Chapter C 12

THE ROLE OF METALLOPROTEINASES IN CORONA VIRUS INFECTION

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Abstract: Infection with neurotropic strains of mouse hepatitis virus (MHV) results in rapid leukocyte infiltration into the central nervous system (CNS). The inflammatory response controls virus replication but fails to mediate sterile clearance. The persistence of viral RNA and inflammatory cells within the CNS is associated with the development of ongoing demyelination. Matrix metalloproteinases (MMPs) are a family of proteases involved in degradation of the extracellular matrix (ECM). During inflammatory responses MMPs are thought to play a significant role in breaking down the basement membrane surrounding blood vessels as well as parenchymal ECM thereby facilitating leukocyte infiltration. MMPs have also been associated with activation of chemokines and perhaps more significantly the degradation of myelin proteins and generation of autoantigens. Recent examination of MMP expression during MHV infection suggests that MMP-3, -9 and -12 are involved in the inflammatory response. The proinflammatory effects of these MMPs are likely tempered by induction of tissue inhibiter of metalloproteinase-1 expression.

Key words: Central nervous system (CNS), demyelination, matrix metalloproteinase (MMP), mouse hepatitis virus, tissue inhibiter of matrix metalloproteinase (TIMP).

INTRODUCTION

Mouse hepatitis virus (MHV) can cause respiratory, enteric, hepatic or neurologic infections depending on the viral strain, age of the host and route of infection (33). MHV infection of the central nervous system (CNS) as a model of demyelinating disease has been studied extensively using strains
derived from either the neurotropic JHM strain (MHV-JHM; MHV-4 serotype) or the MHV-A59 strain, which is both hepatotropic and neurotropic (33,43). As described by others, and ourselves acute MHV infection of the CNS induces a potent inflammatory response involving neutrophils, macrophages, NK, B and T cells (33,43,52). In order to reach the site of infection, however, these cells must overcome physical barriers represented by the blood brain barrier as well as the dense extracellular matrix (ECM) of the CNS parenchyma. The ability of leukocytes to extravasate from blood vessels and cross the parenchymal tissues is presumably dependent on the activity of extracellular proteases. One family of proteases, which are often associated with inflammatory responses are the matrix metalloproteinases (MMPs). The descriptions of MMP regulation and function during normal physiological as well as pathological conditions have been described in numerous publications (32,23,41), thus only a brief summary is provided herein.

**BACKGROUND**

MMPs comprise a large group of endoproteinases that, in conjunction with other proteases, mediate degradation during remodeling of the extracellular matrix (ECM). Twenty four different MMPs have been identified and classified as collagenases, gelatinases, stromelysins, matrilysin and membrane type MMPs (MT-MMPs) based on their substrate specificities and protein domain structures (24,34). These proteases are produced by a wide range of cell types, including endothelial, inflammatory and stromal cells (18,23,32). Regulation of MMP activity has been classically defined as occurring at three distinct levels. Primary regulation of MMP activity occurs at the transcriptional level (5,12,22,30,40). MMP gene expression can be induced by a wide range of signals including acute phase cytokines such as IL-1α and -β, IL-6 and TNF-α, and chemokines such as MCP-1, MIP1β, and RANTES (6,12,22). A second level of regulation for MMP activity is post-translational, as MMPs require proteolytic cleavage of their proenzyme form to become activated (4,34). Following translation, most proMMPs are released into the extracellular space. By contrast, a subgroup of membrane associated MMPs, the MT-MMPs, may play a role in the processing of secreted proMMPs to their active form (20). The final level of control for MMP activity resides in their regulation by a small group of specific inhibitors, the tissue inhibitors of metalloproteinases (TIMPs) (7). TIMPs function primarily as specific inhibitors, binding to MMPs in a 1:1 stoichiometry. Interestingly, there is
evidence that TIMPs may also act as chaperone proteins during the processing of MMPs from proenzyme to active form, suggesting that they can promote as well as inhibit MMP enzymatic activity, at least for MMP-2 (42,44).

MMPs and their inhibitors are involved in remodeling of the ECM during normal physiological conditions. However they have also been associated with diverse pathological processes from rheumatoid arthritis to tumor invasion and metastasis (16,25). A number of MMPs and TIMPs have also been associated with the CNS inflammatory/demyelinating disease multiple sclerosis (MS) in humans (2,32) as well as its rodent model experimental autoimmune encephalitis (EAE) (10,38). In the case of MS, these include MMP-1, -2, -3, -7 and -9 and TIMP-1 (2,11,32). These MMPs and TIMPs have been detected by immunohistochemistry in both inflammatory infiltrates and activated glia within acute MS lesions as well as perivascular infiltrates. Following EAE induction in mice, MMP-3, -9, -12 and -14 as well as TIMP-1 gene expression were induced within the CNS (38). MMP-1 and -10 were also induced although to a lesser degree than the aforementioned genes (38). The induction of MMP-7 mRNA expression was not detected but the presence of MMP-7 protein has also been reported during EAE in rats (10). The consistent association of MMP and TIMP expression with inflammatory demyelinating disease suggests that MMPs play either a direct or indirect role in promoting CNS pathology (2,27,32). However, as discussed below, identifying specific MMPs and their exact role in promoting inflammatory/demyelinating has proven to be difficult.

**MMP AND TIMP EXPRESSION DURING CORONAVIRUS INFECTION**

*In vitro* infection of human astrocytic and microglial cell lines with human coronavirus induced up-regulation of MMP-2 and -9 protein suggesting that virus infection can up-regulate MMP expression within the CNS (15). The mechanism by which MMPs were up-regulated by infection where not known, however, virus infection of the glial cell lines induced expression of IL-6, TNF-α and MCP-1, which are all inducers of MMP expression (15). Transfer of non-infectious supernatants from infected cultures to uninfected cells was sufficient to induce expression of MMP-2 and -9. MMP expression, including MMP-2 and -9, is also elevated in naïve transgenic mice, which express IL-6 and TNF-α within the CNS (38). These observations suggest that viral infections induce expression of chemokines/cytokines, which in turn induce MMP expression in neighboring cells (15,38).
Recent examination of MMP gene expression within the brains of mice infected with lethal and attenuated MHV-JHM variants showed that MMP-3 and -12 mRNA were rapidly up regulated during acute infections (51, 53). By contrast, infection did not alter transcription of the genes encoding MMP-2, -9, -11 or -14, which were constitutively expressed in the CNS of naïve BALB/c mice (51). These data are summarized in Table 1. Kinetic analysis of MMP expression indicated that MMP-3 and MMP-12 expression peaked by 6 days post infection (p.i.) in accord with viral load, however, expression was significantly higher in lethally infected mice (51,52). Comparisons of MMP/TIMP expression in infected irradiated and control mice revealed relatively little loss in MMP or TIMP expression in immunosuppressed mice (51). These results indicated that CNS resident cells were responsible for the majority of MMP-3, and -12 gene expression detected within the brain and that this gene induction was relatively independent of the presence of inflammatory cell infiltration. Expression of MMPs constitutively expressed in naïve mice (MMP-2, -9, -11, -14) were unaffected by immunosuppression.

Table 1: MMP and TIMP expression within the CNS during MHV infection

| Virus induced expression | Constitutive expression | Not Detected |
|-------------------------|-------------------------|--------------|
| MMP-3                   | MMP-2                   | MMP-1        |
| MMP-9<sup>b</sup>       | MMP-11                  | MMP-7        |
| MMP-12                  | MMP-14                  |              |
| TIMP-1                  | TIMP-2                  |              |
|                         | TIMP-3                  |              |

<sup>a</sup> RNA was prepared from brains of MHV-JHM infected mice. Relative gene expression was determined by RNase protection assay.

<sup>b</sup> Analysis of MMP-9 expression by RNase protection assay did not reveal an increase in MMP-9 expression in RNA prepared from total brain. However, analysis of MMP expression from CD45<sup>hi</sup> inflammatory cells isolated from the CNS indicated that MMP-9 expression was increased during MHV infection.

Four TIMPs have been characterized and all are capable of inhibiting a range of MMPs (7,23). Basal expression of TIMP-1 is low but readily induced in response to a multitude of inflammatory signals (5,7). By comparison, TIMP-2, -3 and -4 are expressed constitutively and alterations in their expression are less frequently associated with inflammatory responses (26,31,38). Examination of naïve and MHV-JHM infected brains revealed that TIMP-2 and -3 were unaffected by the infection (51) (Table 1). By contrast, MHV infection induced rapid expression of TIMP-1 (51) (Table 1). TIMP-1 expression peaked by 6 p.i. in conjunction with MMP-3 and -12 expression (51,52). TIMP-1 expression was higher in lethally infected mice compared to sublethally infected mice suggesting that expression is dependent on viral load and/or virulence. TIMP-1 expression has been reported to be associated with both tissue resident cells as well as most
inflammatory cells (7). Expression levels of TIMP-1 were higher in irradiated, immunocompromised mice compared to control animals, indicating that most TIMP-1 is produced by CNS resident cells (51).

Analysis of whole brain samples for MMP RNA and protein failed to detect induction of MMP-9 expression during MHV infection (51), which was in sharp contrast to its prominence in MS. However, subsequent analysis of individual cell populations sorted from infected brains indicated that MMP-9 gene expression is up regulated several fold among infiltrating inflammatory cells (Zhou, unpublished data) (Table 1). Similarly, a strong induction in TIMP-1 expression within the inflammatory cell populations (Zhou, unpublished data) suggests that T cells are, at least in part, a source of both MMP-9 and TIMP-1 as both of these genes are co-expressed by T cells (35). Furthermore, analysis of cell extracts prepared from infiltrating cells revealed that MHV infection also induced a sharp rise in the level of intracellular MMP-9 protein (51, 53). The increase in intracellular MMP-9 protein was attributed to the presence of polymorphonuclear cell infiltrates in response to infection (51, 53). Neutrophil synthesis of MMP-9 differs from other cell types in two key ways. First, in contrast to mononuclear cells, which release MMP-9 directly into the extracellular space, neutrophils store MMP-9 proenzyme in granules for release during degranulation (35), therefore permitting neutrophils to rapidly release large quantities of MMP-9 in the absence of de novo synthesis. Second, expression of MMP-9 in neutrophils is not linked to co-expression of TIMP-1 as is the case for T cells (35). Thus, MMP-9 from neutrophils is regulated at the level of degranulation as opposed to gene transcription and co-expression of TIMPs. These data suggest MMP-9 is likely released from both mononuclear and polymorphonuclear infiltrates during JHMV infection. Thus, with the exception that MMP-7 was not detected during MHV infection (51), the overall expression patterns for both MMPs (-3, -9 and -12) and TIMP-1 during MHV infection, EAE and MS are extremely similar.

**ROLE OF MMPS IN DEMYELINATION**

Linkage between MMP/TIMP expression during demyelinating disease has been well chronicled (32,38,51). By contrast, determining a definitive role for MMPs during demyelinating disease has proven to be far more elusive. During inflammatory processes within the CNS, MMPs most likely play two key roles: 1) Breaking down the basal lamina surrounding the blood brain barrier, thereby allowing inflammatory cells to enter the CNS (35); and 2) breaking down connective tissues linking tightly packed CNS resident cells, thereby allowing inflammatory cells to migrate along chemokine gradients towards the sites of infection/injury (18,50). Other key
mechanisms in the genesis of inflammatory demyelination have been associated with MMPs. These include activation of cytokines and chemokines, such as the conversion of TNF-α from pro to active form (8) and increasing the potency of the chemokine IL-8 (48). Furthermore, activated MMP-3 can convert pro-MMP-9 into its active form (13). Thus MMP-3 produced by CNS resident cells may be involved in activating pro-MMP-9 synthesized by inflammatory cells. Activation of these proinflammatory proteins by MMPs increases the potential for immune mediated damage to the CNS.

A number of MMPs including -3, -9, and -12, which are common to many demyelinating diseases, are capable of breaking down proteins of the myelin sheath (8,9,39). The consequences of this are two fold. First, induction of an inflammatory response to a foreign antigen within the CNS may nonspecifically initiate destruction of the myelin sheath through the release of MMPs. Second, generation of potential autoreactive self-antigens by MMP mediated breakdown of myelin proteins may initiate specific responses against oligodendroglia resulting in additional demyelination (36,39).

Of the MMPs associated with MHV infection of the CNS, MMP-9 and its specific inhibitor, TIMP-1, are of particular interest for several reasons. MMP-9 and TIMP-1 are produced by both activated inflammatory as well as CNS resident cells (19,35,47). MMP-9 is specific for type IV collagens, which make up the basement membrane surrounding the blood brain barrier (49). This suggests that MMP-9 contributes to the ability of activated inflammatory cells to cross this barrier. Support for the role of MMP-9 in T cell trafficking comes from MS patients undergoing IFN-β treatment, one of the few therapeutics shown to have a positive effect. Although no single conclusive mechanism for the anti-inflammatory activity of IFN-β has been demonstrated, MMP-9 gene expression is down regulated by IFN-β (30,45,46). Conversely, TIMP-1, which inhibits MMP-9, is up regulated by IFN-β (37). This suggests that one of the mechanisms by which IFN-β works is through inhibition of MMP-9 mediated inflammatory cell trafficking. These data are supported by treatment of EAE mice with MMP inhibitors, which have generally prevented disease induction or reduced clinical symptoms when treatment was initiated after active disease was apparent (17,21,28).

**CONCLUSIONS**

MMP and TIMP expression are closely associated with the human demyelinating disease MS as well as experimental animal models of
demyelinating disease. MMP expression within the CNS is most likely upregulated by the presence of inflammatory cytokines. However, as stated previously, confirmation of a specific role for MMPs in the inflammatory process is lacking. The use of knockout mice to determine the role of specific MMPs in inflammatory responses have generated mixed results, particularly in regard to blood brain barrier breakdown and inflammatory cell infiltration across endothelial cell barriers (1,3,14,29). This may in part be explained by the large number of MMPs with overlapping specificities as well as the presence of other proteases. Thus, although MMP expression is clearly associated with inflammatory responses during demyelinating disease, the role of individual MMPs as active participants or simply as markers remains to be determined.

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