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REVIEW

# Matrix metalloproteinases in the CNS: interferons get nervous

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## Abstract

Matrix metalloproteinases (MMPs) have been investigated in context of chronic inflammatory diseases and demonstrated to degrade multiple components of the extracellular matrix (ECM). However, following several disappointing MMP clinical trials, recent studies have demonstrated unexpected novel functions of MMPs in viral infections and autoimmune inflammatory diseases in unanticipated locations. Thus, MMPs play additional functions in inflammation than just ECM degradation. They can regulate the activity of chemokines and cytokines of the immune response by precise proteolytic processing resulting in activation or inactivation of signaling pathways. MMPs have been demonstrated to cleave multiple substrates of the central nervous systems (CNS) and contribute to promoting and dampening diseases of the CNS. Initially, believed to be solely promoting pathologies, more than 10 MMPs to date have been shown to have protective functions. Here, we present some of the beneficial and destructive roles of MMPs in CNS pathologies and discuss strategies for the use of MMP inhibitors.

**Keywords** Matrix metalloproteinase (MMP) · Interferon (IFN) · Inflammation · Extracellular matrix (ECM) · Virus · Multiple sclerosis (MS)

## Abbreviations

| | |
|---|---|
| AIDS | Acquired immunodeficiency syndrome |
| BBB | Blood brain barrier |
| CNS | Central nervous system |
| CVB3 | Coxsackievirus type B3 |
| ECM | Extracellular matrix |
| ECs | Ependymal cells |
| HIV | Human immunodeficiency virus |
| IFN | Interferon |
| MBP | Myelin basic protein |
| MMP | Matrix metalloproteinase |
| MS | Multiple Sclerosis |
| RSV | Respiratory syncytial virus |
| SLE | Systemic lupus erythematosus |
| SLEDAI | Systemic lupus erythematosus disease activity index |
| TIMP | Tissue inhibitor of metalloprotease |

## Introduction

Matrix Metalloproteinases (MMPs) should no longer be regarded as being disease promoting detrimental extracellular proteases—especially given the chequered history of MMP inhibitor drugs [1]. These were developed and trialed at a time when MMPs were few in number, substrates even fewer, and their in vivo roles mostly only deduced from admittedly compelling in vitro studies. While their biological activity is linked to the balance between the levels of MMPs and their inhibitory TIMPs in inflammatory diseases, with a shift in the MMP/TIMP ratio commonly associated with disease [2, 3], the multitude of beneficial disease-dampening functions of MMPs ever increases. So much so, we contend that the major role of MMPs is in fact in temporal modulation of inflammatory and immune processes by precise regulation of the bioactivity of signaling molecules and their pathways. This is to maintain extracellular homeostasis by invoking negative feedback loops to dampen inflammation over time and stimulate tissue resolution. Overall,

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MMPs are multitasking proteins [4], often with moonlighting functions [5], with additional roles to mere matrix degradation in both the extra- and intra-cellular compartments. Recent evidence further pushes this paradigm shift with critical new roles revealed for MMPs in initiating and then terminating interferon responses and signaling pathways in viral infection and autoimmunity. Here, we describe these in relation to diseases of the central nervous system (CNS).

## MMPs: inside the matrix

The CNS is composed of the brain and spinal cord, both structurally and functionally unique organs, and central to life and thought. One arm of neuroscience is to understand the complex neural circuitry of brain and spinal cord. Many studies intend to decipher psychiatric and neurological disorders; however, the underlying molecular mechanisms of various neuropathologies have yet to be elucidated. Nonetheless, given the unimaginable complexity of ~ 100 trillion neurons and their connections, relatively few neurological disorders and disease occur. In the healthy CNS, the microenvironment is a guiding factor that affects neurological development and function [6]. Though not a prominent anatomical feature of the CNS, the regulation and remodeling of the neural extracellular matrix (ECM) are essential to the maintenance of homeostasis in the brain and thought [6–10].

MMPs are key enzymes influencing physiological and pathological processes due to their proteolytic remodeling capabilities [6, 10, 11]. Despite recent advances in understanding that the ECM serves more than a simple role in cell adhesion, structural integrity, and cell signaling [7, 11], the significance of neural ECM signaling and interactions between neural cells remains elusive. MMPs are secreted by many neural cells [12] and contribute to early CNS development as well as synaptic remodeling that continuously shapes the brain throughout adulthood [6, 12–16]. Several studies demonstrate that MMP-mediated proteolysis drives the structural and functional changes that occur during the development and homeostasis of the CNS [17–20].

An important component of embryonic development is the neural stem cell niche that provides a continual supply of new neural cells, including neurons and glia, for the postnatal brain. The maintenance of this stem cell niche is highly dependent on micro-environmental cues and cell to cell interactions [21]. The specific organization of cytoarchitecture and ECM environment delineating the niche guides the fate of neural stem cells and plays a role in regulating their regenerative potential. MMPs have long been ascribed as proteases primarily responsible for the turnover and remodeling of ECM substrates [21], a function that is crucial in the development and maturation of stem cell populations in processes such as neurogenesis. To generate the adult neural stem cell niche, the early postnatal ventricular–subventricular zone (V-SVZ) undergoes rapid and complex reorganization. MMP-12 has been implicated in several aspects of this process. Both intracellular and extracellular MMP-12 is involved in guiding the fate of postnatal stem cell niches in the V-SVZ of the brain [21], owing to its ability to remodel the ECM and inactivate protease inhibitors. Furthermore, elevated MMP-12 expression has been identified in developing ependymal cells (ECs) that line the cerebrospinal fluid filled ventricles in the brain, suggesting another role of MMP-12 in regulating the maturation of ECs [21].

Recently, studies have begun to elucidate the role that MMPs play in regulating neural circuit remodeling [12, 17–21]. MMP-9 has been involved in hippocampal synaptic plasticity and plasticity related processes such as long-term potentiation in murine models [17–19]. Several studies have characterized the expression of MMPs across the brain, with many revealing that the zymogen forms of MMPs are more commonly present in comparison with their active counterparts [6], although there are many stimuli within the neural environment that can cause the activation of MMPs and the precise substrates of these active MMPs remain widely unknown and unexplored [10, 22, 23]. In addition, the localization and function of MMPs vary greatly across differing brain regions [7]. For example, although MMP-9 may support beneficial physiological processes such as the maintenance of synaptic plasticity in the hippocampus [17–19], it has also been suggested to facilitate blood brain barrier (BBB) disruption in neurodegenerative diseases such as multiple sclerosis (Fig. 1) [24–27] and in collagen scanning [28, 29]. It is, therefore, crucial to further characterize the function of individual MMPs and their roles within *the Matrix*; it is also important to consider that maladaptive remodeling of the neural ECM may contribute to diseases of the CNS.

## MMPs: outside the matrix

Matrix metalloproteinases, as their name suggests, cleave multiple ECM proteins and so remodel the matrix. However, only ~ 27% of MMP substrates are ECM and ECM-associated proteins, whereas 73% of the known MMP substrates are non-ECM proteins [30]. These include chemokines, cytokines, cell-surface receptors, angiogenic factors, aminoacyl transferases, growth factors, and proteins involved in immune signaling [1, 30, 31]. Importantly, MMPs should not be regarded as just detrimental in inflammatory diseases, as multiple beneficial roles for MMPs have been characterized [1, 32]. The tight regulation of MMPs is fundamental to ensure that both their beneficial and detrimental roles are exerted in moderation. Changes in the MMP/TIMP ratios can reveal key biological functions [33, 34]; it is now well

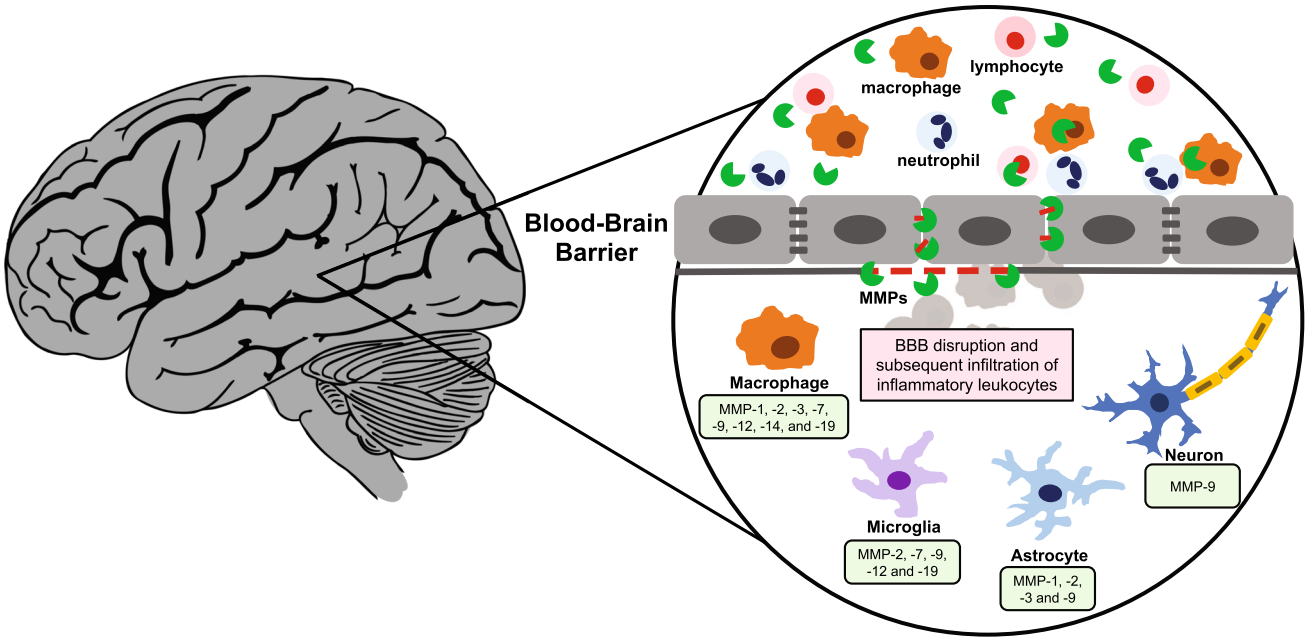


**Fig. 1** Schematic representation of diverse immune cells secreting proteases and break down the blood brain barrier. Proteases are depicted as green pacmans

characterized that MMPs can be both drug targets and anti-targets depending on the tissue localization, cell types, and stage of the disease [1, 32]. This concept is highlighted by a series of papers describing the roles of MMPs in cleaving and modulating the biological activity of virtually all of the 54 human chemokines [35]. Thus, neutrophils are attracted to sites of injury or infection by 8 CXCL chemokines, one of which, IL8 (CXCL8) is activated by neutrophil-specific MMP-8 in a feedforward mechanism [36], but in vivo, MMP-8's major role is to inactivate the cognate serpin inhibitor of elastase, alpha 1 antitrypsin [37], the more potent activator of IL8. All eight of the Glu-Leu-Arg (ELR) + CXC chemokine chemoattractants for neutrophils are cleaved and inactivated by macrophage-specific MMP-12 in a feedback loop [38]. Two CCL chemokines, CCL15 and CCL23, are activated by MMP activity to chemoattract macrophages, the most potent being MMP-12 in a feedforward mechanism [39]. Multiple MMPs can cleave and inactivate CCL chemokines, switching these to antagonists, to terminate macrophage infiltration [40, 41]. Other examples include SDF1alpha and beta inactivation by MMP-2 and other MMPs, and the shedding of membrane anchored CX3CL (fractalkine) by MMP-2 which generates a soluble antagonist chemokine [42].

Finally, non-proteolytic roles of MMPs have also been identified and are implicated in cell adhesion, proMMP activation, cell migration, and invasion [43–45]. The hemopexin C-terminal domain [46–48] of MMP-14 binds native type I collagen and opposes MMP cleavage of collagen, whereas the fibronectin triple repeats of MMPs facilitate MMP-1 cleavage of triple helical collagen by opening up the helix [49]. Thus, MMPs are no longer mere matrix degraders but have been widely demonstrated to play key roles in the initiation and resolution of inflammation. It is now time to exit *the Matrix* and to start characterizing the misunderstood roles of MMPs outside *the Matrix*.

## MMPs are central in the nervous system

MMPs are typically expressed at low levels in the healthy adult CNS. However, following injury or neurological disorders, the protein levels of various MMPs become modulated (Tables 1, 2). Typically, MMP-9 is hardly detectable in the healthy CNS, but is upregulated in diseases such as multiple sclerosis [26, 50]. Although MMP-9 can be expressed in epithelial or endothelial cells, the increase of MMP-9 levels is most likely due to the infiltration of neutrophils, monocytes, and macrophages to the site of injury or inflammation in the brain following disruption of the BBB (Fig. 1) [51–54]. Given its ability to degrade the ECM and tight junction proteins, MMP-9 has been directly implicated in mediating BBB permeability, although this effect could be partially linked to MMP-2 as well [55–58]. In healthy individuals, the highly selective properties of the microvasculature of the CNS allows for the transport of ions, metabolites and cells into the delicate tissues of the brain and spinal cord to be tightly regulated [59]. Damage to this barrier, potentially

**Table 1** Roles and expression of selected MMPs in human CNS diseases

| Human MMPs | Disease | Biological roles and references |
|---|---|---|
| MMP-1 | Alzheimer's disease | ↑ Levels Alzheimer's disease cortex [74] |
| MMP-2 | Amyotrophic lateral sclerosis | ↓ During duration of disease [75] |
| | HIV/AIDS | ↑ Levels in HIV-associated demented patients [76]; ↑ neuronal apoptosis [77] |
| | Multiple sclerosis | Unchanged mRNA in MS brain lesions [24] |
| | Stroke | ↑ Activity in infarcted cerebral tissue [78] |
| MMP-3 | Multiple sclerosis | Unchanged mRNA in MS brain lesions [24] |
| MMP-7 | HIV/AIDS | ↑ levels in HIV-associated demented patients [76] |
| | Multiple sclerosis | ↑ mRNA levels in MS [24] |
| MMP-9 | Acute disseminated encephalomyelitis | ↑ Serum levels at acute stage [79] |
| | Amyotrophic lateral sclerosis | ↑ levels in CSF in patients with rapid progression of disease [75] |
| | HIV/AIDS | ↑ Levels in HIV-associated demented patients [76] |
| | Multiple sclerosis | ↑ In cerebrospinal fluid (CSF) [50, 80–83]; ↑ mRNA and plasma protein levels in MS patients [24, 26, 84, 85]; ↑ protein levels in serum/leukocytes of MS patients [65, 86] |
| | Seizure | ↑ Levels in seizure patients [87] |
| | Stroke | ↑ Activity [78] and levels [88] in infarcted cerebral tissue |
| MMP-10 | Stroke | ↑ Levels in infarcted cerebral neurons [88]; proMMP10 as a marker following acute ischemic stroke [89] |
| MMP-12 | Multiple sclerosis | ↑ in active demyelinating lesions [90] |
| MMP-23 | $K^+$ channels regulation | Blocks $K^+$ channels [91] |
| MMP-28 | Multiple sclerosis | ↑ Expression within demyelinated lesions [92] |
| TIMP-1 | Acute disseminated encephalomyelitis | ↑ Serum levels at acute stage [79] |
| | Multiple sclerosis | Unchanged mRNA in plasma [26]; ↑ protein levels in serum of MS patients [86]; ↓ protein levels in serum of MS patients [93] |
| TIMP-2 | Multiple sclerosis | mRNA unchanged but ↑ unbound TIMP2 in plasma of MS patients [26]; Elevated protein levels in serum of MS patients [86] |
| | Stroke | ↑ Levels in infarcted cerebral tissue [88] |

through the aberrant activity of MMPs and additional proteases, permits the infiltration of inflammatory leukocytes into the CNS that may drastically enhance the neuroinflammatory response, culminating in the onset of CNS disease [60].

Multiple sclerosis (MS) is one of many neuroinflammatory diseases in which aberrant MMP activity has been characterized (Table 1) [61]. Experimental autoimmune encephalomyelitis (EAE) is a widely utilized murine model used to study the pathogenesis of human MS (Table 2) [62]. MMPs have been implicated in the pathogenesis of MS due to their ability to cause loss of BBB integrity and propagate the neuroinflammatory environment [63]. Fragmentation of myelin as a result of MMP-mediated proteolysis has also been implicated in the immunopathogenesis of MS [64], primarily due to the supporting evidence of increased levels of proteases in the brains of MS patients [27, 64, 65] and the ability of these enzymes to enhance the destruction of the myelin sheath and release immunogenic peptides [64, 66]. Most MMPs, including MMP-2, MMP-3, and MMP-9, can cleave myelin basic protein (MBP) to release peptides that contain immunodominant epitopes (Table 3) [64, 66–68]. Interestingly, the charge micro-heterogeneity of MBP may make it more susceptible to MMP cleavage [69]. The previous studies have also suggested that proteolytic cleavage of myelin-derived antigens prior to their ingestion by antigen-presenting cells may influence the strength and specificity of the subsequent immune response [70–72], for example, MT3-MMP via the Nogo-66 receptor cleavage [73]. Thus, classifying the posttranslational modifications that affect the functions, charges, and generation of MBP isoforms that are vulnerable to proteolytic degradation may be a novel approach to gain a better understanding of the underlying biological mechanisms in MS. However, the role of MMPs in regulating neuronal inflammatory cells that then effect destruction remains largely ignored.

## Hijacking the matrix: link between viral infections, MMPs and CNS pathologies

MMPs have been demonstrated to generate neurotoxic products that lead to neuronal apoptosis in acquired immunodeficiency syndrome (AIDS) [77] and to regulate immune

**Table 2** Roles and expression of selected MMPs in Mouse and Rat CNS disease models

| Mouse/rat MMPs | Model or disease | Biological roles and references |
|---|---|---|
| MMP-2 | Experimental autoimmune encephalomyelitis | Unchanged mRNA levels during disease course in rats [94] |
| | Focal cerebral ischemia | ↑ Expression in rat [57] |
| | Spinal-cord injury | *Mmp2*$^{-/-}$ mice have ↓ recovery [95] |
| MMP-3 | Cuprizone model of toxic demyelination | ↑ mRNA expression in the early phases of demyelination and the remyelination phase in mice corpus callosum. ↑ protein levels in astrocytes [96] |
| | Experimental autoimmune encephalomyelitis | Unchanged mRNA levels during disease course in rats [94] but elevated in mice [97] |
| | Neuroinflammation | ↓ Neutrophils count in *Mmp3*$^{-/-}$ in comparison with wild-type mice [98] |
| MMP-7 | Cuprizone model of toxic demyelination | Unchanged mRNA in this model [96] |
| | Experimental autoimmune encephalomyelitis | ↑ Expression in rat CNS during the development of symptoms [94] but not in mice [97]; *Mmp7*$^{-/-}$ mice are resistant to EAE [99] |
| MMP-8 | Experimental autoimmune encephalomyelitis | *Mmp8*$^{-/-}$ mice exhibit ↓ in the number of CNS-infiltrating cells and demyelinating lesions as compared to wild-type counterparts [100] |
| MMP-9 | Alzheimer's disease | MMP-9 rescued insulin survival signaling in vitro and in early stages in the 5XFAD model of AD [101] |
| | Amyotrophic lateral sclerosis | ↑ Motor neuron disease and ↓survival in *Mmp9*$^{-/-}$ mice [102] |
| | Epilepsy | ↓ Kindled seizure progression in *Mmp9*$^{-/-}$ mice [103, 104] |
| | Experimental autoimmune encephalomyelitis | ↑Expression in rat and mice CNS during the development of symptoms [94, 97]; ↓ severity in *Mmp9*$^{-/-}$ mice [105, 106] |
| | Focal cerebral ischemia | ↑ Expression in rat [57]; ↓ ischemic lesion volumes in *Mmp9*$^{-/-}$ compared with wild type littermates [107] |
| MMP-10 | Cuprizone model of toxic demyelination | Unchanged mRNA in this model [96] |
| MMP-11 | Cerebral artery occlusion | ↑ Levels following stroke [108] |
| | Cuprizone model of toxic demyelination | ↑ mRNA expression in the remyelination phase in mice corpus callosum [96] |
| | Experimental autoimmune encephalomyelitis | Unchanged mRNA levels during disease course in rats [94] |
| MMP-12 | Aging neuroinflammation | ↑ Cerebral mRNA and protein expression during aging [109] |
| | Cuprizone model of toxic demyelination | ↑ mRNA expression in the early phases of demyelination mice cortex and both in the corpus callosum and cortex in the peak of demyelination. ↑ protein levels in microglia, astrocytes and cells of oligodendrocyte lineage [96] |
| | Experimental autoimmune encephalomyelitis | ↑ Expression in rat and mice CNS during the development of symptoms [94, 97]<br>↑ Severity and disease burden in *Mmp12*$^{-/-}$ mice as compared to wild-types [110–112] |
| | Ischemic stroke | ↑ In middle cerebral artery occlusion subjected rats [113] |
| | Spinal cord injury | ↑ Functional recovery of hindlimb strength in *Mmp12*$^{-/-}$ mice as compared to wild-types [114] |
| MMP-13 | Cuprizone model of toxic demyelination | Unchanged mRNA in this model [96] |
| | Experimental autoimmune encephalomyelitis | Unchanged mRNA levels during disease course in rats [94] |
| MMP-14/MT1-MMP | Cuprizone model of toxic demyelination | ↑ mRNA expression in the early phases of demyelination and the remyelination phase in mice corpus callosum [96] |
| MMP-15/MT2-MMP | Cuprizone model of toxic demyelination | ↓ mRNA expression in the peak of demyelination in mice [96], |
| MMP-24/MT5-MMP | Cuprizone model of toxic demyelination | ↓ mRNA expression in the peak of demyelination in mice [96], ↑ promotes pro-amyloidogenic regulation of APP metabolism and *Mt5-mmp*$^{-/-}$ mice rescued amyloid pathology, cognitive decline and inflammation [115]. |
| | Sciatic nerve injury | *Mt5-mmp*$^{-/-}$ mice did not develop neuropathic pain after sciatic nerve injury [116] |
| | Thermal pain stimulation | *Mt5-mmp*$^{-/-}$ mice displayed ↑ sensitivity to noxious thermal stimuli [117] |
| MMP-25/MT6-MMP | Experimental autoimmune encephalomyelitis | ↑ Proteolysis inactivates crystallin-αβ that is a suppressor of MS [118] |
| MMP-28 | Experimental autoimmune encephalomyelitis | ↑ Expression within demyelinated lesions [92] |
| TIMP-1 | Cuprizone model of toxic demyelination | ↑ mRNA expression in the early phases of demyelination mice cortex and both in the corpus callosum and cortex in the peak of demyelination [96] |

**Table 2** (continued)

| Mouse/rat MMPs | Model or disease | Biological roles and references |
|---|---|---|
| | Epileptic rodent model | ↑ Expression to regulate the nervous system [119] |
| | Experimental autoimmune encephalomyelitis | ↑ Expression in mice CNS during the development of symptoms [97] |
| TIMP-2 | Cuprizone model of toxic demyelination | ↑ mRNA expression in the peak of demyelination in mice corpus callosum [96] |
| TIMP-3 | Cuprizone model of toxic demyelination | ↑ mRNA expression in the early phases of demyelination in corpus callosum and cortex, and the remyelination phase in mice corpus callosum [96] |
| TIMP-4 | Cuprizone model of toxic demyelination | ↑ mRNA expression in the early phases of demyelination in cortex and the remyelination phase in mice corpus callosum [96] |

**Table 3** Selected substrates of MMPs related to the CNS

| Substrates: gene name | Substrates: protein name | MMPs that can cleave the substrate | References |
|---|---|---|---|
| APP | Amyloid protein precursor | MMP-1, -2, -3, -9, -14, -16, -24 | [120–124] |
| CRYAB | Alpha-crystallin B chain | MMP-9, -25 | [118, 125] |
| DAG1 | Dystroglycan | MMP-2, -9 | [126–128] |
| ENO2 | Gamma-enolase | MMP-1, -2, -8, -9, 14 | [129] |
| GRIN1 | Glutamate receptor ionotropic, NMDA 1/N-methyl-D-aspartate receptor | MMP-7 | [130] |
| IFNA | Interferon alpha | MMP-12 | [131] |
| IFNB | Interferon beta | MMP-9 | [132] |
| IFNG | Interferon gama | MMP-12 | [31] |
| IL1B | Interleukin-1 beta | MMP-1, -2, -3, -9, -14 | [133–135] |
| MAG | Myelin-associated glycoprotein | MMP-2, -7, -9 | [136] |
| MBP | Myelin basic protein | MMP-1, -2, -3, -7, -8, -9, -10, -12, -14, -15, -16, -17, -24, -25 | [64, 66, 67, 69, 118, 137–139] |
| SNAP25 | Synaptosomal-associated protein 25 | MMP-7 | [140] |
| SNCA | Alpha-synuclein | MMP-1, -2, -3, -9, -14 | [141, 142] |
| TAC1 | Substance P of Protachykinin-1 | MMP-8, -9 | [143, 144] |
| TJP1 | Tight junction protein ZO-1 | MMP-9 | [139, 145] |
| TNF | Tumor necrosis factor | MMP-1, -2, -3, -7, -9, -12, -14 | [133, 137, 146–149] |

responses during viral infections [150]. Elevated expression of MMP-9 in the CSF of human immunodeficiency virus (HIV)-infected patients has been detected [151], and MMP-2, MMP-7, and MMP-9 have been demonstrated to be elevated in HIV-associated demented AIDS patients [77, 78]. Upon viral entry and replication, the host cell secretes multiple response immune signals including proteases and cytokines. The interactions between viruses, host proteases, cytokine signaling, and CNS pathologies are only starting to be characterized. However, a potentially widespread mechanism was described [77]. In HIV, MMP-14 was induced on neuronal cell surfaces, which activated proMMP-2 secreted from macrophages or microglial cells infected with HIV [77]. The activated MMP-2 then cleaved the chemokine SDF-1 [152], the resulting N-terminally truncated product missing residues 1–4 only, then switched receptor binding specificity [153] from CXCR4 to CXCR3, and was neurotoxic. In human HIV patients cleaved SDF1 was detected in elevated amounts in the CNS [77] and anti-HIV treatment induced beneficial reductions in neuronal autophagy in lentiviral infection [154].

## Interferons and MMPs

Cytokines are key players in the regulation of a functioning immune system, but upon dysregulation, they become contributors to multiple pathologies [155]. Interferon-α (IFNα) is a well-studied cytokine that plays critical roles in immunobiology and is implicated in most autoimmune diseases, viral infections, and bacterial infections, and despite its key roles, the extent of its regulation and signaling pathways is not well established [156–158]. In exploring this, Marchant et al. [131]. characterized a novel unexpected function of

MMP-12 that translocates to the nucleus during infection by coxsackievirus type B3 (CVB3) or respiratory syncytial virus (RSV). MMP-12 then bound the IκBα promoter upon virus entry into the cells and was essential for antiviral IFNα expression and secretion. In infected mice lacking *Mmp12*, IFNα is not secreted, resulting in more than 30% death rate in otherwise nonlethal viral infections by CVB3 or RSV. Furthermore, extracellular functions of MMP-12 during viral infections include a negative feedback loop; MMP-12 was demonstrated to cleave IFNα, but not IFNβ, at the C-terminal binding site to its receptor (IFNαR2), leading to the termination of the IFNα pathway and reductions in interferon systemic toxicity [131]. Thus, MMP-12 controls IFNα, but not IFNβ responses, through bona fide intracellular transcription regulation and extracellular proteolytic processing resulting in an effective protective anti-viral IFNα response.

CVB3 infection in *Mmp9*$^{-/-}$ mice resulted in elevated myocardial injury and foci of infection in comparison with wild-types; in contrast, no difference was observed in *Mmp8*$^{-/-}$ mice [159]. Elevated immune infiltrate along with increased levels of IFNβ1 and IFNγ was observed in *Mmp9*$^{-/-}$ mice in comparison with their wild-type counterparts [159]. In addition, Nelissen et al. [132] demonstrated that MMP-9 cleaves and inactivates IFNβ in the context of multiple sclerosis. Minocycline, a tetracycline antibiotic, was demonstrated to reduce the risk of conversion from clinically isolated syndrome to multiple sclerosis [160] through the downregulation of MMP-9 activity [107, 108], which prevented MMP-9 processing of IFNβ in experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis [106, 108]. Alternatively, neutralizing antibodies to IFNβ down-regulated the expression of MMP-9 without affecting TIMPs expression [161]. In an EAE model in Lewis rats, treatment with the broad-spectrum metalloprotease inhibitor BB-1101 reduced the clinical scores through the inhibition of the release of tumor necrosis factor (TNFα) [94], though this was later interpreted to be due to reduced ADAM17 activity, the well characterized TNFα sheddase. Taken together, the combination of MMP-9 inhibitors and lower formulations of IFNβ may indicate a more efficacious way of inhibiting multiple sclerosis and certain viral infections. The precise mechanisms of action have not been fully investigated and will most likely reveal novel roles of MMP-9 in diverse pathologies.

Basal IFNα and IFNβ production are required for synergistically regulating IFNγ activity. IFNγ can enhance its own expression in natural killer (NK) cells [162], enhance IFNα/IFNβ signaling in a feedback loop through the phosphorylation of STAT1 [163], and work in tandem with TNFα to promote inflammation [164]. In contrast to IFNβ, IFNγ exacerbates multiple sclerosis symptoms in humans [165, 166] and induces CNS demyelination in mice [167]. Dandekar et al. demonstrated a role for IFNγ in demyelination by the activation of macrophages/microglia [168]; however, the post-translational role of IFNγ was not characterized. Dufour et al. recently demonstrated that MMP-12 cleaves the C-terminal end of IFNγ at two sites to remove the IFNγ receptor binding peptide leading to a reduction of the JAK-STAT1 pathway [31]. Processing of both human and murine IFNγ terminated the pSTAT1-Y$^{701}$ and decreased the total STAT1 levels after 24 h. Genetic ablation of *Mmp12* in the mouse led to a general increase of total IFNγ levels and an IFNγ pro-inflammatory protein signature (S100A8, S100A9, iNOS, and STAT1) in a model of acute peritonitis. In two animal models of autoimmunity, *Mmp12*$^{-/-}$ mice suffered from increased systemic inflammation and elevated IFNγ, iNOS, and MHCII in their joints, lymph nodes, and kidneys. In human lupus nephritis, *MMP12* levels were decreased and IFNγ were increased in patients with increasing systemic lupus erythematosus disease activity index (SLEDAI) scores. MMP-12's proteolytic truncation of IFNγ has a profound effect on the resolution of inflammation and cytokine signaling in autoimmune disease.

## MMP therapeutic perspectives: beyond the matrix

Both beneficial and detrimental roles of MMPs have been demonstrated and these physiological functions are disease, tissue, and microenvironment dependent. This duality in their functions may partially explain why so few MMP inhibitors are now used in the clinic. Should we entirely give up on MMP inhibitors, although they have profound impact on most inflammatory diseases? Using unbiased global approaches such as proteomics and N-terminomics, a plethora of novel MMP substrates have recently been identified [4, 126, 138–140]. As an alternative, targeting the substrates of MMPs may be an indirect approach to controlling MMPs' biological roles without inhibiting their benefits [32, 169]. Considering short-term treatments could be another way to circumvent interfering with the beneficial roles of MMPs as not all MMPs are expressed at the same time and in the same tissue/cells. MMPs play detrimental roles in many more pathologies than cancer and rheumatoid arthritis (e.g., viral infections, MS, SLE) and may still be considered as potential drug targets, although usage of MMP activity as disease indicators seems more realistic in a clinical setting.

In the movie *the Matrix*, the main character is faced with a dilemma between a red pill that will show him the truth about *the Matrix* and a blue pill that would return him to his former life. In the MMP field, we are currently facing a similar dilemma and are at a comparable crossroad: do we '*ingest the red pill*' to adopt a novel view of MMPs' biological roles that predominantly extend beyond mere matrix degradation or do we '*choose the blue pill*' and repeat our

past mistakes by overlooking that most MMP substrates may not be always associated with the matrix? As demonstrated by Yong, Metz and colleagues [170, 171], '*choosing the red pill*' can be beneficial; for example, Minocycline, a broad spectrum tetracycline antibiotic, reduced the risk of conversion from a clinically isolated syndrome to multiple sclerosis [171] through the downregulation of MMP-9 activity in an indirect manner [107, 108]. Therefore, controlling MMP activity is feasible through indirect means and should be considered in the context of interferon signaling. Novel inhibitor programs for the control of MMP activity or the regulation of the non-proteolytic roles of MMPs may potentially see the light in the next years, as we are currently changing our initial views of this protease family. In addition, a more profound understanding of the repertoire of MMP substrates might reveal novel functions in immune processes of the CNS. We can benefit from reprogramming our understanding of the roles of MMPs within *the Matrix* and make the investigation of their functions within the CNS even more fascinating as we are unraveling new connections of biological, metabolic and signaling pathways regulated by MMP activity.

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