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Tissue Inhibitors of Matrix Metalloproteinase-3, Potential Therapeutic Target against Multiple Sclerosis

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ABSTRACT

The Matrix Metalloproteinase Proteins (MMPs) comprise a large group of endoproteinases that cleave most, if not all, components of the extracellular matrix. The activities of MMPs are modulated by manipulation in the levels of natural MMP inhibitors, the "Tissue Inhibitors of Metallo Proteinases" (TIMPs). In a pathological processes of Multiple Sclerosis (MS), the MMP-2 and 9 (Gelatinase) are over expressed and balance of TIMP and MMP expression is perturbed, leading to locally increased proteolytic activity of Gelatinase and uncontrolled degradation of the Blood Brain Barrier (BBB) and myelin basic protein. Therefore, Gelatinase are the main mediators in the evolution of MS and TIMP has been proposed as a novel therapeutic target for MS therapy.

Key words: Multiple sclerosis, matrix metallo proteinase proteins, tissue inhibitors of metalloproteinases, therapeutic target

INTRODUCTION

Matrix Metallo Proteinases (MMPs), naturally occurring superfamily of endoproteinases, are composed of at least 26 members of zinc-containing enzymes produced by many cell types and sharing structural and functional features. Based on structural and functional considerations, MMPs have been classified into different families and subfamilies as follows: collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), metalloelastases (MMP-12), the MT-MMPs (MMP-14, -15, -16, -17, -24 and 25), matrilysins (MMP-7 and -26), stromelysins (MMP-3, -10 and -11) and sheddases such as TNF-converting enzymes (TACEand ACE) (Akhavan *et al*., 2011; El-Meghawry El-Kenawy *et al*., 2006; Murphy and Nagase, 2008; Mott and Werb, 2004).

MATRIX METALLOPROTEINASES ROLES

MMPs function is to catalyze the breakdown of connective tissues extracellular matrix proteins by their ability to hydrolyze various components of tissue or matrix (Page-McCaw *et al*., 2007; Ra and Parks, 2007). They are also involved in cleavage of cell surface receptors,

growth factors, cell-adhesion molecules, cytokines and chemokines, as well as other MMPs and unrelated proteases. Furthermore, MMPs are thought to play a major role in processes including cell-proliferation, differentiation and -migration (adhesion/dispersion), angiogenesis, apoptosis and host defense (Hu *et al*., 2007; Kamel *et al*., 2009; Gupta and Kumaran, 2006a).

Apart from their role in degrading connective tissue, over-expression or over-activation of an MMP, or an imbalance between an MMP and a natural (i.e., endogenous) Tissue Inhibitor of a Matrix Metallo Proteinase (TIMP) has been linked to a pathogenesis of diseases characterized by the breakdown of connective tissue or extracellular matrix (Nagase *et al*., 2006; Fingleton, 2007; Gupta and Kumaran, 2006b).

MATRIX METALLOPROTEINASES AND MULTIPLE SCLEROSIS

Recent evidence indicates the contribution of MMPs to the pathogenesis of Multiple Sclerosis (MS) and its animal model, Experimental Autoimmune Encephalomyelitis (EAE) (Leppert *et al*., 2001; Nikfar *et al*., 2010). This evidence is based in part on the observation that all important effector cells potentially involved in the pathogenesis of EAE, such as T-lymphocytes, macrophages, astrocytes and microglial cells, apparently express different MMPs (Bar-Or *et al*., 2003; Elahi, 2011; Miabi *et al*., 2010).

Increased levels of MMP-9 were detected in the CSF of rodents with EAE. MMP-7 and -9 were considerably increased at the advanced phase of EAE. The administration of MMP-9 and MMP-2 resulted in breakdown of the Blood Brain Barrier (BBB) (Rosenberg 2002; Dressel *et al*., 2007).

In another study, it was demonstrated that when MMP-7, -8 and -9 were injected into the brain parenchyma of rats in an EAE model, leukocyte recruitment and BBB breakdown were observed (Rosenberg, 2009; Yang and Rosenberg, 2011).

Leppert *et al*. (2001) presented that MMP-9 enhanced trans basement membrane migration of T- lymphocytes. Recent evidence showed that expressed MMPs at the BBB and their corresponding ligands present on immune cells are of major importance for the transendothelial migration of T-cells across the BBB (Yang *et al*., 2011). Previous studies confirmed that these T cell migrations from BBB play essential role in organ- specific autoaggression (Persidsky, 1999; Clemons *et al*., 2005).

The myelin is another potential target for proteolytic MMPs, since these MMP proteases cleave myelin basic protein into immunodominant and encephalitogenic fragments (Zhao *et al*., 2010; Walker and Rosenberg, 2010). Thus, gelatinase would act as immediate effector molecules in the process of demyelination and could perpetuate the immunoinflammatory response. Therefore, it seems that gelatinase is the main mediator in the evolution of autoimmune CNS demyelination.

The study suggested that pathological hallmarks of multiple sclerosis are associated with overexpression of gelatinase, or a lack of their natural tissue inhibitors.

The evidence for the functional involvement of MMPs in the MS makes them attractive targets for therapeutical intervention.

RATIONALES FOR THE HYPOTHESIS

Different natural inhibitors and inhibitory mechanisms of metalloproteinases have been identified. The major inhibitors are Tissue Inhibitors of Metalloproteinases (TIMPs) whose primary function is to limit the degradative actions of the MMPs and be involved in myelination promoting effects (Clark *et al*., 2007; Nagase and Murphy, 2008; Ao *et al*., 2008).

Table 1: Properties of tissue inhibitors of matrix metalloproteinases

Properties	TIMP-1	TIMP-2	TIMP-3	TIMP-4
Protein kDa	28	21	24	22
Extracellular localization	Secreted	Secreted	ECM Bound	Secreted
N-Glycolization	Yes, Two	No	Yes, one	No
In vivo expression	Ovary, uterus	Lung, brain	Brain, kidney, lung	Brain, heart, muscle
MT-MMP inhibition	No	Yes	Yes	Yes
Pro-MMP-2/9 association	MMP-9	MMP-2	MMP-2/9	MMP-9

Four TIMPs, numbered TIMP-1 through TIMP-4 based on their order of discovery have been identified in mammals Table 1 (Brew *et al*., 2000). Among the four TIMPs, TIMP-3 has the broadest inhibition spectrum as it inhibits several members of the metalloproteases especially the gelatinases (Kashiwagi *et al*., 2001; Wang *et al*., 2006).

Irrespective of effects on MMPs, TIMP`s ability to confer neuroprotection against excitotoxic injury or neural damage in nervous system (Chen *et al*., 2009) has potential clinical relevance, making TIMP regulation in multiple sclerosis of even greater interest.

It will be possible to design TIMP-3 with selective specificities for the gelatinases based on recent evidences for the TIMP (Nagase and Brew, 2003; Hamze *et al*., 2007). Therefore, it has been proposed that such "Designer TIMP-3" may be valuable for gene therapy of Multiple sclerosis.

CONCLUSION

Individual TIMPs differ in their efficacy for various MMPs. TIMP-3 possesses exclusive properties that set it apart from other family members. While all TIMPs are secreted into the extracellular space, TIMP-3 binds tightly to the extracellular matrix, suggesting that its actions are localised to the cell surface. Therefore, it may limit proteolytic damage to the extracellular matrix. The inhibitory effects of TIMP-3 on gelatinase also reduce proteolytic disruption of the BBB and lymphocyte recruitment into the brain that represent a critical event in disease pathogenesis of multiple sclerosis. Finally, our hypothesis proposes that, the natural gelatinase inhibitor, TIMP-3 possess proteinase inhibitory properties that may be exploited for therapeutic benefit in pathology of multiple sclerosis.

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