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# Elevation of matrix metalloproteinases (MMPs) in multiple sclerosis and impact of immunomodulators

V. Wee Yong *, Rana K. Zabad, Smriti Agrawal, Angelika Goncalves DaSilva, Luanne M. Metz

*Hotchkiss Brain Institute and Department of Clinical Neurosciences, University of Calgary, 3330 Hospital Drive, NW, Calgary, Alberta, Canada T2N 4N1*

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**Abstract**

The matrix metalloproteinases (MMPs) are implicated in the pathology of multiple sclerosis (MS). This review summarizes the consequences of upregulation of MMP members in MS as well as in an animal model of the disease, experimental autoimmune encephalomyelitis (EAE). The pathogenic roles of MMPs are considered, especially in the transmigration of leukocytes into the CNS. We review the evidence that interferon-beta, an immunomodulator that is commonly used in MS, affects MMP expression in the disease. The potential of minocycline as a therapy in MS, based on its activity as an MMP inhibitor, is discussed. Besides affecting MMPs, minocycline may have other actions that help account for its possible utility in MS.


*Keywords:* EAE; Interferon-beta; Metalloproteinases; Minocycline; Multiple sclerosis

## 1. General introduction

The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that have important roles in development and physiology. The normal adult central nervous system (CNS) contains low levels of most MMP members [1] but several MMPs are significantly upregulated in various neurological disorders of the CNS [2]. The elevated level of MMPs in the CNS is the result of the increased expression of MMPs by neural cells, and by leukocytes that infiltrate into the CNS upon injury. The upregulated MMPs in the CNS have several potentially detrimental roles, including the promotion of neuroinflammation, disruption of the blood–brain barrier, demyelination and toxicity to axons and neurons (reviewed in [2,3]). It is tempting to employ inhibitors of MMP activity to abrogate increased MMP expression within the inflamed CNS, such as that occurring in MS, and there are logical reasons for this approach. However, it is also increasingly appreciated that MMPs fulfill beneficial roles in the CNS [4], including mediation of tissue repair. This stresses the need to employ MMP inhibitors judiciously in MS and other chronic disorders, although the evidence supports a favorable response to MMP inhibitors in MS.

In this review, we summarize current understanding of MMP elevation in MS and introduces the parallel literature in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. The impact of interferon-beta, an immunomodulatory agent used to treat MS, in modulating MMPs is discussed. Finally, the potential use of minocycline to impair MMP activity in MS is reviewed.

## 2. Elevation of MMPs, particularly MMP-9, in MS

Studies of brain tissue, serum and cerebrospinal spinal fluid (CSF) from patients with MS have consistently found an upregulation of several MMPs in MS. In particular, MMP-9 has been shown to be altered in MS in several studies. We will first evaluate data from brain samples, and then the serum and CSF results.

Elevated MMPs have been detected in autopsy brains of people with MS. Using immunohistochemistry and brain sections obtained from patients who died of MS, increased

* Corresponding author. Tel.: +1 403 220 3544; fax: +1 403 283 8731.
*E-mail address:* vyong@ucalgary.ca (V.W. Yong).

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expression of MMP-2, -7, and -9 in macrophages and lymphocytes around perivascular cuffs has been described [5–7]. In another study, MMP-12 staining was reported to be prominent in macrophages that are found in MS lesions [8]. This detection of MMPs by immunohistochemistry is supported by detection of elevated MMP-7 and -9 RNA levels in MS lesions [7].

Studies of MMP levels in serum and CSF have also been conducted. Many of these studies focused on MMP-9 since this MMP can be easily detected using gelatin zymography and also because ELISA kits that measure its level are available from a number of commercial companies. In this regard, serum MMP-9 content is increased in the serum of patients with relapsing–remitting MS. Furthermore, the elevation of MMP-9 tends to be observed in MS subjects with active disease as manifested by an ongoing clinical relapse or by the presence of gadolinium enhancement on magnetic resonance imaging (MRI) [9–12]. The elevated serum MMP-9 levels in MS have also been found to correlate with increased gadolinium enhancements on MRI either that month [10] or the following month [11,12]. These findings correspond with the role of elevated MMPs in disrupting the integrity of the blood–brain barrier since gadolinium enhancement is reflective of blood–brain barrier disruption.

In concordance with these serum studies, CSF results have also implicated MMP-9 in MS. MMP-9 content is elevated in the CSF of 45 of 45 relapsing–remitting MS patients examined compared to controls [13]. In another study [14], MMP-9 level in the CSF was increased in people with active relapsing–remitting MS compared to stable patients. Recently, levels of the active form of MMP-9 were found to be elevated in the CSF of MS patients, particularly during active disease (clinical or MRI) when compared to samples from other inflammatory neurological disease controls and non-neurological controls [15].

The involvement of MMP-9 is further emphasized by Correale and Molinas [16] who evaluated the levels of MMP-9 in the serum of patients with clinically isolated syndromes (CIS), the first attack of suspected MS, from patients with definite MS, and controls. They found an increase in serum MMP-9 level in patients with CIS compared to controls and a further increase in the group with clinically definite MS. Moreover, CIS patients were followed over time and those that converted to clinically definite MS had further elevations of their serum MMP-9 level whereas levels remained stable in CIS patients that had not progressed.

The role of MMP-9 is further suggested by studies of the ratio of MMP-9 to tissue inhibitor of metalloproteinase (TIMP)-1 in serum. TIMP-1 is a physiological antagonist of MMP-9. Lichtinghagen et al. [17] reported a higher ratio of MMP-9: TIMP-1 in active MS cases versus controls, correspondent with higher proteolytic activity. In genetic studies, a polymorphism of the MMP-9 promoter has been found to be associated with an earlier age of onset of MS [18], although this was not confirmed in another cohort [19].

While these studies have implicated MMP-9 in relapsing–remitting MS, other MMPs have also been found to be upregulated. Using in situ hybridization of leukocytes, an increase in the number of leukocytes expressing MMP-1, -3, and -7 was reported [20]. PCR analysis from leukocytes from MS patients showed increased MMP-7 and -14 RNA [21]. We reported that in monocytes from patients with MS, increased levels of MMP-2, MMP-14 and TIMP-2 were present [22]; this tripartite is normally involved in regulating the activation of MMP-2 further implicating increased proteolysis occurring in MS [22]. Recently, Kanesaka et al. [23] noted that serum level of MMP-3 in MS was higher within a month of a relapse than that during remission, suggesting that this MMP has a role in disease exacerbation.

Besides relapsing–remitting MS, other forms of MS have also been examined for expression of MMPs. Sastre-Garriga et al. [24] reported that serum MMP-9 levels were significantly lower in patients with primary progressive MS, identified by the absence of relapses and infrequent gadolinium enhancing activity on MRI, compared to the relapsing–remitting form. Avolio et al. [25] reported that the MMP-9: TIMP-1 ratio in serum was higher in relapsing–remitting MS than in primary progressive MS, but the converse was found for MMP-2:TIMP-2 ratio. This suggests that an increase in MMP-2:TIMP-2 ratio marks chronic progression in MS while high MMP-9:TIMP-1 activity characterizes the relapsing–remitting form of the disease. These results await confirmation.

Overall, there is good evidence for alteration of several MMPs, particularly MMP-9 [26], in patients with MS.

## 3. Migratory capacity of leukocytes and the relationship to MMP expression

The transmigration of leukocytes into the CNS is a characteristic feature of MS. MMPs are implicated in the transmigratory process by virtue of their processing of adhesion molecules and also by selective degradation of basement membranes that surround blood vessels. In tissue culture studies, the transmigration of leukocytes across reconstituted basement membranes has been found to be dependent on MMP activity [2]. Furthermore, the relative migratory capacity of T helper 1 (Th1) CD4+ lymphocytes, which are pro-inflammatory and implicated in the pathogenesis of MS, has been compared to regulatory Th2 cells. Th1 cells migrated more efficiently than Th2 cells and this correlated with higher levels of MMP-2 and -9 in Th1 versus Th2 cells [27].

In the vasculature of the brain in mice, Agrawal et al. [28] have described that there are two basement membrane barriers surrounding blood vessels in the normal CNS: the first membrane lies outside of endothelial cells and the second (“parenchymal” basement membrane) lies further within the CNS abutting astrocytes. While the existence of these two barriers is not obvious in the normal CNS, they become clearly delineated in the inflamed CNS when

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leukocytes fill the spaces between. Surprisingly, penetration of leukocytes across the first basement membrane abutting blood vessels is not MMP dependent, while transmigration across the parenchymal basement membrane is [27]. Thus, in EAE afflicted animals, inhibition of MMPs caused leukocytes to be trapped in the space between the two basement membranes as they were unable to penetrate across the parenchymal basement membrane into the CNS after transiting across the first basement membrane [28]. This work is the most compelling to date of the requirement of metalloproteinase activity for leukocytes to migrate into the CNS parenchyma in vivo.

In summary, in vitro as well as in vivo observations support a pathogenic role of MMPs in facilitating leukocyte transmigration into the CNS, an important feature of MS.

## 4. MMPs are Increased in EAE

Analyses of MMPs from EAE afflicted animals have taught us many lessons about MMPs in inflammatory conditions. First, many MMPs are simultaneously elevated during peak disease in EAE. In this regard, we reported that spinal cord samples from animals at peak EAE disease severity had elevation of 11 of 20 MMPs analyzed (MMP-2, -3, -8, -9, -10, -11, -12, -13, -14, -25) [1]. We also determined that five MMPs were down regulated at the level of transcripts and that four of these were of the membrane-type subfamily of MMPs (MMP-15, -16, -17, and -24; the remaining down regulated MMP being MMP-21). The significance of the down regulated MMPs, particularly those of the membrane-type forms, is unclear at this present time.

Another group [29] has analyzed the spinal cord of animals with EAE following the adoptive transfer of myelin reactive T cells. The authors documented increases of MMP-12 and TIMP-1 in macrophages, MMP-8 in granulocytes and ADAM-12 in T cells. Finally, elevation of several MMP members have also been reported by others in the spinal cord or brain of mice or rats afflicted with EAE [30–33].

The roles of particular MMPs in EAE were examined in mice deficient for various MMPs. A function for MMP-9 in promoting neuroinflammation is suggested by the finding that young (3–4 weeks) but not older (7–8 weeks) MMP-9 null mice were less susceptible to development of EAE than wildtype controls [34]. MMP-2 null mice have been reported to have an earlier onset and more severe disease compared to wildtype controls but this observation was related to a compensatory increase in MMP-9 in the MMP-2 null mice [35]. More recently, it was found that while MMP-2 and -9 single null mice did not have altered susceptibility to EAE disease, the loss of both MMPs resulted in the inability to induce any disease [28]. These results (Table 1) point to important roles for MMPs in promoting EAE disease activity.

In addition to MMP-2 and -9, other MMPs may play roles in EAE. We determined that MMP-12 was highly expressed in the spinal cord following EAE disease in mice. However, MMP-12 null mice had a worse disease outcome than wildtype controls suggesting that MMP-12 is not detrimental but may be necessary for repair or to modulate the inflammatory response [1].

Overall, these studies in animals highlight functions of MMPs in regulating inflammation in EAE. Not discussed here are other detrimental roles of MMPs such as their involvement of demyelination, axonal injury, and cell death (reviewed in [2]).

## 5. Modulation of MMPs

A number of synthetic inhibitors of MMP activity have been developed and these have been shown to decrease the incidence and severity of EAE. These inhibitors include: GM6001 [36,37], Ro31–9790 [38], BB1101 [39], UK221, 316 [40] and d-penicillamine [41].

A semi-synthetic tetracycline derivative, minocycline, also has MMP inhibitory actions [42]. In mice afflicted with EAE, we demonstrated that minocycline reduced the expression and activity of MMP-9 in T cells and that administration of minocycline to EAE afflicted animals alleviated disease severity and neuropathology [43].

These studies in mice have been translated to a clinical trial of minocycline in 10 patients with relapsing–remitting MS. We observed that in patients beginning the 3 month run in phase with gadolinium-enhancing MRI activity, this activity was markedly reduced within the first 2 months of treatment with minocycline [44]. This rapid resolution of gadolinium-enhancing MRI activity is consistent with a role for MMPs in attenuating disruption of the blood–brain barrier, and we hypothesized that reduced MMP-9 activity during treatment would support this mechanism.

We collected serum samples from the patients in the minocycline trial before and at several time points following minocycline treatment. We observed that serum MMP-9 activity was reduced during treatment compared to pre-treatment values and that this was maintained for up to 18 months during treatment, the last time point examined in this study [45].

A commonly used immunomodulatory agent in MS is interferon-beta, of which there are three commercial preparations. We [46] and another group [47] simultaneously reported that interferon-beta reduces the production of MMP-9 by T cells and that this corresponds with a decrease in the ability of T lymphocytes to transmigrate a basement

Table 1
Altered susceptibility of MMP null mice to EAE

| MMP | Outcome | Reference |
|---|---|---|
| MMP-2 | Null mice had worse EAE scores than wildtype controls, and this was attributed to a compensatory increase in MMP-9 | [35] |
| MMP-9 | Young, but not older, null mice were less susceptible to EAE | [34] |
| MMP-12 | Null mice had a worse outcome than wildtype | [1] |
| MMP-2 and -9 | Double null mice were protected from EAE | [28] |

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membrane barrier in tissue culture. This suggests that interferon-beta regulates MMP levels and that this could well be an important mechanism of its efficacy in relapsing–remitting MS. This manifestation also corresponds with the evidence that interferon-beta rapidly reduces gadolinium-enhancing MRI activity [48]. Furthermore, it has been noted that MMP-9 activity in dendritic cells, a cell type that can initiate an inflammatory response in MS, is diminished by interferon-beta treatment in culture [49].

Clinical studies support the possibility that interferon-beta regulates MMP levels in patients with MS. Boz et al. [50] obtained blood and CSF samples from 14 patients with relapsing–remitting MS before and 6 months after interferon-beta therapy. They reported that after interferon-beta treatment, serum MMP-9 as well as MMP-9:TIMP-1 ratio were significantly decreased. Furthermore, there was an increase in CSF levels of TIMP-1. Trojano et al. [51] examined changes of serum MMP-9 levels over a 24-month period in patients starting interferon-beta and reported that a significant decrease was found by 3 months of treatment, the first time point evaluated, and that this was maintained for 18 months. They also noted that patients with neutralizing antibodies to interferon-beta tended to have higher MMP-9 levels. Galboiz et al. [52] found that interferon-beta treatment was associated with significant suppression of MMP-9 and -7 transcript levels in peripheral blood leukocytes from MS subjects. In another study, 21 relapsing–remitting patients had simultaneous measurements of MMP-9:TIMP-1 levels and MRI before and during 48 weeks of interferon-beta therapy. The serum MMP-9:TIMP-1 ratio, as well as the numbers of gadolinium enhancing lesions, was decreased during treatment. Moreover the serum MMP-9:TIMP-1 ratio was a good predictor of the number of gadolinium-enhancing lesions [53]. In yet another study, Karabudak et al. [54] reported that while MMP-9 levels did not change during a 1 year period with interferon-beta therapy, levels of TIMP-1 increased.

Overall, these studies support the likelihood that a major mechanism of interferon-beta in MS is the modulation of MMP levels and activity, or the increase in levels of physiological inhibitors of MMPs, such that the transmigratory capacity of leukocytes into the CNS is reduced. We note that there is no indication that glatiramer acetate, another medication commonly used in MS and which generates anti-inflammatory Th2 lymphocytes, affects MMP levels as a major mechanism of action [48].

The similarities or differences between interferon-beta and minocycline in affecting MMPs are summarized in Table 2. These characteristics suggest the potential for their use in combination. Indeed, Nelissen et al. [55] demonstrated that MMP-9 could destroy interferon-beta and this was inhibited by minocycline through antagonism of MMP-9 activity, thereby prolonging the actions of interferon-beta. Furthermore, Guiliani et al. [56] tested the combined effects of minocycline and interferon-beta in mouse EAE and found that their combination led to a greater alleviation of EAE disease severity score and histological outcomes compared to either medication alone. Although it is unclear if the combination of minocycline and interferon-beta in alleviating EAE was due to MMP inhibition, the results suggest that multiple approaches to block MMP activity could be used together to achieve a greater outcome to alleviate disease.

Table 2
Comparisons between interferon-beta and minocycline on MMPs

| Immunomodulator | Effect on MMP | Clinical significance |
|---|---|---|
| Interferon-beta | In vitro | Clinical trials |
| | ❖ Decrease in MMP-9 production by T cells and reduced transmigration of T cells across a biological membrane | ❖ Reduction of gadolinium enhancing lesions |
| | ❖ Decrease of MMP-9 activity in dendritic cells | ❖ Decrease in MMP-9 level and MMP-9/TIMP-1 ratio in the sera of treated patients |
| | | ❖ Increase in TIMP-1 in the CSF of treated patients |
| Minocycline | EAE | Clinical trials |
| | ❖ Attenuation of disease severity and neuropathology | ❖ Reduction of gadolinium enhancing lesions |
| | ❖ Decrease in MMP-9 activity and expression in T cells | ❖ Decrease in MMP-9 activity in the sera of treated patients |

Please refer to the text for the references to these points.

## 6. Conclusions

There are now several studies documenting the increased expression of several MMPs in serum, leukocytes, CSF and CNS of patients with MS. The chronic upregulation of most of these MMPs have undesirable consequences including the possibility that they contribute to neurodegenerative events within the CNS. The data are compelling that the transmigratory behavior of leukocytes is MMP dependent and that interferon-beta impacts this activity through MMP inhibition. A potentially useful agent in MS, minocycline, may also impact the disease process through MMP inhibition although other mechanisms for minocycline to curb disease activity are also possible [42]. Nonetheless, chronic MMP inhibition has to be treated cautiously since MMPs are known to have a variety of useful functions in the CNS including regulating events relevant to remyelination and axonal re-growth [4]. Whether these are impaired in MS patients treated chronically with agents, such as interferon beta and minocycline, that have MMP inhibitory activity needs to be determined. It is rational to argue however, that since MS is predominantly a disease of neuroinflammation, the inhibition of MMPs and thus leukocyte transmigration should be therapeutic, even though these treatments may antagonize some of the beneficial properties of the MMPs in repair [4,57,58].

Overall, there are many emerging and complex properties of the MMPs. Many of these molecules also interact with

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other families of proteins in the microenvironment, including chemokines, cytokines, and growth factors (reviewed in [4]). The biology of MMPs in the nervous system, and the regulation of their activities to curb disease, deserves our attention.

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