a receptor for the guidance factor netrin-1, which potentiates ligand–receptor interactions and consequent netrin-mediated axon outgrowth of cultured rat embryonic DRG neurons (Galko and Tessier-Lavigne, 2000). The same inhibitors provoke pathfinding errors in retinal ganglion cell axons along the optic chiasm during *Xenopus* development (Webber et al., 2002). The Kuzbanian protein (the *Drosophila* homolog of vertebrate ADAM-10) is required for normal axon extension (Fambrough et al., 1996) and controls midline crossing of axons in the CNS via proteolytic activation of the Slit/Robo receptor complex in commissural axons (Schimmelpfeng et al., 2001). ADAM-10 also controls axon stabilization and progression through the proteolytic cleavage of chemorepellent ephrins (Hattori et al., 2000) via a mechanism that requires the formation of an ADAM-10/Eph receptor complex that precedes Eph cleavage (Janes et al., 2005). Although most studies principally suggest the involvement of ADAMs in axon guidance, recent reports posit that MMP-3 and MMP-2 contribute to axon guidance and dendrite extension of embryonic cultured cortical neurons in response to Sema3C and Sema3A signaling, respectively (Gonthier et al., 2007, 2009). In the same culture model, a truncated form of TIMP-1 lacking the C-terminal domain inhibits neurite outgrowth via its MMP-inhibitory N-terminal domain, most likely by targeting MMP-2 (Ould-yahoui et al., 2009). Altogether, these data reinforce the idea that metzincins and TIMPs may work in concert to regulate neurite extension/pathfinding during development.

### *Metzincins and TIMPs in postinjury plasticity*

Metzincins also play a role in postinjury plasticity, particularly via the regulation of the glial scar. The glial scar effectively confines the lesion but also constitutes a major obstacle for axon regeneration, partially because of the accumulation of inhibitory molecules (e.g., CSPGs, myelin ligands). Pioneer studies demonstrated that MMP-2-mediated CSPG proteolytic processing promotes axonal outgrowth of DRG neurons and unveils the growth-promoting effect of associated laminin (Zuo et al., 1998). Analogous effects on neurite outgrowth were reported for MMP-24-mediated CSPG cleavage in cultured DRG neurons (Hayashita-Kinoh et al., 2001). Furthermore, the inhibitory effect of CNS myelin on DRG neurite outgrowth is removed by

the ADAM-17-mediated cleavage of the neurotrophin receptor p75, acting upstream of Rho-A inactivation (Ahmed et al., 2006).

The involvement of TIMPs in glial scar formation finds support in the high levels of astrocytic TIMP-1 and TIMP-2 observed in nonregenerating areas after optic nerve injury compared with lower levels found in regenerating areas (Ahmed et al., 2005). Also, the finding that TIMP-1 is mitogenic for astrocytes, unlike broad-spectrum MMP inhibitors (Ogier et al., 2005, 2006), suggests a role for TIMP-1 in postinjury gliosis through a mechanism independent of MMP inhibition. Accordingly, knocking out TIMP-1 targets such as MMP-2 or MMP-9 has no effect on astrocyte mitogenesis in culture (Hsu et al., 2008). This is similar to the MMP-independent actions of TIMP-2 on neuronal differentiation via the interaction of TIMP-2 and integrin $\alpha 3\beta 1$ (Pérez-Martínez and Jaworski, 2005). These studies illustrate a yet relatively unexplored domain of the signal transduction pathway(s) triggered by TIMPs or MMPs independent of proteolysis modulation.

After spinal cord injury, *in situ* zymography reveals increased gelatinase activity along regenerating axons in the scar tissue (Duchossoy et al., 2001). Accordingly, MMP-2 KO mice exhibit reduced spontaneous axon regeneration and functional recovery with a concomitant increase in CSPG levels after moderate spinal cord injury (Hsu et al., 2006). The same authors suggest that MMP-9 contributes to the early deleterious effects of spinal cord injury (Goussev et al., 2003) and to astrocyte motility during glial scar formation (Hsu et al., 2008). However, MMP-9 action may follow some region and/or lesion specificity because the formation of the glial scar is not altered in the cortex or striatum of MMP-9 KO mice after focal ischemia (Copin and Gasche, 2007). Other authors have shown in KO mice with spinal cord injury that MMP-9 facilitates remyelination via processing of the inhibitory proteoglycan NG2 (Larsen et al., 2003), whereas MMP-12 mediates the permeability of the blood–spinal cord barrier and activation of mononuclear phagocytes (Wells et al., 2003). MMP-24 KO mice do not display dorsal horn A$\beta$ fiber sprouting normally observed after sciatic nerve injury, suggesting a possible explanation for the absence of mechanical allodynia in the mutant mice (Komori et al., 2004). These data stress the beneficial and detrimental effects of MMPs and point to MMP-9 as probably the best example of this functional duality.

Excitotoxic neuronal hyperactivity is also a strong inducer of MMP and TIMP expression. Kainate (KA)-induced seizures in rats sequentially upregulate TIMP-1 in hippocampal dentate granule cells and reactive astrocytes (Rivera et al., 1997). In the same animal model, transient upregulation of MMP-9 expression and gelatinase activity in dendritic areas of the dentate gyrus (DG) have been related to postseizure tissue remodeling of this area (Szklarczyk et al., 2002), whereas MMP-9 appears to be deleterious for pyramidal hippocampal cells (Jourquin et al., 2003). Transient early postseizure upregulation of MMP-9 is followed by steady augmentation of MMP-2 over 4 weeks, coincident with mossy fiber sprouting (Jourquin et al., 2005). The same study showed that TIMP-1 KO mice undergoing seizures do not exhibit MMP upregulation or axonal sprouting, suggesting that coregulation of TIMP-1 and MMPs is necessary to support postseizure sprouting. The implication of MMPs in axo-dendritic remodeling finds additional support in invertebrate models in which *Drosophila* MMPs are required to degrade dendrites before large-scale reorganization of sensory neuron dendritic arbors during metamorphosis (Kuo et al., 2005). Thus, several MMPs may cooperate in sequential events in which an initial disruption of the dendritic arbor paves the way for eventual sprouting of hippocampal mossy fibers.

The effect of MMPs in neuronal regeneration has recently lead researchers to question whether the regenerative properties of exogenously grafted cells could rely on MMP activity-based mechanisms. Several MMPs, including MMP-2 and MMP-9, and the four TIMPs are expressed in neural precursors *in vivo* and *in vitro* (Frölichsthal-Schoeller et al., 1999; Ben-Hur et al., 2006; Lee et al., 2006). MMP-9 is abundantly expressed in neuroblasts migrating from the SVZ into the injured striatum in response to focal ischemia in mice, and MMP inhibitors interfere with this migration (Lee et al., 2006). Transplantation of CNS progenitor cells into explants of degenerating retina promotes neurite extension in response to increased MMP-2 secretion by host glial cells and the concomitant proteolytic processing of the neurite outgrowth inhibitors CD44 and neurocan (Zhang et al., 2007). Likewise, MMP-2 produced by rat olfactory ensheathing cells cocultured with adult retinal cells promotes axon growth coincident with CSPG cleavage (Pastrana et al., 2006). Altogether, these findings highlight positive roles for metzincins in cell-mediated injury repair through the mobilization of endogenous neural cell precursors and the remodeling of the lesion environment by grafted cells.

In summary, the data reviewed herein brings about compelling evidence about the functional relevance of metzincins and TIMPs at the crossroads of physiological and postinjury neural plasticity. Much work remains to be done for a comprehensive vision of the biology of these molecules and the way we may control them in the prospects of designing neuroregenerative therapies.

## Metzincins and TIMPs contribute to learning and memory as well as human neuropsychiatric disorders

In addition to developmental plasticity (discussed above), there are multiple physiological and pathological phenomena relying on plasticity within the adult brain, including learning and memory, epileptogenesis, and drug addiction, to name just a few. Several experimental paradigms mimicking some aspects of plasticity have also been identified, with long-term potentiation (LTP) and long-term depression (LTD) being the most prominent. Myriad molecules have been proposed to play a role in brain plasticity. Most studies focus on external information conveyed to neurons predominantly by means of neurotransmitters, neurotrophins, cytokines, and steroids. However, much less is known about a major extracellular molecular brain structure surrounding neuronal synapses, i.e., ECM and cell adhesion molecules. Because plasticity is associated with postsynaptic structural alterations, proteolytic ECM modifications likely contribute to plasticity.

### *MMPs/TIMPs in long-term potentiation and learning*

The first indication that the MMP/TIMP system plays a role in neuronal plasticity was provided by Nedivi et al. (1993) who demonstrated TIMP-1 mRNA upregulation within the DG on both KA-induced seizures and stimuli leading to LTP. KA treatment provokes a massive neuronal excitation that results in neuronal loss in the CA1/CA3 hippocampal subfields but spares the DG, which undergoes plastic reorganization instead (Zagulska-Szymczak et al., 2001). Szklarczyk et al. (2002) suggested that MMP-9 might also be relevant for neuronal plasticity because they found that MMP-9 mRNA, protein, and enzymatic activity were all selectively increased in the DG after KA-evoked seizures. Interestingly, MMP-9 and TIMP-1 are subject to gene regulation

by AP-1, a transcription factor composed of Fos and Jun proteins that has been closely associated with neuronal plasticity (Jaworski et al., 1999; Kaczmarek et al., 2002; Rylski et al., 2009).

Several reports support a role for MMPs in physiological LTP at diverse brain regions. The pivotal role for MMP-9 in LTP was first established by Nagy et al. (2006) who revealed that MMP-9 protein levels and proteolytic activity were rapidly increased by stimuli that induce late-phase LTP. Furthermore, using MMP-9 KO mice, as well as broad-spectrum MMP inhibitors, the authors reported deficient late-phase LTP in hippocampal slices at the CA3 to CA1 pathway. A role for MMPs, using broad-spectrum inhibitors, has also been reported for DG–CA3 (mossy fiber) LTP in the hippocampus (Wójtowicz and Mozrzymas, 2010). Inhibition of MMP activity with MMP-3 and MMP-9 antisense oligonucleotides, chemical MMP inhibitors, or neutralizing antibodies also altered hippocampal LTP (Meighan et al., 2006; Bozdagi et al., 2007; Meighan et al., 2007; Wang et al., 2008; Conant et al., 2010). Notably, hippocampal MMP-3 expression and activity increased during trauma-induced synaptogenesis, and MMP inhibition altered functional and structural correlates of deafferentiation-induced sprouting in the DG (Reeves et al., 2003; H. J. Kim et al., 2005; Falo et al., 2006). In addition to hippocampal LTP, blocking MMP-9 by either a specific chemical inhibitor or TIMP-1 overexpression impaired late-phase LTP, but not its induction, in the subiculum to prefrontal cortex pathway (Okulski et al., 2007). Disruption of MMP-9 activity also abolished late-phase LTP in the basolateral to central nucleus of the amygdala, but LTP in the cortical pathway leading to the lateral amygdala remained essentially intact (M. Balcerzyk, V. Lioudyno, A. Kiryk, T. Górkiewicz, P. Michaluk, M. Gawlak, G. M. Wilczyński, L. Kaczmarek, E. Knapska, unpublished observations). Together, these data indicate that MMPs are involved in various aspects of LTP, with MMP-9 needed for late-phase LTP and MMP-3 for LTP induction. In this context, it is noteworthy that MMP-3 acts upstream of MMP-9 (i.e., MMP-3 regulates MMP-9 activation) (Ogata et al., 1992).

Given the role of MMPs in hippocampal LTP, it comes as no surprise that MMP inhibition has also been linked to memory deficits in behavioral learning paradigms (Nagy et al., 2006, 2007; Wright et al., 2007, 2009; Brown et al., 2009; Wiediger and Wright, 2009). Specifically, MMP-3 was activated by passive (inhibitory) avoidance and habituation of the head-shake response (Wright et al., 2006; Olson et al., 2008), and MMP-9 activity was increased after Morris water maze, head-shake response, and passive avoidance (Meighan et al., 2006; Wright et al., 2006; Nagy et al., 2007). Furthermore, MMP-9 KO mice displayed poor memory in contextual fear conditioning and appetitive learning in the IntelliCage system (Nagy et al., 2006; Brown et al., 2009; M. Balcerzyk, V. Lioudyno, A. Kiryk, T. Górkiewicz, P. Michaluk, M. Gawlak, G. M. Wilczyński, L. Kaczmarek, E. Knapska, unpublished observations). However, no effect of MMP-9 KO was demonstrated for discrete cue conditioning or aversive learning in the IntelliCage system (Knapska et al., 2006; Nagy et al., 2006; M. Balcerzyk, V. Lioudyno, A. Kiryk, T. Górkiewicz, P. Michaluk, M. Gawlak, G. M. Wilczyński, L. Kaczmarek, E. Knapska, unpublished observations). Because the lateral amygdala has been specifically implicated in the two latter paradigms, these findings are in accord with the LTP data discussed above. These studies clearly support a role for MMPs in learning but also demonstrate specificity driven by anatomic location and/or molecular substrates.

The subcellular localization of MMPs makes them ideally suited for the regulation of neuronal plasticity. For example, MMP-9 mRNA, protein, and enzymatic activity are present at the

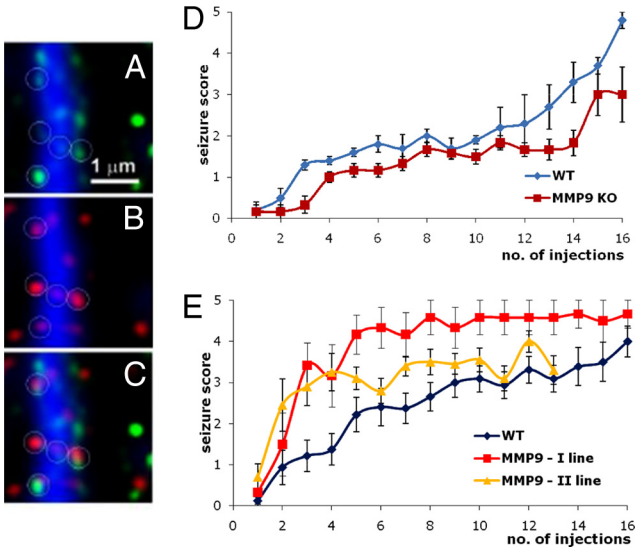


**Figure 3.** MMP activity is expressed at synapses, and MMP-9 plays a role in aberrant plasticity subserving epileptogenesis. ***A***, MMP (gelatinolytic) activity revealed by *in situ* zymography (green) along a dendrite (blue, MAP-2 antibody staining). ***B***, Dendritic spines (red, antibody staining against drebrin) along a dendrite. ***C***, Colocalization of gelatinolytic activity and spine marker. ***D***, MMP-9 KO mice and their wild-type siblings were treated to chemical kindling (an epileptogenic process) by repeated intraperitoneal injections of pentylenetetrazole (35 mg/kg, every 2–3 d). Seizure score reflects increasing severity of convulsions from 1 to 5. Note that MMP-9 KO are less susceptible to epileptogenesis. ***E***, Pentylenetetrazole kindling in wild-type (WT) and transgenic (TG) rats overexpressing an autoactivating form of MMP-9 in neurons; two lines of transgenic rats were generated and subjected to kindling. Note that the transgenic rats are more prone to the epileptogenesis (for details on ***A–C***, see Gawlak et al., 2009; for details on ***E*** and ***D***, see Wilczynski et al., 2008).

postsynaptic domains of excitatory synapses (i.e., at dendritic spines) (Konopacki et al., 2007; Sbai et al., 2008; Wilczynski et al., 2008; Gawlak et al., 2009) (Fig. 3*A–C*). LTP-producing stimuli evoke local MMP-9 release, which affects spine morphology (Wang et al., 2008; Bilousova et al., 2009). Specifically, MMP-9 drives dendritic spine enlargement and LTP coordinately, thus playing an instructive role in establishing persistent modifications in both synapse structure and function (Wang et al., 2008).

The following molecular scenario may underlie MMP-9 involvement in synaptic plasticity. When glutamate binds to its receptor (e.g., NMDA receptor), a signaling cascade is set in motion that results in local MMP-9 release. The exact nature of the molecular events taking part in MMP-mediated plasticity remains elusive; however, $\beta$-dystroglycan, ICAM-5, and integrins, especially $\beta$1 integrins, appear to be involved (Nagy et al., 2006; Michaluk and Kaczmarek, 2007; Tian et al., 2007a; Michaluk et al., 2009; Conant et al., 2010). Because MMP-9 is proteolytically activated outside the cell and cannot be recuperated, translation, release, and/or activity trigger signals that initiate an MMP-9 replenishment process. This involves production of the c-Fos/AP-1 transcription factor, MMP-9 gene expression, translocation of MMP-9 mRNA toward dendrites and synapses, and local dendritic translation. Given its role in neuronal cell loss (Michaluk and Kaczmarek, 2007), excessive MMP-9 could be harmful; thus, its gene expression is prevented by transcriptional silencers, including AP-1 of a different composition (i.e., JunB) (Rylski et al., 2009). MMP activity is also regulated by interaction with TIMPs.

TIMPs have also been shown to affect learning and memory. In an olfactory maze, TIMP-1 KO mice were significantly impaired in making correct odor reward, whereas TIMP-1 overexpressing mice performed better than their wild-type controls

(Jourquin et al., 2005; Chaillan et al., 2006). In TIMP-2 KO mice, a deficiency in fear-potentiated startle response has been revealed (Jaworski et al., 2005). Finally, TIMP-3 KO mice exhibited deterioration in cognitive function in the water maze and decreased habituation in the open-field test (Baba et al., 2009).

*ADAMTS and ADAM family members in neuronal plasticity*

Although less well characterized, ADAMTS and ADAM family members also contribute to synaptic plasticity. Brevican, the most abundantly expressed member of the lectican family of CSPGs in the adult brain, stabilizes synapses and inhibits neuronal plasticity. ADAMTS-mediated brevican cleavage is enhanced in response to KA treatment (Yuan et al., 2002) and entorhinal cortex lesion (Mayer et al., 2005) and may modulate synaptic reorganization. Cleavage of the neuronal pentraxin receptor by ADAM-17/tumor necrosis factor-$\alpha$ converting enzyme (TACE) is required for metabotropic glutamate receptor subunit 1/5 (mGluR1/5)-dependent internalization of AMPA receptor and mGluR1/5-dependent LTD in both the hippocampus and cerebellum (Cho et al., 2008). Although a role for ADAM-21 in neurogenesis and plasticity has been proposed (Yang et al., 2005), potential ADAM-21 substrates have yet to be identified (Yang et al., 2006). ADAM-10, an $\alpha$-secretase, cleaves amyloid precursor protein within the A$\beta$ sequence and thus prevents amyloid peptide formation. ADAM-10 overexpressing mice display enhanced cortical plasticity (Bell et al., 2008) and rescued LTP deficiency in the AD model mice (Postina et al., 2004) and positively influences learning and memory (Schmitt et al., 2006). Thus, ADAM-10 may serve as a therapeutic target for AD (Endres and Fahrenholz, 2010).

*MMPs in epilepsy*

Various conditions believed to be subserved by abnormal synaptic plasticity have been reported to involve MMP-9. For instance, epileptogenesis produced by pentylenetetrazole kindling was disturbed in MMP-9 KO mice and, conversely, promoted in MMP-9 overexpressing rats (Wilczynski et al., 2008) (Fig. 3*D*,*E*). A role of MMP-9 in the development of epilepsy has also been supported by studies in pilocarpine- and 4-aminopyridine-treated animal models (Kim et al., 2009; Takács et al., 2010).

*MMPs in addiction*

A functional role for MMPs and TIMPs has also been revealed in drug addiction. Intracerebral injection of a broad-spectrum MMP inhibitor suppressed acquisition of cocaine-dependent place preference and attenuated cocaine-primed reinstatement after extinction of the response (Brown et al., 2007). Furthermore, increased MMP-9 was observed in the medial prefrontal cortex after cocaine reinstatement of the conditioned place preference (Brown et al., 2007). Moreover, increased MMP-2 and MMP-9 activity in both neurons and glia were observed in the frontal cortex and nucleus accumbens after methamphetamine addictive treatment and diminished behavioral response to treatment was noted in both MMP-2 and MMP-9 KO mice (Mizoguchi et al., 2007b). Furthermore, both strains of mutant mice exhibited resistance to the inhibitory effect of treatment on dopamine transport activity (Mizoguchi et al., 2007b). Similar effects were observed after application of an MMP-2/9 inhibitor (Mizoguchi et al., 2007a). In addition, repeated methamphetamine treatment increased TIMP-2 expression, and antisense TIMP-2 oligonucleotide enhanced the behavioral effects as well as methamphetamine-induced dopamine release in the nucleus accumbens (Mizoguchi et al., 2007a). Moreover, repeated drug treatment reduced dopamine $D_2$ receptor-dependent signaling in wild-type mice but not MMP-9 or MMP-2 KO mice (Mizoguchi et al., 2007a). Recently, W. T. Liu et al. (2010) have reported that MMP-9 in the spinal cord contributes to morphine withdrawal-like behavioral signs in mice. It has also been reported that ethanol-induced impairment of water maze learning correlated with reduced hippocampal and prefrontal cortex MMP-9 activity (Wright et al., 2003).

The aforementioned results linking the MMP/TIMP system to drug addiction obtained with animal models are also reinforced in humans. Serum MMP-9 levels are greater in alcoholics (Sillanaukee et al., 2002), and alcoholics exhibit a twofold increased frequency of an MMP-9 promoter polymorphism known to result in greater MMP-9 expression (Samochowiec et al., 2010). Conversely, cocaine abusers have less MMP-9 activity in the hippocampus, probably as a result of upregulation of RECK gene expression (Mash et al., 2007).

*MMPs in neuropsychiatric disorders*

The aforementioned MMP-9 promoter polymorphism also displays increased frequency in bipolar disorder but decreased frequency in schizophrenia (Rybakowski et al., 2009a,b), yet MMP-9 and TIMP-1 are markedly increased in plasma samples derived from schizophrenic patients (Domenici et al., 2010). Furthermore, a possible relationship between MMP-3 gene polymorphism and susceptibility to schizophrenia was also reported (Kucukali et al., 2009).

Data linking MMP-9 with human cognition are more equivocal. The MMP-9 promoter polymorphism is associated with altered executive function, tested using the Wisconsin Card Sorting Test, in males suffering from bipolar disorder (Rybakowski et al., 2009c) but not in healthy individuals with the same gene polymorphism (Rybakowski et al., 2009d). Similarly, another MMP-9 promoter polymorphism did not correlate with episodic memory deficits (Vassos et al., 2008). Bruno et al. (2009) found inverse correlations between global cognitive score and Mini-Mental State Examination score with MMP-9 activity, when analyzing human subjects with either AD or mild cognitive impairment versus no cognitive impairment. They also reported greater MMP-9 activity in the human frontal and parietal cortex in both AD and mild cognitive impairment brains. MMPs, MMP-9 in particular, have been shown as amyloid-degrading enzymes, and their expression is altered in AD victims (for review, see Nalivaeva et al., 2008).

In conclusion, the data presented herein, as well as in more in-depth reviews (Dzwonek et al., 2004; Ethell and Ethell, 2007; Michaluk and Kaczmarek, 2007; Milward et al., 2007; Agrawal et al., 2008; Mizoguchi et al., 2008; Rybakowski, 2009; Wright and Harding, 2009), strongly support a functional involvement of metzincin proteases and their inhibitors in the phenomena of synaptic plasticity. However, this area of neuroscience is still in its infancy given the immense complexity of potential proteolytic targets, including ECM and cell adhesion molecules, neurotrophins, and their receptors. Therefore, although these studies have clearly added a new dimension to our understanding of brain plasticity, additional studies are certainly warranted.

## Metzincins and TIMPs promote cell death in inflammatory neuropathologies

MMPs participate in a number of pathological processes through the inflammatory disruption of the blood–brain barrier (BBB). Metastatic cancer cells, which secrete type IV collagenase (i.e., MMP-2), cross blood vessels by attacking basal lamina proteins to enter the tissues (Liotta et al., 1980). A more direct link between BBB disruption and endogenous MMP production was established in animals with intracerebral hemorrhage (Rosenberg et al., 1994).

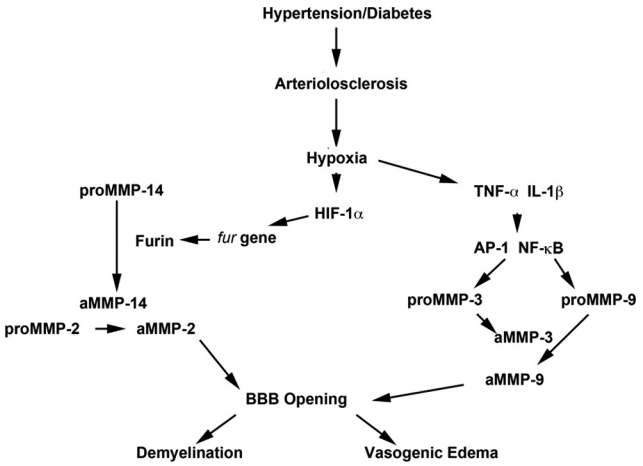


**Figure 4.** Role of MMP-mediated proteolysis in loss of BBB integrity. Schematic diagram of a potential mechanism for MMP-mediated demyelination in vascular cognitive impairment. Hypertension and/or diabetes causes arteriolosclerosis of the blood vessels. Hypoxic hypoperfusion of the deep white matter results in induction of HIF-1$\alpha$ and cytokines (TNF-$\alpha$ and IL-1$\beta$). HIF-1$\alpha$ induces the *fur* gene and the protein furin, which activates proMMP-14 to the active form (aMMP-14). Then, aMMP-14 activates proMMP-2 to the active form of MMP-2. Cytokines induce the AP-1 and nuclear factor $\kappa$B (NF-$\kappa$B) transcription factors to produce proMMP-3 and proMMP-9. Active MMP-3 activates proMMP-9. Thus, MMPs open the BBB, leading to vasogenic edema in the white matter and demyelination.

Another early indication of a pathologic role for MMPs in BBB disruption came from studies in EAE. Administration of a broad-spectrum MMP inhibitor, GM6001 (*N*-[(2*R*)-2(hydroxamidocarbonylmethyl)-4-methylpantanoyl]-L-tryptophan methylamide), reduced brain damage through a mechanism that involved BBB repair (Gijbels et al., 1993). Moreover, patients with MS have increased MMP-9 levels in their CSF during an acute attack, concurrent with BBB disruption (Gijbels et al., 1992). Infectious diseases of the brain, including bacterial meningitis, viral encephalitis, and human immunodeficiency virus, are similarly associated with increased MMP-9 levels in CSF (Leppert et al., 2001). These studies and others clearly show that MMPs comprise a final common pathway for vascular injury in neuroinflammation secondary to a wide variety of brain insults (Lo et al., 2003; Yong, 2005).

*MMPs in cerebral ischemia/hypoxia*

Cerebral ischemia and hemorrhage initiates a complex pattern of MMP expression that is important in both the injury and repair. Shortly after the initiation of an ischemic insult in animals, basal lamina disruption is observed and is associated with MMP-2 expression (Hamann et al., 1995; Heo et al., 1999). Because MMPs are present in latent forms, mechanisms of activation must be brought into play (Fig. 4). With the onset of oxygen deprivation, hypoxia inducible factor-1$\alpha$ (HIF-1$\alpha$) activates genes that are important in adapting the brain to the hypoxic conditions, including genes involved in anaerobic metabolism, angiogenesis, red blood cell production, and growth factor production. Notably, HIF-1$\alpha$ activates the proprotein convertase furin, which activates MMP-14, formation of a trimolecular complex between MMP-14, TIMP-2, and proMMP-2, and active MMP-2 formation. Thus, the initial phase of BBB disruption is mainly mediated by furin, MMP-14, and MMP-2. Ultimately, this combination affects the basal lamina and the tight junction proteins claudin and occludin (Furuse et al., 1998; Hawkins and Davis, 2005). After initial structural changes in tight junction proteins, there is resolution of BBB opening within several hours in the ischemic/reperfusion suture model (Yang et al., 2007).

The second phase of BBB opening occurs after a delay of 24–48 h and is mediated by inducible MMPs (e.g., MMP-3 and MMP-9), initiating a more destructive phase of tissue damage. This phase takes longer to resolve than the initial opening and is accompanied by cell death in the infarct core and ongoing apoptosis in the penumbra (Lo et al., 2003). During this phase, destruction of the basal lamina increases the risk of hemorrhage, which begins as hemorrhagic transformation but, if sufficiently severe, can result in a large intracerebral hemorrhage (Hamann et al., 1995; Montaner et al., 2001). Several lines of evidence implicate MMPs in this destructive phase, including a study showing that MMP-9 KO mice have smaller strokes, less BBB damage, and improved behavior relative to their wild-type littermates (Asahi et al., 2001).

Tissue plasminogen activator (tPA) is the only Food and Drug Administration-approved stroke treatment (Anonymous, 1995), yet hemorrhage risk increases when tPA is given to patients, especially >3 h after stroke onset. Several mechanisms have been suggested for this enhanced bleeding. One likely scenario is that tPA crosses an impaired BBB and once inside the brain releases plasmin, which is a major activator of MMPs (Cuzner and Opdenakker, 1999). In support of this hypothesis, tPA administration increases MMP-9 expression (Tsuji et al., 2005), and there is a strong correlation between serum MMP levels and intracerebral hemorrhage severity (Montaner et al., 2001). Another suggested mechanism involves the interaction between microglial low-density lipoprotein receptor-related protein 1 and tPA, which increases MMP-9 expression and activity, resulting in the degradation of claudin-5 and the development of cerebral edema (Zhang et al., 2009). The strong correlation of increased serum MMP-9 levels during stroke led to the suggestion that it may serve as a stroke biomarker (Kelly et al., 2008). However, MMP-9 detection is currently too time consuming to be clinically useful for early diagnosis.

MMP inhibitors may prove useful adjuvants to tPA in the treatment of stroke. Animals exposed to ischemia for >5 h have a very high incidence of hemorrhage and many die when reperfused. Short-term use of broad-spectrum MMP inhibitors blocks BBB disruption, prevents tPA from entering the brain, and reduces both hemorrhage and death during reperfusion. One such agent, minocycline, a tetracycline derivative with anti-inflammatory properties, blocks MMPs and prevents ischemic damage to the blood vessels (Fagan et al., 2004; Murata et al., 2008). Another agent, BB-94 [Batimastat, (2*R*, 3*S*)-$N^4$-hydroxy-*N*1-[(1*S*)-2-(methylamino)-2-oxo-1-(phenylmethyl)ethyl]-2-(2-methylpropyl)-3-[(2-thienylthio)methyl]butanediamide], a hydroxymate-based drug that binds to the zinc active site, effectively reduces tPA-induced injury (Lapchak et al., 2000; Pfefferkorn and Rosenberg, 2003). Although MMP inhibitors may be clinically efficacious in the treatment of acute disorders (e.g., stroke), the poor clinical trial outcomes for MMP inhibitors in cancer (discussed below) precludes its use in chronic disorders (e.g., MS, vascular dementias).

*MMPs in multiple sclerosis*

MS, an autoimmune CNS demyelinating disease that affects young adults, has a significant inflammatory component that is related to MMP action on the BBB and myelin (Noseworthy et al., 2000; Yong et al., 2007). Myelin can be degraded into immunogenic fragments of myelin basic protein (MBP) by the addition of MMPs, particularly MMP-9 (Chandler et al., 1995; Opdenakker et al., 2001). Furthermore, MMP-7 KO mice displayed reduced inflammation and cell entry into the brain as well as across an *in vitro* cell culture system, suggesting that MMP-7 may contribute

to the inflammatory response (Buhler et al., 2009). BB-1101 (2 S-ally-N-hydroxy-3 R-isobutyl-N-(1 S-methylcar-bamoyl-2-phenylethyl)-succinamide), a broad-spectrum inhibitor of MMP activity and TNF processing reduces the clinical signs and weight loss in an acute EAE model in Lewis rats (Clements et al., 1997).

Although the expression of the classic MBP transcripts is restricted to myelin-forming cells, splice variants of MBP, called Golli-MBP, can be generated by a membrane-bound MMP, MMP-25, to create similar immunogenic peptides. Autoactivation of proconvertases (PCs), furin and PC2, activates MMP-25 in macrophages, leading to immunogenic MBP fragments that are presented in the major histocompatibility complex on the cell surface. This results in T-cell activation and homing to the brain, MBP attack, and inflammation that increases macrophage infiltration and the activation of multiple MMPs, thereby contributing to additional MBP destruction (Shiryaev et al., 2009). Immunomodulation with $\beta$-interferon reduces MMPs, as does treatment with the anti-inflammatory agent minocycline; however, minocycline causes only a minor reduction in disease severity (Yong et al., 2007). In contrast, short-term use of high-dose steroids (e.g., methylprednisolone), commonly used in acute MS flares, dramatically reduces elevated MMP-9 levels in CSF and corresponds with closure of the leaky BBB, likely by blocking the proinflammatory AP-1 sites in the MMP-9 promoter (Rosenberg et al., 1996).

*MMPs in neurodegenerative diseases*

Because of the aging of the populations in developed countries and the improved living conditions in underdeveloped countries, a marked increase in the number of patients with vascular diseases is expected, with vascular cognitive impairment (VCI) alone or in combination with AD representing the largest group of dementias (Skoog et al., 1998). Biomarkers to identify these patients at an early stage are needed to better classify patients and to allow for smaller more focused clinical trials (van der Vlies et al., 2009; Wallin et al., 2010). VCI, which is the new term that encompasses all forms of vascular-related cognitive loss and includes both multi-infarct dementia and vascular dementia, is a major cause of impaired mobility, focal neurological findings, and intellectual loss in the elderly (Hachinski et al., 2006). An important link exists between vascular disease and acceleration of AD, as demonstrated in the nun study (Snowdon et al., 1997). This link is thought to be through inflammation initiated by the presence of amyloid in the brain. Amyloid is known to increase MMP-2 and MMP-9, which could affect the blood vessels or directly damage cells (Deb et al., 1999; Yin et al., 2006). Although BBB disruption may be important in both AD and VCI, direct evidence is only available in VCI in which abnormal BBB permeability was demonstrated by increased albumin in the CSF and contrast-enhanced magnetic resonance imaging (MRI) studies (Wallin et al., 2000; Hanyu et al., 2002; Farrall and Wardlaw, 2009; Wardlaw et al., 2009).

Small vessel disease attributable to hypertension and other vasculopathies leads to large white matter hyperintensities (LWMHs) on MRI. Autopsy studies of patients with VCI reveal MMP expressing inflammatory cells around the blood vessels, including MMP-2 in astrocytes and MMP-3 in macrophages (Rosenberg et al., 2001). Leakage of serum proteins in brains of patients with VCI suggests damage to the BBB (Akiguchi et al., 1998). Additional support for a role of MMPs in VCI comes from the finding of elevated MMP levels in the CSF of patients with VCI (Adair et al., 2004). BBB examination in patients with VCI demonstrated increased permeability in the center of LWMHs, with active leakage only in select regions. This differs from the BBB leakage seen in MS, which appears ring-like (Rosenberg, 2009b). The increased permeability found with quantitative methods (i.e., Patlak plots) provides a more sensitive measure of leakage than Gadolinium enhanced MRI in which images are collected a short time after contrast injection and only major changes in BBB disruption are seen (Ewing et al., 2003).

Binswanger's disease, which is characterized by intellectual impairment, gait and continence problems, and lacunar strokes (Caplan, 1995), similarly has inflammation around abnormal cerebral blood vessels. Patients with Binswanger's disease exhibit altered MMPs in the CSF and brain, suggesting this is a neuroinflammatory disease (Rosenberg, 2009a). Animal studies support an inflammatory mechanism. Bilateral carotid artery occlusion (BCAO) in the rat causes a hypoxic hypoperfusion that is proposed to be a model for VCI (Tomimoto et al., 2003). After 3 d of BCAO, vasogenic edema, increased MMP activity, and vascular damage is seen in the white matter (Sood et al., 2009). Bilateral carotid stenosis with small metal coils in the mouse leads to BBB leakage with white matter damage, which is attenuated in the MMP-2 KO mouse (Nakaji et al., 2006). The role of the various MMPs is unclear and may depend on a variety of factors. When a rat is exposed to 8% oxygen for 48 h, simulating the altitude of Mt. Everest (7500 m), vascular permeability was increased via an MMP-9-mediated mechanism that could be blocked with an inhibitor of vascular endothelial growth factor (Bauer et al., 2010). Additional studies will be needed in rat models with hypertension to more closely simulate the human condition.

*Metzincins and cell death*

Multiple mechanisms likely contribute to the cell death observed in neuroinflammatory pathologies. Metzincins may regulate cell death via their traditional sheddase activities. For example, TACE releases TNF-$\alpha$ and TNF receptors from the cell membranes, whereas MMP-3 acts at the membrane to release FAS and FAS receptor. When TIMP-3 blocks the action of MMP-3 and TACE, the death-promoting functions of FAS and TNF-$\alpha$ are facilitated (Wetzel et al., 2008). Moreover, TIMP-3 KO mice are protected from hippocampal cell apoptosis caused by a transient global ischemic injury (Walker and Rosenberg, 2009). A novel intranuclear role of MMPs in DNA damage and cell death may also contribute (Yang et al., 2010). Nuclear proteins, poly-ADP-ribose polymerase-1 (PARP-1) and x-ray cross-complementary factor 1 (XRCC1), as well as DNA repair enzymes are important in DNA fragmentation and cell apoptosis. Using a 90-min middle cerebral artery occlusion in rats, increased MMP-2 and MMP-9 activity was detected in ischemic neuronal nuclei by 3 h and was associated with DNA fragmentation at 24 and 48 h of reperfusion as well as intranuclear cleaved PARP-1 and XRCC1. However, rats treated with a broad-spectrum MMP inhibitor, BB-1101, blocked the ischemia-induced degradation of both PARP-1 and XRCC1. Free radicals may contribute to intranuclear MMP activity as shown by the elevation of oxidized DNA, apurinic/apyrimidinic sites, and 8-hydroxy-2′-deoxyguanosine, in ischemic brain cells at 3 h reperfusion. Again, BB-1101 markedly attenuated the early increase of oxidized DNA. Finally, tissue from stroke patients showed intranuclear MMP expression. Together, these observations suggest a novel role for MMPs in neuronal apoptosis in ischemic injuries, which may be important in other forms of non-ischemic injury.

## Metzincin and TIMP regulation of tumor progression and tumor suppression

Gliomas, the most common primary CNS malignancy in adults, are histologically and molecularly heterogeneous tumors with strikingly different prognoses. Because of enhanced sensitivity to chemotherapy and radiotherapy, patients with oligodendrogliomas display a fairly good prognosis (i.e., 5 and 10 year survival

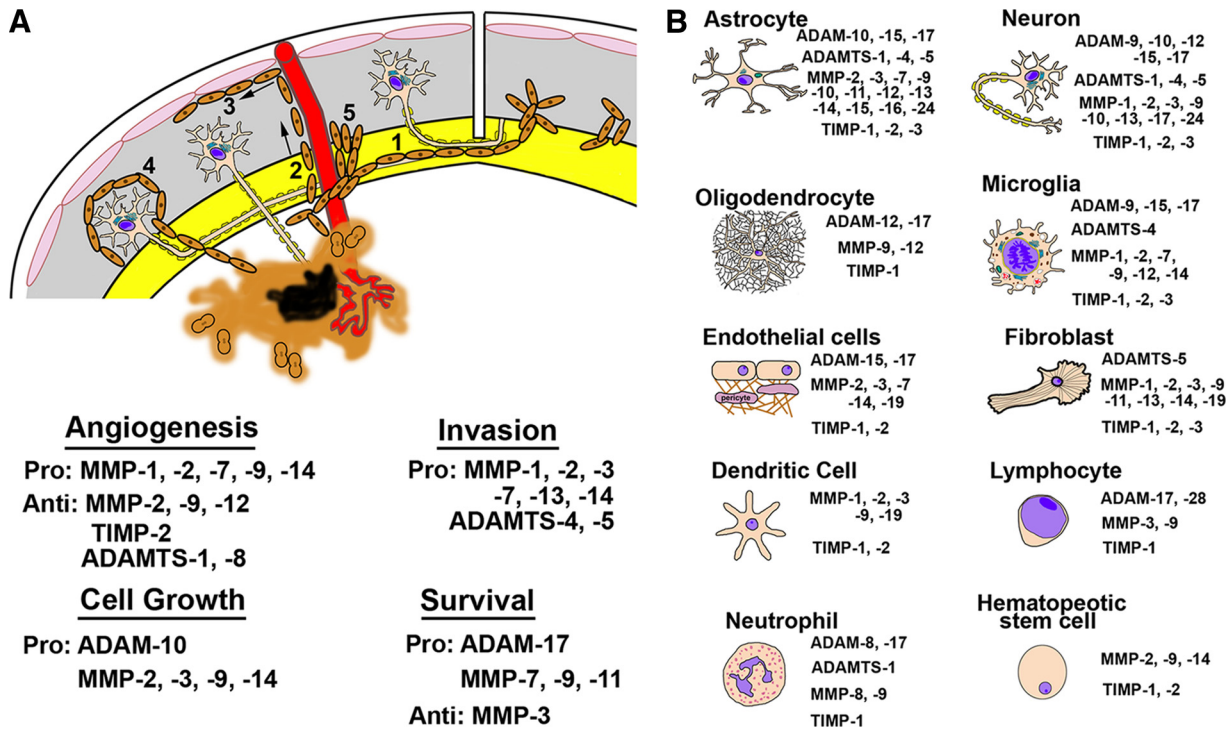


**Figure 5.** Role of metzincins in tumor invasion. ***A***, Primary malignant brain tumors grow as masses with irregular borders and contain regions of necrosis (black) and angiogenesis. The greatest glioma treatment challenge is tumor cell invasion. The most common route of invasion is along white matter tracts, including the corpus callosum into the contralateral hemisphere (1). Cells also migrate along the basement membrane of blood vessels (2) and spread subpially (3). Although some cells form satellites around neurons (4), others will terminate their migration at the white– gray interface (5). Metzincin proteases play multiple roles in tumor progression, with some possessing suppressive functions. ***B***, Nonexhaustive representation of metzincins and TIMPs expressed in various cell types. This presentation comes with several caveats. First, all cell types have the "potential" to express a broad spectrum of metzincins. Second, not all proteases have been profiled with reliable tools in all cell types. Third, exclusion from the table does not preclude expression by that cell type under different physiological or pathological states. Nonetheless, the table stresses the concept that metzincins/TIMPs are not only produced by tumor cells but also by resident parenchymal and stromal cells. Thus, chemotherapies must take into account the normal physiological functions within these cell types.

rates of 73 and 49%, respectively) (Henderson and Shaw, 2001). Median survival of patients with low-grade astrocytomas [World Health Organization (WHO) grade II] is 4 years, whereas patients with anaplastic astrocytoma (WHO grade III) have a median survival of 18 months. Despite the use of multiple aggressive treatment modalities, patients with glioblastoma multiforme (GBM) (WHO grade IV astrocytoma), the most common glioma, have a median survival rate of 14 months with <30% of patients surviving to 1 year and <10% surviving 2 years after diagnosis (Wen and Kesari, 2008). Although many molecular targets for glioma therapy have been identified (Furnari et al., 2007; Nakada et al., 2007), sadly, this prognosis has only increased from a 10 month median survival in the past 5 years.

*Metzincins contribution to glioma progression*

The primary treatment challenge of astrocytomas is the insidious propensity of tumor cells to aggressively invade not only into the adjacent normal brain but to disperse to distant sites, making surgical resection palliative rather than curative (Giese et al., 2003). In marked contrast, tumors that metastasize to the brain tend to form non-infiltrating masses with well demarcated borders that are amenable to surgical resection, suggesting that factors intrinsic to glioma cells underlie their invasive potential. Astrocytomas, which preferentially originate from white matter fibrillary astrocytes, do not randomly infiltrate into the normal brain. Glioma cells show preferential migration along the leptomeninges, perivascular spread along blood vessel basement membranes, and perineuronal satellitosis around neurons in the gray matter (Fig. 5*A*) (Louis, 2006). However, the most frequent route of glial tumor cell invasion is along white matter tracts, with some glioma cells even crossing the corpus callosum into the contralateral hemisphere. Although these routes may simply serve as the path of least resistance, another possible explanation is that specific ECM substrates mediate glioma cell adhesion and promote migration. However, CNS myelin is a very inhibitory substrate not only for neurite outgrowth but also for the migration of several cell types, including astrocytes (Caroni and Schwab, 1988; Schwab and Caroni, 1988). Therefore, to exert their unique invasive potential, glioma cells must be able to alter their extracellular microenvironment to override the migratory inhibitory effects of myelin.

Proteases are ideal candidates to regulate tumorigenesis in that their expression is upregulated by growth factors and inflammatory cytokines that regulate proliferation, they promote cell migration via ECM destruction, and many support angiogenesis. MMP, ADAM, and ADAMTS proteases all contribute to the sculpting of the tumor microenvironment (Mochizuki and Okada, 2007; Murphy, 2008; Rocks et al., 2008; Kessenbrock et al., 2010). For review of other proteases dysregulated in glioma (e.g., the serine protease urokinase-type plasminogen activator and cysteine proteases cathepsin B, D, and L), readers are referred to the most recent reviews on the subject (Levicar et al., 2003; Rao, 2003). Multiple MMPs are upregulated in glioma, including MMP-1, MMP-7, MMP-10, MMP-11, and MMP-19 (Nuttall et al., 2003), but, not surprisingly, the most studied are the gelatinases MMP-2 and MMP-9 (Forsyth et al., 1999). Of particular relevance for pericellular proteolysis are the MT–MMPs, of which MT1–MMP, MT2–MMP, MT5–MMP, and MT6–MMP are upregulated in glioma (Llano et al., 1999; Velasco et al., 2000; Nuttall et al., 2003). Most importantly, MT1–MMP plays a key

role in glioma cell ability to spread and migrate on myelin (Paganetti et al., 1988; Amberger et al., 1994; Beliën et al., 1999). ADAM-8 and ADAM-19 expression is upregulated in glioma and correlates with increased invasion, but the substrates have yet to be identified (Wildeboer et al., 2006). ADAM-10 promotes glioblastoma cell migration via N-cadherin cleavage (Kohutek et al., 2009), whereas ADAM-12 contributes not only to glioma invasion but also proliferation through shedding of heparin-binding epidermal growth factor (Kodama et al., 2004). Hypoxia-induced ADAM-17 contributes to glioma cell invasiveness through activation of the EGF receptor (EGFR) signaling pathway (Zheng et al., 2007). Conversely, expression of the constitutively active EGFR·vIII variant in GBM is associated with upregulated MMP-1 and MMP-13 expression and increased invasion (Lal et al., 2002). ADAMTS-4 and ADAMTS-5, which are upregulated in glioma cells (Held-Feindt et al., 2006), contribute to their invasiveness by cleavage of brevican. In normal brain, brevican inhibits neurite outgrowth and cell motility (Yamada et al., 1997). Brevican is overexpressed in glioma (Jaworski et al., 1996) in which it is cleaved by ADAMTS-4/ADAMTS-5 (Matthews et al., 2000; Nakada et al., 2005). Brevican cleavage products increase invasion (Zhang et al., 1998; Viapiano et al., 2005, 2008) by promoting EGFR activation and the secretion and accumulation of fibronectin on the cell surface (Hu et al., 2008). This significant upregulation of metzincin protease expression in glioma would be expected to be associated with a compensatory increase in inhibitor expression. In keeping with their roles as tumor suppressors, TIMP-3 overexpression suppresses glioma cell infiltration (Baker et al., 1999) and RECK is downregulated in glioma (Correa et al., 2006). Other inhibitor studies are more equivocal. Some studies show that TIMP-2 and TIMP-3 expression does not correlate with tumor grade (Lampert et al., 1998; Groft et al., 2001), others show a positive correlation for TIMP-1 and TIMP-2 and aggressiveness (Nakano et al., 1995; Lampert et al., 1998; Groft et al., 2001; Nuttall et al., 2003), and others report low TIMP-1, TIMP-2, and TIMP-4 expression levels in malignant glioma (Mohanam et al., 1995; Kachra et al., 1999; Groft et al., 2001). In the presence of low TIMP expression, one would expect rampant proteolysis. However, given the dual roles of TIMPs in MMP inhibition and proMMP activation, this cannot be assumed and net proteolysis is likely dependent on the repertoire of MMPs expressed.

Both TIMPs and MMPs subserve biological activities independent of their "traditional" roles. This is best characterized for TIMP-2, which exerts effects (e.g., cell cycle arrest, angiogenesis inhibition) independent of either protease inhibition or activation via integrin $\alpha3\beta1$ (Seo et al., 2003; Pérez-Martínez and Jaworski, 2005; Stetler-Stevenson, 2008a). Alternatively, TIMP-2, via interaction with MT1–MMP, could stimulate invasion-promoting ERK signaling (Sounni et al., 2010). This may partly explain the unsolved paradox that, despite being a "metalloproteinase inhibitor," high levels of TIMP-2 positively correlate with an unfavorable prognosis in many caner types (Strongin, 2010). The PEX domain of several MMPs also exerts biological activities independent of the full-length enzyme. The PEX domain of MMP-2 and MMP-9 inhibits endothelial and glioma cell proliferation and migration as well as reduces angiogenesis (Brooks et al., 1998; Bello et al., 2001; Ezhilarasan et al., 2009). Moreover, intratumoral injection of neural stem cells (NSCs) secreting MMP-2 PEX reduced tumor volume by 90% but decreased angiogenesis by 45% and cell proliferation by 24% (S. K. Kim et al., 2005). Because the NSCs migrated to the tumor boundary, it opens the possibility of using NSCs or mesenchymal stem cells (MSCs) engineered to exploit these MMP-independent functions in glioma treatment (Kosztowski et al., 2009).

*Metzincins as glioma therapeutic targets*

To effectively treat gliomas, several challenges will need to be overcome. First, glioma is already invasive at time of diagnosis, and the degree of invasiveness does not necessarily correlate with the degree of malignancy in that low-grade astrocytomas display increased infiltration distance whereas GBMs display increased infiltration rates (Guthrie and Laws, 1990; Giese et al., 1996). After GBM surgical resection, glioma recurrence is universal. However, because in >95% of the cases the tumor is within 2–3 cm of the resection site (Burger et al., 1983; Gaspar et al., 1992), localized anti-protease therapy may prove beneficial in preventing recurrence, thus making glioma a chronic and not fatal disease. Second, in many cases, the host-derived protease is the key contributor to invasion (Fig. 5*B*) (Taniwaki et al., 2007) as exemplified by the critical role played by microglial MT1–MMP expression in glioma progression (Markovic et al., 2009). Thus, treatment will also affect normal resident brain cells. Third, glioma cells migrating *in vitro* (Merzak et al., 1994; Giese et al., 1996) and *in vivo* (Dalrymple et al., 1994; Schiffer et al., 1997) show a lower proliferation rate and reduced apoptosis (Cho and Klemke, 2000; Mariani et al., 2001). Thus, inhibiting glioma cell migration will make them more susceptible to conventional cytotoxic therapy. Finally, glioma possesses multipotent cancer stem cells (CSCs) (Singh et al., 2004) that are resistant to conventional chemoradiotherapies attributable to quiescence, increased expression of multi-drug resistance transporters, more efficient DNA repair, and increased activation of survival pathways (e.g., Akt–phosphatidylinositol 3-kinase) (Stiles and Rowitch, 2008). MMPs play a role in the migration of stem cells, including targeting bone marrow-derived MSCs to glioma (Wang et al., 2006; Ho et al., 2009). Therefore, increased MMP activity may not only promote the growth and survival of CSCs but also the homing of endogenous stem cells toward tumors.

In contrast to other tumors that metastasize via hematogenous or lymphatic dissemination, glioma cells extensively invade within the brain but rarely metastasize (i.e., between 1.3 and 20% in clinical and autopsy series, respectively) (Ng et al., 2005). Although short life expectancy may be a contributor to reduced extracranial dissemination, other factors likely play a role. For example, although glioma cells migrate along basement membranes, they do not intravasate into blood vessels (Bernstein and Woodard, 1995). Furthermore, even those tumor cells that enter the circulation, via the disrupted BBB, are unable to robustly grow outside the CNS. Although the molecular basis for reduced glioma cell metastasis outside of the CNS is not known, it suggests the existence of brain-derived factors that promote cell adhesion/retention within the CNS, perhaps via interaction with tumor stromal cells (Kessenbrock et al., 2010) or the host-tumor interface (Noël et al., 2008).

Despite the clear involvement of metzincin proteases in *in vitro* studies and animal models, none, little, or even adverse effects on cancer progression were reported in the initial MMP inhibitor clinical trials (Coussens et al., 2002; Pavlaki and Zucker, 2003). There is a multitude of reasons for these disappointing results. First, most inhibitors targeted the active zinc-biding site and, thus, lacked specificity. Second, the adverse musculoskeletal effects induced by MMP inhibition demonstrated the importance of MMPs in normal physiological processes. Most importantly, these trials provided evidence that at least some of the pleiotropic effects of metzincin proteases may antagonize tumor

growth; thus, some proteases serve as tumor suppressors (Overall and Kleifeld, 2006; López-Otín and Matrisian, 2007). Several metzincin members exert anti-tumor effects, including MMP-3, MMP-8, MMP-9, MMP-11, MMP-12, MMP-19, and MMP-26, ADAM-23, and ADAMTS-1, ADAMTS-8, ADAMTS-9, ADAMTS-15, and ADAMTS-18 in various model systems. MMP-8 is a tumor suppressor (Gutiérrez-Fernández et al., 2008) whose activity is reduced by both somatic mutation (Palavalli et al., 2009) and epigenetic suppression (Chernov et al., 2010). ADAM-22 inhibits proliferation via an integrin-dependent mechanism (D'Abaco et al., 2006). ADAMTS-8, a protease with anti-angiogenic properties, is downregulated in glioma by a mechanism other than promoter hypermethylation (Dunn et al., 2006). Although ADAMTS-13 displays lower expression in glioma relative to normal brain (Böhm et al., 2003), its expression does not correlate with grade; thus, its role in glioma progression is not well understood. The only TIMP that is regarded as a tumor suppressor is TIMP-3, which is silenced via promoter hypermethylation (Gonzalez-Gomez et al., 2003; B. L. Liu et al., 2010) or microRNA-21 (Gabriely et al., 2008). These beneficial proteases/inhibitors need to be taken into account when developing the next generation of anti-metzincin-based therapies. Furthermore, other non-MMP anti-protease therapies need to be sought (Lah et al., 2006).

The outlook for the treatment of malignant glioma is not without hope. Although improved surgical (e.g., neuroendoscopic and fluorescence-guided surgery) and radiotherapeutic approaches alone will prolong life expectancy, the most exciting advances will likely come from the development of personalized chemotherapies (Van Meir et al., 2010). The recent identification of four distinct glioblastoma subclasses (Phillips et al., 2006; Verhaak et al., 2010) emphasizes the need to create individualized therapeutic approaches. If unique protease signatures can be identified in preoperative biopsy specimens, then therapies can be based on each patient's unique molecular profile.

### Concluding prospective

Metzincins and their inhibitors are clearly both foes and friends in nervous system physiopathology. However, many questions on the biology of these proteins remain open, and addressing them represents a tremendous challenge for the years to come. We still have an incomplete knowledge of the spatiotemporal pattern of expression of most metzincins and very limited knowledge of their *in vivo* substrates. The identification of the latter appears daunting and needs to be addressed, for example, with high-throughput proteomic approaches, if we are to better discern the physiological and pathological consequences of proteolytic cleavage. This includes a better understanding of the diversity and activity of novel bioactive molecules generated, for instance, from shedding of receptor ectodomains. Also, much remains to be learned about the subcellular localization of the proteolytically active forms of the enzymes in neural and neurovascular cells. The development and implementation of tagged probes, as specific as possible, suitable for both biochemical and microscopic techniques would be a major breakthrough to achieve this goal. What are the extent and functional relevance of intracellular and intranuclear localization of metalloproteinases that we are just starting to unveil? What signal transduction pathways are activated during intracellular and extracellular proteolytic processing? What are the other functions of non-active proteinases and inhibitors, and what proteins do they interact with at the plasma membrane? We have seen that some TIMP-mediated effects do not depend on their ability to inhibit metzincins but rather depend on interactions with pericellular receptors (e.g., integrins). Do metzincins elicit activities independent of proteolysis in the nervous system? The lack of proteolytic activity exhibited by some ADAMs, albeit biologically active, and activity of the MMP PEX domains suggests that this may be the case. Why the same enzyme may exert both detrimental and beneficial effects, as is, for instance, the case with MMP-9 in many respects, and why in turn do several enzymes appear to convey similar functions? Functional redundancy among members of the large metzincin family is a caveat for understanding their activities on specific substrates, and therefore the foreseeable efforts in the development of conditional KO mice should be a major asset in better understanding the roles of metalloproteinases. Finally, increasing our basic knowledge on the biology of the metzincin/TIMP system should improve the specificity and the efficacy of potential therapeutic strategies aiming at either inhibiting the detrimental or promoting the beneficial effects of metalloproteinase activity in the nervous system.

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