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REVIEW

DIVERSE ROLES OF MATRIX METALLOPROTEINASES AND TISSUE INHIBITORS OF METALLOPROTEINASES IN NEUROINFLAMMATION AND CEREBRAL ISCHEMIA

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Abstract—Regulation of the extracellular matrix by proteases and protease inhibitors is a fundamental biological process for normal growth, development and repair in the CNS. Matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs) are the major extracellular-degrading enzymes. Two other enzyme families, *a d*isintegrin *a*nd *m*etalloproteinase (ADAM), and the serine proteases, plasminogen/plasminogen activator (P/PA) system, are also involved in extracellular matrix degradation. Normally, the highly integrated action of these enzyme families remodels all of the components of the matrix and performs essential functions at the cell surface involved in signaling, cell survival, and cell death. During the inflammatory response induced in infection, autoimmune reactions and hypoxia/ischemia, abnormal expression and activation of these proteases lead to breakdown of the extracellular matrix, resulting in the opening of the blood–brain barrier (BBB), preventing normal cell signaling, and eventually leading to cell death. There are several key MMPs and ADAMs that have been implicated in neuroinflammation: gelatinases A and B (MMP-2 and -9), stromelysin-1 (MMP-3), membrane-type MMP (MT1-MMP or MMP-14), and *t*umor necrosis factor-α *c*onverting enzyme (TACE). In addition, TIMP-3, which is bound to the cell surface, promotes cell death and impedes angiogenesis. Inhibitors of metalloproteinases are available, but balancing the beneficial and detrimental effects of these agents remains a challenge.

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Abbreviations: BBB, blood–brain barrier; BL, basal lamina; COX, cyclooxygenase; CSF, cerebrospinal fluid; ECs, endothelial cells; HIF-1α, hypoxia inducible factor-1α; IL-1β, interleukin-1β; JAM, junctional adhesion molecule; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; MT1-MMP, membrane-type 1 matrix metalloproteinase; TACE, tumor necrosis factor-α converting enzyme; TIMP, tissue inhibitor of matrix metalloproteinase; TJPs, tight junction proteins; TNF-α, tumor necrosis factor-α; tPA, tissue plasminogen activator; uPA, urokinase-type plasminogen activator; ZO, zona occludens.

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Contents

During neuroinflammation and ischemia, molecular cascades are initiated with the purpose of removing damaged cells and preparing the brain for repair (Dirnagl et al., 1999). This dual role necessitates a full understanding of the timing of the injury phases and of those involved in repair. Early after the injury, constitutive proteases are activated and begin the process of disassembling the extracellular matrix, opening the blood–brain barrier (BBB), and initiating cell death by apoptosis (Rosenberg et al., 1998; Heo et al., 1999; Yang et al., 2007). The second stage of injury involves matrix metalloproteinases (MMPs) in processes of angiogenesis and neurogenesis (Lee et al., 2006; Wang et al., 2006; Zhao et al., 2006). In this second phase, treatment with MMP inhibitors may interfere with repair (Rosell and Lo, 2008; Sood et al., 2008). Remodeling of the extracellular matrix characterizes the third phase when gliosis forms impenetrable scar tissues that block the regrowth and re-projection of axons. The action of the MMPs on the basal lamina and tight junction proteins (TJPs) in endothelial cells (ECs) is the final common pathway for opening of the BBB, which allows cells to enter the CNS and attack invading organisms. This is probably a protective mechanism during CNS infection, but when no infection exists, this inflammatory response contributes to tissue damage. When matrix proteins around neurons are degraded, there is loss of contact and cell death by anoikis (Gu et al., 2002). While a great deal has been learned in the past decade as information on the MMPs and tissue inhibitor of matrix metalloproteinases (TIMPs) has emerged from many laboratories, the multiple functions of the MMPs and

TIMPs have made the search of clinically useful MMP inhibitors a challenge.

The first enzyme in the large gene family now known as the MMPs was discovered in the regenerating frog tail (see for discussion (Brinckerhoff and Matrisian, 2002)). The next major breakthrough in MMP biology was the discovery that metastatic melanoma cells secrete a 72-kDa type IV collagenase (MMP-2) to facilitate tumor cells' passage from the blood into the tissues (Liotta et al., 1980). This important discovery led to a great deal of interest by the pharmaceutical industry to identify MMP inhibitors for the treatment of cancer (Overall and Lopez-Otin, 2002). Initially the emphasis of drug discovery and clinical trials was on the role of the MMPs in cancer with many agents entering clinical trials (Coussens et al., 2002). The results were disappointing because long-term use of these agents resulted in overgrowth of extracellular matrix in joints, which was painful. Subsequently, a shift has occurred with the realization that short-term use of MMP inhibitors may be possible in neurological disorders, particularly for treatment of cerebrovascular and cardiovascular diseases (Hu et al., 2007). This selective review will focus on the role of the MMPs in the neuroinflammatory response to injury with special emphasis on cerebral ischemia. This article will not cover the role of MMPs in other neurodegenerative diseases (e.g. multiple sclerosis, inflammatory myopathies) where the inflammation is the underlying cause of the disease. Several recent reviews have been published detailing the basic biology and role in the CNS of the MMPs (Lo et al., 2003; Cunningham et al., 2005; Liu and Rosenberg, 2005; Yong, 2005).

BIOLOGY OF THE MMPs: EXPRESSION AND MECHANISMS OF ACTIVATION

The MMPs are zinc- and calcium-dependent endopeptidases, identified as matrix-degrading enzymes. MMPs cleave most components of the extracellular matrix including fibronectin, laminin, proteoglycans and type IV collagen (Sternlicht and Werb, 2001; Rosenberg, 2002). MMPs are also capable of processing other proMMPs and a number of bioactive molecules, including proforms of cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (Schonbeck et al., 1998; Cauwe et al., 2007), and pro-neurotrophins such as proNGF and proBDNF (Schonbeck et al., 1998; Lee et al., 2001; Sternlicht and Werb, 2001). Regulation of MMP expression and activation is very complex and tightly controlled. MMPs are synthesized as zymogens and are secreted into the extracellular space as inactive zymogens. ProMMPs are activated by disruption of the zinc–thiol interaction between the catalytic site and the pro-domain. The pro-peptide of the zymogen has to be proteolytically cleaved by other MMPs or proteases for an MMP to be active (Sternlicht and Werb, 2001). The proteases plasmin, tissue plasminogen activator (tPA), and urokinase-type plasminogen activator (uPA) are important physiological activators of the MMPs (Fig. 1) (Gasche et al., 2006). Protease-independent activation of the MMPs by S-nitrosylation or oxidation can unmask the catalytic domain producing activation of MMPs without pro-domain cleavage (Gu et al., 2002; Meli et al., 2003; Pei et al., 2006).

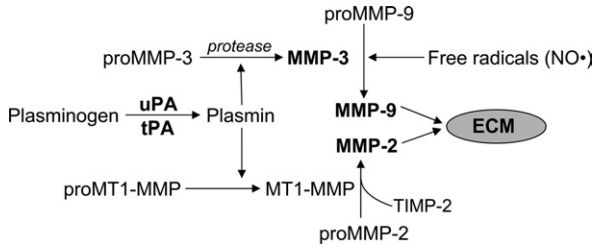

Fig. 1. Mechanisms of activation of MMPs. Plasmin plays an active role in the activation of MMPs. MT1-MMP (MMP-14) binds to TIMP-2 and proMMP-2 leading to the formation of catalytically active MMP-2. ProMMP-9 is activated by MMP-3 and free radicals (nitric oxide, NO·). Plasmin has been shown to activate proMMP-3. Recently, it was shown that there is an intracellular mechanism of activation of MMP-3 which involves a serine protease other than furin (Choi et al., 2008). Although proMMP-3 possesses the furin recognition sequence, the cleavage would leave nine amino acids belonging to the prodomain resulting in a form which is not catalytically active (Choi et al., 2008).

The activities of MMPs are regulated by TIMPs. Four members of this family have been characterized (Brew et al., 2000). TIMP-2 inhibits MMP-2, TIMP-1 inhibits MMP-9 and TIMP-3 acts on MMPs and tumor necrosis factor-α converting enzyme (TACE). Although individual TIMPs have preferences for one or another of the MMPs, they can inhibit all of the MMPs (Brew et al., 2000). TIMP-3 is unique because it is membrane bound. The main substrates inhibited by TIMP-3 include membrane-type 1 matrix metalloproteinase (MT1-MMP), MMP-3 and TACE (Cunningham et al., 2005).

Constitutive expression of MMP-2 provides an ongoing, well-controlled remodeling of the extracellular matrix. MMP-2 remains in the pro or latent form until activated by a molecular cascade that involves a trimolecular complex made up of MMP-2, TIMP-2, and MT1-MMP (Fig. 2). This reaction occurs close to the cell surface where it provides local proteolysis without involvement of the surrounding tissues (Zucker et al., 2003). TIMP-3 reduces the activation of MT1-MMP, which affects the activation of MMP-2.

The early events in the molecular cascade of hypoxia/ischemia probably involve the induction of the proconvertase, furin, by hypoxia inducible factor-1α (HIF-1α) (McMahon et al., 2005). Furin is an activator of MT1-MMP (MMP-14), which is required for the activation of MMP-2 (McMahon et al., 2005). Activation of MT1-MMP by furin has been established for tumorigenesis and can only be proposed for cerebral ischemia. Unlike other MMPs, MMP-2 is constitutively present in large quantities in the normal brain and is found in astrocytes (Fig. 2) and cerebrospinal fluid (CSF). The rate-limiting step is activation, making MT1-MMP critical in the process (Fig. 1). Abnormal increase in MMP-2 expression and activity in hypoxia/ischemia may disrupt basal lamina and tight junctions between ECs leading to BBB disruption. On the other hand, latent MMP-9 is activated by free radicals and MMP-3 during neuroinflammatory and ischemic conditions (Hahn-Dantona et al., 1999;