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The Role of Matrix Metalloproteinases in Neurovascular Unit Integrity in Amyotrophic Lateral Sclerosis

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a debilitating neurodegenerative and neurovascular disorder with multi-factorial molecular mechanisms of pathology. At the very core of B-CNS-B alterations associated with ALS are the keys to barrier immuno penetration by inflammatory cells into the CNS parenchyma, the Matrix Metallo Proteinases (MMPs). MMPs are a vastly diverse family of endo peptidases that possess a multitude of CNS functions, substrates and regulatory mechanisms. This review will examine the accumulated evidence describing MMPs and TIMPs (Tissue Inhibitors of Metallo Proteinases) and discuss the various CNS processes in the neurodegenerative environment that MMPs are implicated in including neuro and systemic inflammation, cell damage and apoptosis, as well as interactions with vascular growth factors. In conclusion, opposing MMP functions and their contribution to B-CNS-B disruption in ALS will be addressed with perspective into potential future studies.

Keywords: Amyotrophic Lateral Sclerosis (ALS); Matrix Metalloproteinase (MMP); Tissue Inhibitor of Metallo Protease (TIMP); Blood – Central Nervous System – Barrier (B-CNS-B); Neurovascular Unit (NVU); Cell Death

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Introduction

The Neurovascular Unit (NVU) has been established to be a substantial contributor in the pathogenesis of Amyotrophic lateral Sclerosis. With NVU's cellular and acellular constituents form which the Blood - Central Nervous System – Barrier (B-CNS-B) is constructed, it represents a dynamic equilibrium in health and disease [1]. Although the endothelial cells are central to the structure of the NVU, other constituents including pericytes, astrocytes, neurons and microglia are involved in regulating barrier function [2, 3]. Pericytes and endothelial cells are ensheathed by the acellular NVU component – the basal lamina, a 30-40 nm thick membrane composed of collagen type IV, heparin sulfate, proteoglycans, laminin, fibronectin and other extracellular matrix proteins [4]. Thus, such structural and functional properties of this neurovascular construct allow for restriction of passage of various proteins, neurotoxic agents and hydrophilic molecules while allowing transport of nutrients and wastes [5, 6]. In health, NVU may produce a transient increase in permeability to allow more efficient access to nutrients. However, a pathologic increase in B-CNS-B permeability has been seen in

neuro degenerative disease and can produce vasogenic edema and penetration of plasma neurotoxins into CNS parenchyma [5]. Many neurodegenerative diseases including Ischemic Stroke, Parkinson's Disease (PD), Alzheimer's Disease (AD) as well as Amyotrophic Lateral Sclerosis (ALS) have been known to show changes in B-CNS-B integrity [5, 7].

Neurovascular unit components of ALS pathology have long been identified as B-CNS-B alterations at structural and functional levels in both patients and animal models [6]. The NVU pathology in ALS includes endothelial cell and astrocytic end feet degeneration [8] as well as reductions in tight junction [9] and adhesion protein expressions [10]. Garbuzova-Davis et al. [11] showed significant accumulation of perivascular collagen IV and fibrin deposits as well as significantly increased micro vascular density in medulla, cervical and lumbar spinal cord of ALS patients. In an earlier study, Garbuzova-Davis group also reported endothelial cell down regulation of Glut-1 and CD146 expression in Cervical and Lumbar spinal cords of ALS mice [12]. Zhong et al. [9] showed diminished endothelial levels of TJ (Tight Junction) proteins ZO-1, occludin, and claudin-5 before disease onset in ALS mouse models. Additionally, Nicaise et al. [13] showed the edematous astrocyte end-feet surrounding vessels contained high concentrations of Aquaporin-4 (AQP4) and suggested that it's over expression is contributory to this perivascular edema in ALS rats.

Among the many participants in the molecular playground of the neurovascular unit are Matrix Metallo Proteinases (MMP's). MMPs are zinc-dependent endo peptidases in the CNS. In addition to maintaining Extracellular Matrix (ECM) homeostasis via modification of ECM structure and growth, MMPs also affect cell surface signaling systems involved in cellular differentiation, proliferation and apoptosis [4, 14]. MMP's (such as MMP-2, -3, and -9) have been implicated in degradation of ECM components including laminin, fibronectin, proteoglycans and collagen type IV [15-17]. As a consequence of matrix protein degradation, MMPs can exert indirect neurotoxic effects or cause neuronal cell death [18]. Additionally, MMP-3 and -9 activate microglia and stimulate the secretion of cytokines (IL-1, IL-6 and TNF-Alpha) and formation of free radicals, which also affects the permeability of BBB [19].

Vascular barriers in the brain and spinal cord provide selective transport of cells and molecules as well as prevent diffusion of harmful substances from the blood, thus maintaining the CNS homeostasis with transport systems specific for influx of required nutrients and efflux of cellular waste [20]. Therefore, it has been suggested that MMP disturbances involved in the structural vasculature components could potentially lead to an increasingly toxic CNS environment [11].

Contrasting results demonstrated variations between studies in perivascular type IV collagen accumulation in ALS and suggested a disturbance in MMP activity, potentially due to defective MMP regulation by damaged endothelial cells, as described in a previous review [21]. Garbuzova-Davis and colleagues[11] reported significant collagen type IV accumulation expanded throughout the vascular basement membrane in gray and white matter capillaries of medulla, cervical and lumbar spinal cords of ALS patients. However, Miyazaki et al. [10] and Ono et al. [22] noted decreased perivascular collagen IV in post-mortem ALS patient spinal cord tissues. Miyazaki's group [10] found MMP-9 activity increased in mice progressively from the pre symptomatic stage in the anterior half of the lumbar cord. Surprisingly, they also showed the contradicting result of increasing collagen IV levels in anterior horns of mice on western blot with progressing disease, which they hypothesized to be due to neuron cell compensation in the neuropil for structural disruption of endothelium.

With over 20 MMPs identified in virtually all cells [14], these proteinases serve a common function in degradation of ECM and cleavage of defined proteins [23]. In relevance to CNS pathology – MMPs are expressed by neurons, endothelial cells, astrocytes, and microglia [6]. In relevance to ALS, MMP-2 and MMP-9 have been shown in the CNS tissue, serum and CSF of ALS patients and animal models, implicating their involvement in the pathogenesis of the disease [24]. Additionally, during inflammation, immune cells such as neutrophils migrate from peripheral blood to CNS parenchyma and also release large amounts of MMP's enhancing the inflammatory reaction and B-CNS-B disruption [6, 25]. MMP's are expressed as zymogens in the Pro-MMP form and require cleavage by proteases for conversion into active form [26].

It has been shown that MMP activity to be regulated in a multi-step fashion involving transcriptional, post-transcriptional and post-translational levels as well as growth factors, cytokines and cell-cell interactions [19]. Direct signaling pathways such as

Mitogen Activated Protein Kinase (MAPK) and Protein Kinase C (PKC) have been demonstrated to be involved in MMP regulation of expression [27]. Free radical production associated with mitochondrial dysfunction in transgenic SOD1 murine ALS models performs a key function in gene regulation signaling which can include MMPs [27]. The active MMPs are inhibited by their endogenous inhibitors (TIMPS), and also other molecules, such as alpha-macroglobulin, thrombospondin-2 and RECK Protein (a membrane bound inhibitor of MMP) [28]. Such inhibition could possibly be involved in attenuation of NVU disruption by MMPs and is an important consideration in our understanding of neurovascular barrier alterations in ALS.

This review will focus on discussion of MMP and TIMP functions s as well as the mechanisms involved in their regulation and overall contribution to B-CNS-B integrity in ALS.

Matrix Metallo Proteinases: Overview

Cellular Sources of Specific MMPs in the NVU

In order to fully realize the complexity of MMP regulation, one must first consider the specific cells that produce them and the specific microenvironment that MMP's participate in. MMP's are present in virtually every cells, but under pathologic conditions, prominent sources of MMPs become evident [14]. In vicinity of NVU, as described in a review article, MMPs are expressed by neurons, endothelial cells, astrocytes, pericytes, microglia [6]. When stimulated, pericytes have been demonstrated to be a significant source of MMP-9 [29]. Endothelial cells, microglia [30], neurons and astrocytes [31] constitutively express MMP-2 (Gelatinase A) and MMP-9 (Gelatinase B) [30-32]. Neurons can also secrete active forms of MMP-3 (as in Parkinson's disease) and consequently lead to their own degeneration [33]. In their discussion on neural regeneration, Muir et al. showed that MMP -2, 3 and 9 were produced by the various astrocyte cell lines (A7 and Neu7) [34]. In demyelination, as also discussed by Muir et al., MMP -2, 7 and 9 are induced in microglia/macrophages [34]. In addition to NVU being a major source of MMP's, immune cells are also capable of MMP production to promote their penetration into the CNS parenchyma via B-CNS-B. Neutrophils, when migrating from peripheral blood into CNS parenchyma, release large amounts of MMPs (i.e. MMP-9), magnifying neuro inflammatory response and B-CNS-B damage [6, 35]. T-Lymphocytes have been shown to express MMP-2 and MMP-9 [36]. During studies in immune mediated models of CNS demyelination, activated T-Lymphocytes expressed MMPs (such as MMP-12), and surprisingly they also expressed TIMPs (TIMP-1) [37, 38].

MMP Functions and Substrates

MMP's are an enormously varied family of endo peptidases produced by a large diversity of NVU and inflammatory related cell types. In addition to maintaining or disrupting B-CNS-B integrity in ALS, MMPs also serve a variety of non-B-CNS-B related functions that may contribute to ALS pathology and process a variety of substrates. MMP's involvement in the pathogenesis of ALS can be exemplified by MMP Polymorphisms contributing to the pathogenesis of disease. For example, the identified C (-162) Polymorphism in MMP-9 gene results in higher promoter activity and is a risk for Sporadic ALS (SALS) [39].

As reviewed in great detail by Newby and others, MMP's (including MMP-2, 3 and 9) degrade components of ECM, including laminin fibronectin, proteoglycans and collagen type IV [6, 15, 26]. MMP's such as MMP-3, MMP-7, and MMP-9 also cleave adhesion molecules, including vascular endothelial cadherin localized in the adherens junctions [6, 40-45]. MMP-7 (Matrilysin) specifically proteolyses several substrates relevant to the NVU including laminin, type IV collagen, beta4-integrin, VE-cadherin, E-cadherin, and the immune suppressor Fas ligand (FasL) [41, 46-48]. Furthermore, MMP-2 and MMP-9 cleave beta-dystroglycan, a transmembrane receptor for ECM on astrocytic endfeet (interacting with laminin 1 and 2), facilitating leukocyte penetration into CNS parenchyma [31, 49, 50].

Surprisingly, MMPs are also able to effectively reduce the inflammatory response as they have been shown participate in the proteolytic processing of cytokines. MMP-3 and to a lesser extent MMP-2, and -9 promote IL1-beta degradation into its biologically inactive form [51, 52]. This degradation could potentially serve as a negative feedback mechanism since IL-1 Beta in itself is a stimulator of MMP expression, such as MMP-2 and -9 [53, 54]. Additionally, MMP-2, MT-MMP-1

(Membrane Type MMP-1), MMP-3 (stromelysin-1) Cleave MCP3 (Macrophage Chemoattractant protein 3), which then serves as an antagonist to several chemokine receptors, potentially limiting chemotactic gradient for leukocyte entry into the CNS [52, 55]. Furthermore, MMP-9 truncates the amino-terminus of IL-8, leading to potentiation of cytokine activity [52, 56]. This may be a positive feedback mechanism of MMP-9 release from neutrophils since IL-8 (and TNF) has been shown to stimulate the release of MMP-9 filled granules in neutrophils [35, 57].

MMPs also act as activators of proteinases within their own family, for example MT-MMP-1 (Membrane-Type MMP-1) is involved with TIMP-1 in activation of Pro-MMP-2 into its active form [28, 58].

In the context of cellular death, MMPs proteolytically process apoptotic proteins TNF-Alpha and FasL from precursor to soluble forms [59]. MMP-2 and -9 have been shown to release the membrane bound TNF-Alpha and FasL. Soluble TNF-Alpha and FasL then induced apoptosis of cultured cells in vitro [60]. Additionally, MMP-9 contributes to apoptosis by proteolysis of laminin during focal cerebral ischemia [17, 61].

Although demyelination hasn't been described as a major contributor to the pathology of ALS, myelin damage in ALS models has been documented [62]. This suggests that MMP mediated demyelination and remyelination processes studied in MS and EAE (Experimental Autoimmune Encephalomyelitis) may also exist in ALS at least to a degree. MMP's, specifically MMP-2,8,9,10, 12 and MT1-MMP and MT-6-MMP have been shown to degrade Myelin Basic Protein (MBP) contributing to myelin damage, most efficient of which was the MT6-MMP or MMP-25 [63]. The resulting murine MBP fragment has also been shown to be immunogenic and stimulated T-Cell proliferation in vitro. Furthermore, a study showing up regulation of Stromelysin-1 (MMP-3) prior to the onset of demyelination in a transgenic mouse model suggested that MMP-3 is a causative factor in demyelinating disease [64].

MMP interaction with vascular growth factors may also have implications for the integrity of the B-CNS-B. The growth factor VEGF (Vascular Endothelial Growth Factor) is processed by a subset of MMPs. MMP-3, 7, 9 and 19 are capable of VEGF cleavage as was shown by Lee et al. [65]. The resulting VEGF fragments then phosphorylated VEGF receptors and induced angiogenic processes.

MMP involvement in degradation of glial scar components has also been elucidated. Secretion of MMP-2 and MMP-3 by some neuronal growth cones have been shown to promote axon growth in vitro, on substrates including peripheral nerve and spinal cord [34]. MMP's could potentially stimulate axon regeneration as they provide a documented role in degradation of glial scar that is inhibitory to axonal regeneration in spinal cord injury [66]. An important component of the glial scar are molecules called Condroitin Sulfate Proteoglycans (CSPGs) that have also been described in reactive astrogliosis seen in ALS [67]. MMP-3 degrades CSPGs implicated in axon regeneration inhibition, including NG2, versican, brevican, neurocan and phosphocan [34]. Specifically, MMP-2 only digests versican and neurocan, but not the other CSPGs [34]. MMP-9 is also capable of degrading the inhibitory NG2 proteoglycan [68]. MMP-9 has been noted in a rat sciatic nerve study to promote Nerve Growth Factor (NGF) induced neurite elongation while the phosphorylated Neurofilament-M, a marker for regenerative elongation, was induced with MMP-9 treatment confirming this association [68].

Lastly, MMP-2 was shown to have a role in astrocyte migration, actin motility, filipodia and lamellipodia, which may play a role in CNS regeneration [31, 69].

Levels of MMP Regulation

MMP activity is regulated in a multistep process at transcriptional, post transcriptional and post-translational levels as well as via growth factors, inflammatory cytokines and cell-cell interactions [28]. Transcriptional level of regulation may take place via induction or inhibition utilizing pathways such as NF-KBeta producing variable effects in different cells [70]. For example, NF-KBeta induced MMP-9 production in rat brain astrocytes via IL-1Beta, but NF-KBeta is inhibiting in monocytes and macrophages via TGF-beta [71, 72]. Studies have shown that ROS (Reactive Oxygen Species) also stimulate production of MMPs such as MMP-9 and MMP-2. Other pathways implicated in MMP-9 induction in rat brain astrocytes were MAPK, PKC, p38, Erk and Jnk [71, 73].

Additionally, MMP's are controlled at levels of activation, and glycosylation [49]. Activation of the inactive Pro-MMP zymogens takes place via an interesting mechanism of trimeric complex formation. For example, pro-MMP activation involves formation of a ternary complex consisting of MT1-MMP, TIMP-2, and Pro-MMP-2 [74, 75]. TIMP-2 facilitates the recruitment of pro-MMP2 to the cell surface after which it is released. MT-1-MMP then mediates an initial cleavage of Pro-MMP-2 to generate an intermediate, which undergoes autolysis to generate a fully activated MMP-2.

Glycosylation also serves as an important mediator of MMP activity. It has been demonstrated that MT1-MMP is an O-Glycoprotein and its glycosylation promotes formation of a stable MT-1-MMP/TIMP-2/Pro-MMP-2 ternary complex and subsequent cell surface activation of MMP-2. Furthermore, MMP-9 is known to be glycosylated and terminally sialylated. Interestingly, desialylation of MMP-9 has been shown to increase the hydrolysis of its peptide substrate in the presence of TIMP-1 [76].

Free radical production that is increased from mitochondrial dysfunction from mutant SOD1 aggregates in mitochondrial matrix of tg SOD1 mice plays a vital role in vital signaling regulation which can include MMPs [27]. Using brain vascular endothelial cells, Haorah et al. showed ROS activation of MMP-1, 2, 9 and decreased TIMP-1 and 2 in a Protein Tyrosine Kinase (PTK)-dependent manner [77].

Another interesting mechanism of regulation is the activation of pro-gelatinase B. An aminoterminal propeptide is present in all members of the MMP family. It contains approximately 80 amino acids and caps the zinc-containing catalytic domain of the MMP resulting in suppression of catalytic activity. This propeptide domain contains the "cysteine switch" sequence and any means that can pull this sequence away from the Zn2+ ion will result in activation of catalytic activity [78]. Detergent mediated desaturation of the MMP (i.e. by SDS) makes Pro-MMP-9 visible on gelatin zymography. If the SDS can be removed completely during the renaturation process and pro-MMP-9 refolds completely, then the zymogen form is not visible anymore on zymography [79].

In conclusion, another potential level of MMP regulation is demonstrated by multimerization of MMP-9. Cell produced MMP-9 multimers were shown to be sensitive to exposure of reductive chemicals and form monomers in such environment in vitro [56]. It has also been demonstrated that dimerization significantly reduces activation rate of Pro-MMP-9 by stromelysin-1 [80].

Inducers of MMP Activity

Induction of MMPs in the NVU can be achieved using a multitude of modalities including but not limited to: inflammatory cytokines, oxidative stress, various ECM components, MMP activating other MMPs and neurotransmitter signaling.

When stimulated by pro-inflammatory cytokines, cultured astrocytes and microglia demonstrated increased expression of MMP-2 and MMP-9 [49]. The cytokine IL-1Beta has been shown in glial cultures to stimulate a robust induction of both MMP-3 and of its potent inhibitor TIMP-1[37, 81]. IL-1 and TNF-Alpha are well documented inducers of MMP-9 activity. Upregulated MMP-9 expression via IL-1 was shown in cultured human neurons and in mouse brain [32], while an increase of TNF-alpha in the blood also induced activation of MMP-9 in the murine brain [82]. As reviewed by Van Den Steen et al., Gelatinase B can be induced by TGF-Alpha, IL-1-alpha, IL-1-beta, IFN-alpha, IFN-gamma and TGF-Beta [83]. Gelatinase A has also been shown to be inducible by TGF-Beta-1 in astrocytes [84]. TNF-alpha, IL-1 Beta and IFN-Gamma upregulated MMP-2 (and MMP-9) in adult rat microglia [30, 85]. In addition to IL-1 and TNF-Alpha upregulation of MMP-2 and -9, IL1 and TNF-Alpha also downregulate TIMP-3, producing an indirect form of MMP upregulation [86]. Lastly, oxidative stress injury (which can accompany an inflammatory response) also involves activation of MMPs, especially MMP-2 and MMP-9, possibly through tyrosine kinase pathway [6].

As mentioned previously, MMPs can also participate in the activation of other MMPS. For example, the membrane type MMP, MT-MMP-1, acts as an activator of MMP-2 activity, while TIMP-2 acts as a bridging molecule between MT-MMP-1 and pro-MMP-2. Thus, net MMP-2 and MT1-MMP activity depends on TIMP-2 concentrations [87]. MMP-3 has been shown to activate the zymogen forms of many other MMPs including MMP-9 [88, 89]. Similar to the above mentioned trimeric complex mechanism of MMP activation, the activation of pro-MMP-9 by active MMP-2 (and also MMP-3) was demonstrated via the MMP-9/MMP-2/TIMP-2 network of interactions [90]. Furthermore, in biochemical studies, MMP-12 was shown to

activate MMP-2 and MMP-3 [49, 91]. Utilizing an inflammatory cytokine, MMP-1 and MMP-3 have been shown to induce the expression of MMP-9 in macrophages by triggering the release of TNF-alpha [92].

Various ECM components and other cellular products can also induce MMP activity. A molecule known as Extracellular Matrix Metalloproteinase Inducer (EMMPRIN or CD147) is highly expressed in the brain capillary endothelium and has been implicated in the induction of MMPs and leukocyte activation [93]. Among the MMPs that were shown to be induced by EMMPRIN are MMP-2, as well as MT1 and 2-MMPs [94]. EMMPRIN has been demonstrated to be elevated in serum of ALS patients [95]. For T-cells it was shown that the ECM component fibronectin can upregulate the production of both MMP-2 and MMP-9 [96, 97]. Additionally, T-lymphocyte alpha-4-beta-1-integrin-mediated adhesion to VCAM-1 (which is expressed in brain endothelium) also induces MMP-2 and MMP-9 production [98].

Neurotransmitter signaling has been implicated in induction of MMP-9. Serotonin-- receptor-4 (5-HT-4R) has been shown to upregulate MMP-9 [99]. Additionally, histamine also has been demonstrated to stimulate production of MMP-9 in cultured human astrocytes [100].

Lastly, evidence has been presented correlating MMP activity and age. According to some studies, the plasma levels of MMP-2 and MMP-7, as well as the inhibitors TIMP 1-4 increases with age, while that of MMP-9 decreases with age [18, 101].

Inhibitors of MMP Activity

There is seems to be some disagreement in the literature in regards to weather MMP inhibition is beneficial or detrimental to pathogenesis of ALS. One study demonstrated a survival extension via pharmacologic inhibition of MMP2 and MMP-9 using the MMP inhibitor Ro 26-2853 in transgenic ALS mice [102]. Another study suggested a deleterious effect of pharmacologic inhibition of MMPs by showing reduced survival of transgenic ALS mice after deletion of the MMP-9 gene [103]. In addition to endogenous MMP inhibitors such as cytokines and TIMPs, certain pharmaceuticals like antibiotics and steroids also inhibit MMPs. Tetracycline derivatives (such as doxycycline) are capable of inhibiting MMPs, specifically MMP-1, 3 and -13, as well as the gelatinases MMP-2 and -9 [104, 105]. Additionally, dexamethasone has been shown to reduce MMP-2 and MMP-9 expression in CNS vascular endothelium and retinal epithelial cells [30]. SB-3CT is a selective inhibitor of MMP-9 and MMP-2 and has been shown to prevent neuronal apoptosis by protecting laminin from MMP-9 proteolysis during focal cerebral ischemia [17, 106].

In addition exogenous MMP inhibition with pharmaceuticals, MMPs can be regulated through endogenous mechanisms as well. The most famous endogenous inhibitors of MMPs - the TIMPs deserve special attention and will be discussed in sections below.

As mentioned previously, proinflammatory cytokines can readily stimulate induction of MMP activity. This induction, however, is balanced by the ability of cytokines to stimulate inhibition of MMPs. The cytokines, IL-4 and IL-10 produced by Th2 T Cells, were shown to inhibit monocyte/macrophage production of gelatinase B at the pre-translational level [83, 107]. Additionally, IL-10 induced the production of TIMP-1, an additive indirect inhibition of Metallo protease activity [108]. Interferon-beta produces a significant down regulation of MMP-9 in activated lymphocytes, inhibiting their trans endothelial migration in the human brain [109]. Interferon-Beta has also been shown to inhibit MMP-2 and MMP-9 in astrocytes, as well as MMP-9 in microglia [110].

Another well documented MMP inhibitor is the adhesive glycoprotein thrombospondin. TSP-2 (Thrombospondin-2) forms complexes with MMP-2 and consequently facilitates scavenger receptor (LRP-1) mediated endocytosis of the TSP-2/MMP-2 complex [111, 112]. Throspondin-1 has also been demonstrated to be an inhibitor of MMP-3 induced Pro-MMP-2 activation and thrombin induced activation of pro-MMP-9 [113]. Since Thrombospondin levels have been shown to be reduced in patients with ALS, its MMP inhibitory role is likely relevant to the pathology of ALS [114]. The membranes bound RECK (Reversion-Inducing Cystein rich protein with Kazal Motifs) protein coordinates ECM integrity regulation and angiogenesis and has been shown to down regulate MMP-2, MMP-9 and MT1-MMP [115-117].

Lastly, although age has been shown to be directly correlated with activity of MMPs, an inverse correlation has also been described as a decrease of MMP-9 activity with advancing age [18, 101].

Tissue Inhibitors of Metalloproteinases

Overview and Cellular Sources of TIMPs

In comparison to the amount of various MMPs identified, there are significantly fewer types of TIMP that have so far been studied. TIMPs -1, -2, -3 and 4 are currently well described in the literature. Out of the four TIMPs, TIMP-3 is bound to ECM, whereas TIMP-1,2, and 4 are secreted in soluble form [28, 118]. TIMP-4 is most abundant in adult brain, followed by TIMP-2 and TIMP-3, while TIMP-1 is the lowest [31]. TIMPs (1-4) are produced constituitively in the brain [119]. In regards to specific cellular sources of TIMPs, TIMP-1,2 and 3 have been shown to be expressed by astrocytes, while microglia only expressed TIMP-2[81]. TIMP-2 and -4 are produced by neurons [34, 120]. Pericytes have also been shown to produce TIMP-3 after interaction with endothelial cells which themselves are capable of TIMP-2 production [121].

TIMPs: Function and Substrates.

TIMPS have been shown to be induced in various neuropathologies including ALS. After ischemia (MCAO in animals) and reperfusion, TIMP-1, 2, and 3 are induced in the brain [34, 122, 123]. In EAE and MS, induction of TIMP-1 has been demonstrated in astrocytes [34, 124]. TIMP-3 is strongly upregulated in degenerating motor neurons in spinal cords of SOD1 mice and has been shown to be involved in neuronal apoptosis [59, 125].

In addition to TIMP involvement in various diseases of the CNS, as their names suggests TIMPs function as inhibitors of MMPs. TIMPs inhibit the proteolytic activity of MMPs in a 1:1 molar stoichiometry, although not with the same efficiency[28]. TIMPs can inhibit all MMPs but again, not at same efficiency [126]. TIMP-2 (at high concentrations) is an inhibitor of MT-MMP-1 and MMP-2 [18, 127, 128]. While TIMP-1 is the most effective inhibitor of MMP-1, MMP-3, MMP-7 and MMP-9 [28], TIMP-2 inhibits MMP-2, TIMP-3 inhibits MMP-2 and MMP-9, whereas TIMP-4 reduces the activity of MMP-2 and MT1-MMP (aka MMP-14) [28]. Distinct from TIMP-1, TIMP-2 and TIMP-3 are effective inhibitors of MT-MMPs [129].

TIMPs: Additional Functions.

TIMPs are not solely inhibitors of MMPs and can also contribute to their activation [34]. As mentioned previously, TIMP-2 is involved with MT-1-MMP in the activation of Pro-MMP-2. MT1-MMP containing plasma membrane extracts have been shown to have increased pro-MMP-2 activation at low TIMP-2 concentrations, whereas at high concentrations, TIMP-2 inhibited pro-MMP-2 activation [58].

Furthermore, TIMPs have been implicated in death signaling and blockage of axon regeneration. TIMPS can also signal via MMP inhibition to enhance stabilization and activation of death receptors (i.e. Fas) [59]. Since MMP's could potentially stimulate axon regeneration by degrading the ECM, TIMP's via down regulations of MMPs, can thereby promote inhibition to axon regeneration. TGF-Beta up regulates TIMP-3, (which down regulates MMPs), stabilizes the ECM and contributes to blockage of axon regeneration [34].

TIMP participation in CNS myelination and angiogenic processes has also been elucidated. Additionally, TIMP-2 has been shown to enhance the expression of RECK, which has inhibitory activity for MMP-2 and 9 and for endothelial cell migration [117, 130, 131]. Further details of TIMP involvement in angiogenic processes and regulation of apoptosis will be provided in the sections below.

TIMPs: Regulation

In comparison to MMPs, TIMPS are a relatively more recent focus of study in the scientific literature; therefore significantly less evidence is available describing TIMP regulation. Cytokines appear to be the major modality that stimulates and inhibits TIMP activity. Interferon-Beta increases levels of TIMP-1, attenuating MMP over activity in MS [49, 132]. Additionally, TIMP-1 has also been shown to be increased by stimulation with TGF-Beta [133]. In a study describing endothelial cells up regulation of TIMP-1 in response to cytokines, TIMP-1 activity induction was observed with IFN-Gamma and the strongest effect with combination of IL-1Beta & TNF-Alpha [86, 134]. Furthermore, since TIMP-1 blocks degradation of IL-1 Beta by several MMPs, this positive feedback mechanism could help maintain TIMP- up regulation and further MMP inhibition [134]. In contrast, stimulation with combinations IL-1Beta/TNF-alpha and IL-1Beta/IFN-Gamma resulted in decreased expression of TIMP-3.

Interestingly, neural activity, including kainite-induced seizures, induced TIMP-1 in neurons (immediately) and astrocytes (later) [34, 135, 136].

Cell Damage and Death

As discussed above, the perpetuation of the inflammatory response by MMPs contributes to neuronal death. Specific evidence implicating MMPs in contributing to neuron death has been presented. MMP-9 up regulation of TNF-alpha and FasL expression in neurons has become a likely possibility after it was shown that MMP-9 deficient G93A mice had increased survival and reduced neuronal TNF-alpha and FasL, molecules involved in apoptosis signaling [137]. MMPs also proteolytically process apoptotic protein FasL from precursor to soluble forms [59]. MMP-3 and -7 have been shown to release the human and murine membrane bound FasL [48]. MMP-2 and MMP-9 were shown to release both soluble TNF-Alpha and FasL, which then induced apoptosis of cultured cells in vitro [60]. Furthermore, MMP-9 activity and TNF-Alpha expression gradually increased with age in G93A mice [137]. MMP-1 and MMP-2 also participate in cell death signaling and are toxic to spinal cord neurons in vitro [52, 138, 139]. Conant et al. have shown that MMP-1 interacts with neuronally expressed alpha(2)beta(1) integrin complex which was associated with a reduction in the phosphorylation of Akt, a kinase that influences caspase activity and cell survival [140]. Additionally, TIMPs can signal through MMP inhibition to enhance stabilization and activation of death receptors (i.e. Fas) [59]. TIMP-3 is strongly upregulated in degenerating motor neurons in spinal cords of SOD1 mice [59, 125]. The sheddase proteins TACE (TNF-Alpha converting enzyme) and stromelysin-1 (MMP-3) regulate apoptosis be removing TNF death receptors from the oligodendrocyte cell surface [123]. A study has shown that TIMP-3 blocks the release of TNF death receptor by TACE, which promotes apoptosis [141]. Furthermore, MMP-9 mediates neuronal cell death via disruption of neuronal ECM interactions, specifically involving laminin [17, 137]. Lee et al. showed MMP-2 and MMP-9 to be upregulated in human brain endothelial cells after ischemia. The reported subsequent ECM fibronectin degradation was linked as a trigger of a form of caspase mediate cytotoxicity. Lastly, an interesting regulatory mechanism to MMP-9 mediated neuronal apoptosis is S-Nitrosylation. In a cerebral ischemia study, Gu et al. colocalized MMP-9 with neuronal nitric oxide synthase and showed that S-Nitrosylation activated MMP-9 in vitro and induced neuronal apoptosis [142].

MMP/TIMP Interactions with Vascular growth factors

VEGF serves a significant role it the pathogenesis of ALS and is possibly a neuro protective agent as suggested by the finding that when VEGF expression was reduced it promoted adult-onset progressive motor neuron degeneration reminiscent of ALS [143, 144]. VEGF has also been shown to promote survival in ALS mice via VEGFR2 binding and when VEGF and VEGFR2 are over expressed, neuro degeneration is delayed [145, 146]. VEGF upregulated GLUT-1 in endothelial cells and can thus promote glucose uptake in the brain and possibly enhance survival in ALS [147, 148]. With respect to VEGF associated B-CNS-B changes, exogenous application of VEGF can increase the permeability of the BBB without causing brain edema as was demonstrated in the mouse brain [149]. Argaw et al. showed how VEGF-A is used by reactive astrocytes to drive vascular permeability and CNS damage in acute inflammatory lesions [150]. VEGF-A binding to VEGFR2 on endothelial cells activated eNOS (endothelial Nitric Oxide Synthase) dependent down regulation of tight junction proteins CLN5 (Claudin) and Ocln (Occludin) leading to disruption of endothelial tight junctions and BBB breakdown [150].

MMP and TIMP interactions with VEGF signaling have also been demonstrated. The primary partners of VEGF are the Angiopoietins. VEGF and Ang-2 (Angiopoietin-2) were shown to enhance MMP elaboration in the mature mouse brain [151]. They found that MMP-9 activity was increased to a greater degree in group treated with VEGF and Ang-2 when compared to VEGF alone [151]. Furthermore, Lee et al. showed that VEGF-A bioavailability is regulated via processing by a subset of MMPs [65]. VEGF-164 isoform was cleaved by MMP-3, 7, 9, and 19. The presence of heparin aided processing by MMP-3 but hindered cleavage of VEGF by MMP-9 [65]. Proteolytic VEGF cleavage was inhibited by TIMP-1 and 2 while digestion by MMP-9 was blocked by TIMP-3 [65]. Additionally, VEGF enhanced MMP expression in vascular SMCs (Smooth Muscle Cells) with a more pronounced effect for MMP-1 and MMP-9, and less prominently for MMP-3 [152]. Both endothelial cells and SMCs are capable of synthesizing VEGF at sites of angiogenesis [152]. . And finally, role of TIMPs in regulation of VEGF has also been suggested. TIMP-2 is a physiological antagonist of intracellular

VEGF signaling [37, 153], while TIMP-3 is capable of Vascular Endothelial Growth Factor Receptor – 2 (VEGF-R2) antagonism and has been shown to inhibit angiogenesis and endothelial cell proliferation [37, 154]. It was also demonstrated that interactions between endothelial cells and pericytes stimulated TIMP-3 expression in pericytes [121]. Thus, MMP's and TIMP's actively participate in neuro protective and vascular permeability altering activities of VEGF.

Opposing MMP Functions and their Contribution to B-CNS-B Disruption in ALS: Conclusion and Perspective into Future Studies

MMPs perform a large plethora of NVU functions in the neurodegenerative environment, including but not limited to: B-CNS-B disruption, processing of inflammatory cytokines, facilitation of cell death signaling, contribution to demyelination and interaction with vascular growth factors potentially affecting neuro protection or further B-CNS-B disruption. Since the permeability of the B-CNS-B is significantly affected in CNS pathology including ALS, it seems feasible that the local molecular distribution of MMP's and TIMP's is much less restricted compared to a closed B-CNS-B and if any of these processes involving MMPs are occurring at the same time there is ample opportunity for them to interact and affect each other's regulation. MMP produced by the neural growth cones for the purpose of neurite extension and neuro regeneration could theoretically also compromise the B-CNS-B and furthermore propagate immuno infiltration of inflammatory cells into the CNS parenchyma by degrading ECM. Similarly, astrocytes producing MMPs for the purpose of immuno penetration of inflammatory cells may also participate in the degradation of CSPGs and facilitate axon regeneration and consequent neuro regeneration of affected neurons. Some sources suggest that the reason MMPs from a specific cellular source perform their intended functions is due to factors present in the specific local environment that restricts a particular MMP activity to a specific functional "niche". Logic suggests that this local environment that restricts activity of MMPs is mediated by the vast amount of regulatory mechanisms directing the activity of MMPs. Future studies may add degrees of complexity to their investigations by studying 2 processes (or more), such as MMP-mediated B-CNS-B disruption and axon regeneration, at the same time while also simultaneously aiming at modifying the regulatory milieu of MMP activity. A study may aim to answer, for example: how does astrocyte activation affect MMP mediated immuno-penetration of inflammatory cells into the CNS parenchyma and VEGF directed endothelial cell proliferation in a mouse model of deleted (or upregulated) MT-MMP-1, a documented activator of MMPs that potentially targets MMP activity to the local environment of cell membrane since it is in itself a membrane type MMP.

Additionally, many studies and review articles (including this one) describe MMP functions that were demonstrated in cellular systems other than the CNS, say aortic valve or tracheal smooth muscle. If functions of MMPs are determined by their local regulatory environment, it is possible that in environments outside of CNS there are variations in functions and regulatory mechanisms of MMPs compared to those within the CNS. If ALS is truly a Neurovascular disease, like Garbuzova-Davis and colleagues had envisioned, MMPs must serve a critically relevant role in NVU homeostasis and B-CNS-B integrity, and therefore should be studied with precision and specifically in the dynamic regulatory environment of the CNS so that the documented MMP functions may be more applicable to the CNS microenvironment. Also, as mentioned previously, MMPs are implicated in immuno penetration of inflammatory cells into the CNS parenchyma, but in a self-regulatory effort to inhibit their own activity, MMP's can also perform the anti-inflammatory role. For example, MMP-2 cleaves MCP3 (Macrophage Chemo attractant Protein-3), which when cleaved then binds to chemokine receptors, acting as an antagonist [52, 155]. This abolishes chemotactic gradient for leukocyte entry, a potentially anti-inflammatory effect [52]. The regulatory microenvironment can theoretically sway the balance of pro-inflammatory versus anti-inflammatory functions of MMPs and if studied in the context of multi-process regulation of MMPs it may uncover methods to ameliorate MMP mediated neurovascular disruption of B-CNS-B and potentially enhance MMP-mediated reparative process such as VEGF associated neuro protective effects or axon regenration. Furthermore, studies showed how genetic deletions and reductions of MMP may increase survival in ALS, but interestingly contrasting studies exist that show MMP deletion to accelerate motor neuron disease [59, 103]. Such variations in outcome suggest variations in the regulatory microenvironment of MMPs such that when MMPs function is swayed towards a neuro protective role, genetic deletions of MMPs produce a deleterious outcome. In contrast,

when MMPs are potentially regulated towards a more disruptive function affecting NVU and B-CNS-B integrity, their deletion produces a reduction in ALS survival. Studying multiple regulatory mechanisms in the microenvironment of the NVU and B-CNS-B simultaneously may uncover methods to regulate MMP activity to serve more of a "partial agonist" role, whereby it may partially stimulate immuno penetration just enough for immune cells to remove the cellular debris and toxins but not enough to overcompromise the B-CNS-B and overpropogate the penetration of immune cells into the CNS parenchyma to a deleterious extent and damage neurons via further ROS production and other mechanisms. Inhibiting MMP expression to various degrees while at the same time stimulating the extracellular post-translational MMP activation via TIMPs, multimerization, glycosylation etc. could in theory produce such a partial agonist effect and consequent differential effects on deleterious and neuroprotective functions of MMPs which may guide future development of treatment modalities for ALS.

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