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Review

Matrix metalloproteinases as therapeutic targets for stroke

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ABSTRACT

Matrix metalloproteinases (MMPs) are important in injury and recovery in ischemic injury. They are proteolytic enzymes that degrade all components of the extracellular matrix (ECM). They are secreted in a latent form, protecting the cell from damage, but once activated induce injury prior to rapid inactivation by four tissue inhibitors to metalloproteinases (TIMPs). Normally the constitutive enzymes, MMP-2 and membrane type MMP (MMP-14), are activated in a spatially specific manner and act close to the site of activation, while the inducible enzymes, MMP-3 and MMP-9, become active through the action of free radicals and other enzymes during neuroinflammation. Because of the complex nature of the interactions with tissues during development, injury and repair, the MMPs have multiple roles, participating in the injury process in the early stages and contributing to recovery during the later stages. This dual role complicates the planning of treatment strategies.

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1. Introduction

Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade all components of the extracellular matrix (ECM) (Vandooren et al., 2014). MMPs are a large family of enzymes that range from the smallest member of the family, matrilysin (MMP-7), to the large transmembrane MMPs, such as MMP-14. They have a standard configuration consisting of the catalytic zinc site, the propeptide portion, which forms a cysteine switch that maintains latency, and various other entities, such as the hemopexin site, the fibronectin binding site, and the transmembrane site. They are secreted in a latent form that protects the cell from damage, and once activated are generally rapidly inactivated by a series of mechanisms, mainly involving the four tissue inhibitors to metalloproteinases (TIMPs). They can be divided into constitutive enzymes, including MMP-2 and MMP-14, and inducible enzymes, MMP-3 and MMP-9. Normally the constitutive enzymes are activated in a spatially specific manner and act close to the site of activation. They maintain the integrity of the basement membranes, preventing overgrowth of the ECM. Inducible enzymes, on the other hand, are held in an inactive state until a neuroinflammatory process begins and they become active through the action of free radicals and other enzymes. Once the inducible MMPs are activated, they are not constrained to act close to the site of activation and lead to more extensive tissue damage. The timing of the activation cascades is critical in determining the role that the enzymes play during normal tissue maintenance, injury and recovery. Because of the complex nature of the interactions with tissues during development, injury and repair, the MMPs have multiple roles, participating in the injury process in the early stages and contributing to recovery during the later stages. This dual role makes planning of treatment strategies complicated (Yang et al., 2011a).

The main constitutive enzymes in the brain are gelatinase A (MMP-2) and membrane type MMP (MMP-14) (Yong et al., 2001). These are present normally in brain cells, particularly in astrocytes where the foot processes are intimately connected to the endothelial cells (EC). Relatively high concentrations of MMP-2 are found in the cerebrospinal fluid (CSF). Activation of MMP-2 involves a trimolecular complex composed on MMP-2, TIMP-2, and MMP-14 (also MT1-MMP) (English et al., 2006). When the three molecules come together the MMP-14 activates the MMP-2, utilizing TIMP-2 as a bridging molecule. Because the MMP-14 is bound to the membrane, the activity of the MMP-2 is constrained to the region close to the activation site. This prevents the MMP-2 from doing extensive damage, but allows for the removal of excess ECM, maintaining the integrity of the basal lamina around the blood vessels.

The inducible MMPs primarily active in the brain are MMP-3 and MMP-9. Microglia, macrophages, and infiltrating neutrophils are the primary sources. Other MMPs involved in injury cascades include MMP-8 and MMP-13 (Cuadrado et al., 2009). Activator protein-1 (AP-1) and nuclear factor-kB (NF-kB) transcription sites are involved in the formation of MMP-3 and MMP-9. Cytokines activate the transcription sites leading to the formation of the latent forms of the enzymes. Once they are formed nitrosylation and other free radical actions lead to their activation. MMP-9 is activated by active MMP-3. Tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-β) are involved the transcription of MMPs. During inflammation there is a number of cytokines released and the exact combination and effect on the MMPs is dependent on the underlying disease process. Both MMPs and cytokines may be expressed in the blood during an inflammatory response to injury and infection. In bacterial meningitis, MMP-8 degrades the tight junction protein (TJP), occludin, a component of the blood–brain barrier (BBB), and induces neuroinflammation (Schubert-Unkmeir et al., 2010). MMP-8 is also critical in mediating microglial activation by modulating TNF-α activity, which suggests a proinflammatory role of microglial MMP-8.

2. Neurovascular unit (NVU)

The neurovascular unit protects the brain microenvironment from substances circulating in the blood. The cells form a series of cellular layers beginning with ECs that form the major interface with the blood. Surrounding the ECs is a basal lamina composed of type IV collagen, laminin, heparin sulfate, fibronectin and other extracellular molecules. Contiguous with the basal lamina and embedded in it are the pericytes, which are the macrophage-like cells that play major roles both in injury and in angiogenesis. The final layer is formed by astrocytic end-feet that encircle the basal lamina.

TJP are located in the clefts that join the ECs together. Tethered to the endothelial membranes are the zona occludens that traverse the cell wall and enter the space between the edges of the cells. Within the clefts are the cells that constitute the tight junctions, namely, occluldin and claudins, which provide the main barrier between the blood and the interstitial fluid. The basal lamina most likely provides a molecular filter through its charge and intertwined proteins. The end-feet of the astrocytes take up molecules and water; they contain the water pores formed by aquaporin (Higashida et al., 2011). When the cells swell, the astrocytic end-feet are the first to absorb the excess water and expand (Kuchiwaki et al., 1990).

MMPs act at several sites in the neurovascular unit to regulate the permeability of the NVU. MMPs are extracellular-degrading enzymes, and a major site of their action is on the proteins in the basal lamina and the TJPs, but recent studies indicate they also act intracellularly (Yang et al., 2007, 2010). Astrocytes normally secrete MMP-2 from the end-feet where they act on the contiguous structures. MMP-9 and MMP-3 are produced by the ECs and particularly by the microglia and by pericytes, which are a major source of MMP-3. Neutrophils are the source of MMP-8 (Owen et al., 2004).

In acute stroke, the first response seen in the MMPs occurs in MMP-2, which is probably due to the fact that it is present in a latent form normally and does not need to be produced. Activation of MMP-2 begins during hypoxia once MMP-14 is activated by furin, which is produced by hypoxia inducible factor-alpha (HIF-1α). Since MMP-2, MMP-14 and TIMP-2 are normally present, the activation of MMP-2 begins the disruption of the ECM proteins in the basal lamina and eventually