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# The Matrix Metalloproteinases and Cerebral Ischemia

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## 1. Introduction

Matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases which can degrade extracellular matrix (ECM) components at physiological pH. Thirty members of MMPs have been found so far [1]. They are widely distributed in plants, vertebrates and invertebrates cells. In human body, MMPs are mainly produced by vascular smooth muscle cells, monocytes, endothelial cells and so on. MMPs are synthesized as latent enzymes (zymogens) that are secreted or membrane-associated and must be proteolytically processed to their active form. Additionally, MMPs can be inhibited by endogenous inhibitors (e.g. TIMPs, tissue inhibitors of metalloproteinases).

### 1.1 Construction and function of matrix metalloproteinases

#### 1.1.1 Construction of MMPs

MMP members have similar structures. They are usually composed of six structural domains with different functions.

#### 1.2 The signal peptide and propeptide domain

Human MMPs (except MMP14) have a signal peptide sequence. The role of the signal peptide is to guide the post-translation substrate to the cytoplasm endoplasmic reticulum. Propeptide domain contains the conserved sequence of Pro-Arg-Cys-Gly-Val/Asn-Pro-Asp (PRCGV/NPD) which is responsible for maintaining the stability of plasminogen. When the propeptide domain is cut off by the exogenous enzymes, MMPs plasminogen can be activated.

#### 1.3 The catalysis domain

There are two zinc ion binding domains and at least one calcium binding domain in the catalysis domain. Of the 2 zinc ion binding domains, one is in the activation center which is responsible for the catalytic process of MMPs. The other one is the structural zinc ion domain. In the catalysis domain, both gelatinase A and B have a insertion sequence of 175 residues. This insertion sequence is the type-fibronectin binding domain. Studies suggest that this domain may be responsible for the integration between gelatinase and its substrate.

#### **1.4 The hinge domain and hemopexin binding domain**

The hinge domain is located between the catalysis and the hemopexin binding domain and is linked with the terminal amino acid residues of the hemopexin binding domain by the disulfide bond. The hemopexin domain contains four duplicate sequences which has the weak homology with hemopexin and vitronectin. This domain is considered to be relevant to most MMPs' substrate specificity and also plays an important role in the integration between MMPs and tissue inhibitors of metalloproteinases (TIMPs).

#### **1.5 The transmembrane domain**

This domain exists in the carboxyl terminal of the Membrane-type MMPs(MT-MMPs) and can fix MT-MMPs to the cell membrane.

MMP members have different characteristics based on the six structural domains.

### **2. Function of matrix metalloproteinases**

MMPs are the essential enzymes that may play a role in the degradation of ECM in the connective tissue. They can degrade almost all components of ECM and play an important role in various physiological and pathological processes in human body. Under physiological conditions, MMPs participate in the process of tissue remodeling such as wound healing, bone resorption, pregnancy, childbirth and breast atrophy. Normal physiological process depends on the control and coordination between MMPs and TIMPs. When infection or other stimulation occurs, the expression and activation of MMP are out of control, which may lead to the excessive degradation of ECM.

MMPs family can be divided into the following six categories based on the structure of their substrate, sequence similarity and characteristics of structural domain.

#### **2.1 Collagenases**

MMP-1, MMP-8, MMP-13 and MMP-18 are included. The main feature of these enzymes is to resolve collagen types I, II, III. Collagenase can also resolve some ECM components and other non-extracellular matrix molecules.

#### **2.2 Gelatinases**

Gelatinase A(MMP-2) and gelatinase B(MMP-9) are included. They are secreted or membrane-associated and must be proteolytically processed to their active form. MMP-2 can digest gelatin, collagen types IV, V, VIII, X laminin, elastin and fibronectin. The molecular weight of MMP-9 is 92KD which is the largest one. MMP-9 can be synthesized by various cells, such as astrocytes, vascular endothelial cells, microglia, neutrophils and macrophages. MMP-9 is mainly affected by the regulation of plasminogen activator and its substrates include gelatinase, collagen types IV, V and elastin<sup>[2]</sup>. Researches have shown that MMP-2 and MMP-9 may play a role in angiogenesis<sup>[3]</sup>, atherosclerosis<sup>[4,5]</sup> and ischemic brain injury<sup>[6]</sup>.

#### **2.3 Stromelysins**

Stromelysin-1(MMP-3) and stromelysin-2(MMP-10) have the same substrate specificity. However, the proteolytic efficiency of MMP-3 is higher than that of MMP-10. In addition to digesting extracellular matrix components, MMP-3 can also activate some pro-MMPs (e.g.

It is extremely important for pro-MMP-1 to produce MMP-1). MMP-11 is also called stromelysin-3, but it is often classified to other types because of its different structural sequence and substrate specificity.

#### **2.4 Matrilysins**

The structure of matrilysins lacks hemopexin domain. Matrilysin-1 (MMP-7) and matrilysin-2 (MMP-26) are included. In addition to degrading ECM, MMP-7 can process cell surface factors, such as pro TNF- $\alpha$  and E-cadherin. The matrilysin-2 (MMP-26) can also digest many ECM components.

#### **2.5 Membrane-type MMPs (MT-MMPs)**

There are six types of MT-MMPs, four types of MT-MMPs are type I transmembrane protein (MMP-14, -15, -16, -24), the other two types are GPI-ankyrin (MMP-17, -25). In addition to MT4-MMP, all other MT-MMPs can activate pro MMP-2. These enzymes can also digest some ECM components. MT1-MMP (MMP-14) has the activity to degrade collagen types I, II, III. MT5-MMP (MMP-24)

is mainly expressed in the cerebellum. MT6-MMP (MMP-25) is almost exclusively expressed in peripheral blood leucocytes, the original astrocytomas and the glioblastomas. However, it is not expressed in the meningiomas.

MT-MMPs have the following characteristics:

- a. Binding with cell membrane and provide the focus area for the decomposition and degradation of extracellular matrix protein;
- b. In the process of migration to the cell membrane, MT-MMPs are responsible for the cell activation of pro convertase pathway. Therefore, different from other types of MMPs, MT-MMPs have the proteolytic activity once it is inserted into the cell membrane.
- c. MT-MMPs have the substrate recognition sites of other types of MMPs and participate in an important pathway to activate other types of MMPs. It has been proved that MT1-MMP participates in the hydrolysis of MMP-2 and MMP-13.

#### **2.6 Other types of MMPs**

There are at least seven types of MMPs which are not mentioned in the previous text. MMP-12 is mainly expressed in macrophages and may take part in the migration of macrophages. MMP-12 can digest elastin and some other proteins. MMP-19 is identified through the liver c-DNA cloning and exists as T-cell antigens in the rheumatoid arthritis patients. Enamelysin (MMP-20) is mainly expressed in newly formed enamel and can digest amelogenin. The function of MMP-22 is not clear. MMP-23 is mainly expressed in the regeneration tissue and Epilysin (MMP-28) is mainly expressed in keratinocytes<sup>[7]</sup>.

### **3. Influence factors to the activation of matrix metalloproteinases**

The activation of MMPs is adjusted by three parts: gene transcription, zymogen activation and endogenous inhibitors.

#### **3.1 Gene transcription**

The genetic study has confirmed that there is promotor polymorphisms in MMP-1, -3, -9, -12 which affects the expression of MMPs gene<sup>[8]</sup>. The expression of MMPs mRNA is affected by

a variety of chemical factors, such as ECM components, carcinogens, oncogene, neural hormones, cytokines and corticosteroids. For example, TNF- $\alpha$  affects the expression of MMPs gene by affecting the multi-cell system transcription factors (the latter is combined with the specific response elements in the MMPs gene enhancer); Tissue-type plasminogen activator (tPA) and urokinase can induce the expression of MMP-9<sup>[9,10]</sup>. The signal transduction mechanism of MMPs' activation remains to be elucidated. Previous studies suggest that MAPK pathway may be relevant to MMPs gene expression, transcription factor (AP-1 and NF-KB) is closely relevant to activation of MMPs<sup>[10]</sup>. The signal transduction mechanisms in different types of cells or for different types of MMPs may be different.

Mengshol et al<sup>[11]</sup> have showed that p38, JNK and NF-KB are essential for IL-1 to induce cartilage cells to produce MMP-13. For the production of MMP-1, p38 is still essential while JNK and NF-KB are not essential. Studies have also shown that some factors such as glucocorticoid and TGF- $\beta$ , can inhibit MMP gene expression at the genetic level.

### 3.2 Zymogen activation

After translation and modification, the vast majority of MMPs mRNA is secreted to ECM in the form of zymogen. And it will be activated after hydrolysis of the propeptide domain. The activation mechanism found now includes stepwise activation, activation by MT-MMP, and cell activation. The initial activation of MMP is often associated with plasmin parenzyme, elastase, kallikrein. Among them, plasmin is considered to be the most powerful physiological activator in human body. In addition, SH-reagent (iodoacetic acid, HOCL, oxidized glutathione), denaturant (urea, SDS, NaSCN) and heat treatment have the ability to hydrolyze propeptide domain.

### 3.3 Endogenous inhibitors

The proteolytic activity of MMP is inhibited by non-specific and specific inhibitors. Non-specific inhibitors include  $\alpha$  2-macroglobulin,  $\alpha$  1-antiprotease and BB-94(batimistat). Specific inhibitors are the tissue inhibitors of metalloproteinases(TIMPs). TIMPs, which are the coding proteins of multi-gene family, are the natural inhibitors of MMPs. The expression of TIMPs is regulated during development and tissue remodeling. To date, a total of four types of TIMPs have been found in vertebrates. They form the high affinity complexes with activated MMPs at the molar ratio of 1:1 and inhibit the degradation of ECM by blocking the catalysis domain of MMPs. TIMP-1 inhibits the activity of most MMPs, except for MT1-MMP and MMP-2; TIMP-2 inhibits majority of MMPs except MMP-9. In addition, TIMP-2 can form the complexes with MT1-MMP in the cell membrane which may have the regulation to activate the proteolytic activity of MMP-2; TIMP-3 inhibits MMP-1, -2, -3, -9, -13; TIMP-4 inhibits MMP-1, -3, -7, -9 and is highly expressed in human heart. Corresponding to MMPs, TIMPs play a negative role in the regulation of the ECM metabolism. They can prevent the activation of MMPs, inhibit the function and affect the extent of protein breakdown and duration of injury<sup>[12]</sup>. In some excessive matrix degradation diseases, the imbalance between MMPs and TIMPs leads to a net increase in overall activity of MMPs<sup>[13]</sup>.

Although TIMPs play an important role in preventing excessive matrix degradation caused by MMPs, recent research shows that TIMP-1 and TIMP-2 are the multifunctional proteins with different biological functions. It has been reported that TIMP-1 and TIMP-2 demonstrate growth factor-like activity and inhibit the angiogenesis; while TIMP-3 is associated with apoptosis<sup>[7]</sup>.



TIMPs inhibit the MMPs activity by two steps. In the stage of zymogen activation, TIMP-2 can form a stable complex with pro MMP-2, as well as TIMP-1 and pro MMP-9. Therefore, they can impede the zymogen self-activation of pro MMP-1. In the stage of activated MMPs, both TIMP-1 and TIMP-2 can directly form a tight 1:1 complex with the activated MMPs and inhibit their activity. Naturally, the TIMP-MMP complexes may also be activated under certain conditions.

#### **4. Role of matrix metalloproteinase in cerebral ischemia**

In recent years, there is growing research interest on MMPs in central nervous system. In the normal central nervous system, MMP-2 and MMP-9 have been found in perivascular cells, brain vascular endothelial cells, astrocytes and microglia. The microglia in cultured rat can secrete MMP-9 once they are activated. Human hippocampal pyramidal cells can also synthesize MMP-9. It is reported that MMP-9 mRNA can be expressed in the developing mouse embryo brain, suggesting that MMP-9 is related to neurodevelopment. Studies also show that MMP-2 is related to the regeneration of axons. A growing number of scholars believe that MMPs play an important role in the pathologic processes of central nervous system diseases<sup>[5]</sup>.

##### **4.1 MMPs and pathogenesis of stroke**

Atherosclerosis is one of the underlying vascular risk factors for developing cerebrovascular disease. It is reported that the gelatinase of MMPs plays a key role in the process of intimal injury and the formation of atherosclerotic lesions. The endothelial cells covered on the plaque have the activity to express MMP-2 and MMP-9. The over-expression of MMPs can dissolve collagens and significantly change the proportion of plaque composition which leads to the relative increase in lipid content and increases the plaque instability. Then the plaque cap thinnings and splits, eventually leading to the occurrence of cerebral ischemia disease<sup>[14,15]</sup>. Studies have shown that MMP-8 and MMP-1, MMP-12 might play a decisive role in maintaining the stability of atherosclerotic plaques<sup>[16]</sup>. The rupture of atherosclerotic plaque partially depends on the activity and content of MMP-9<sup>[17]</sup>. Another study reported that the focal increase of MMP-9 activity was an early warning of acute plaque rupture.

##### **4.2 MMPs and ischemic brain injury**

In the normal state, cerebral vascular endothelial cells can not express or only express a small amount of MMP-9<sup>[18]</sup>. By the animal experiments, Fukuda<sup>[19]</sup> confirmed that ischemic brain tissue could produce some active proteases and these proteases led to the rapid and significant degradation of microvessels. Another studies suggested that cerebral ischemia and reperfusion could induce the expression of MMPs. Especially, the activity of MMP-2 and MMP-9 would increase, which was related to cerebral microvascular permeability, blood-brain barrier (BBB) permeability, BBB damage, inflammatory cell invasion and cerebral edema<sup>[6,12,13,20]</sup>. Gidday et al<sup>[21]</sup> showed that MMP-9 in ischemic brain tissue played a pro-inflammatory role which helped neutrophil leukocytes migrate from the blood circulation into the tissue. At first, MMP-9 caused BBB damage, then MMP-9 contributed to the proteolysis of microvascular basement membrane and eventually led to neurological

damage. The possible mechanism may be the following: In the ischemic brain tissue, MMP-9 is mainly expressed in vascular endothelial cells, the increased MMP-9 may act on the tight junctions and basement membrane among the BBB endothelial cells which leads to the BBB damage, increase of permeability and vasogenic brain edema. The worst is the occurrence of herniation<sup>[22]</sup>. In addition, the degradation of vascular basement membrane makes neutrophil leukocytes exudated to the brain tissue. MMP-2 and MMP-9 expressed by macrophages may contribute to their entry into the ischemic lesions and promote the wound healing after focal stroke <sup>[13]</sup>. However, MMP-9 expressed by neutrophil leukocytes may also contribute to the ischemic damage of brain. Zalewska et al<sup>[23]</sup> proposed that activated MMP-9 may act on a certain link of the cell apoptosis cascade in the hippocampus CA1 area after transient ischemic brain. Previous experimental studies also showed that MMP-9 could degrade the myelin basic protein of brain white matter and lead to the damage after ischemic brain<sup>[24]</sup>. Early studies have showed that injecting MMP-2 to the rat brain can contribute to the opening of BBB. MMP-2 and MMP-9 destroy the capillary tight junctions and basement membrane by protein hydrolysis after brain ischemia, thus leading to vasogenic brain edema. In 1996, Rosenberg et al<sup>[25]</sup> monitored of the expression of MMP-9 in rats with first onset cerebral infarction. They found the upregulated expression of MMP-9 4 hours after the occlusion of middle cerebral artery,. Within 12 hours and 24 hours, the expression of MMP-9 in the infarction site significantly increased which was consistent with the peak of the vasogenic brain edema, suggesting that MMP-9 played an important role in secondary brain damage and vasogenic edema. Montaner' et al<sup>[26]</sup> also showed that the activity of MMP-9 abnormally increased in the early stage of stroke and pro-inflammatory response, while the activity of MMP-2 appeared in the repair phase of vascular regeneration. Autopsy results showed that one week after infarction, MMP-9 was expressed in neutrophils, and one week later the macrophages expressing matrilysin and MMP-2 were observed. Montaner et al also found that the level of plasma MMP-2 was higher in the patients with previous history of stroke. The above results suggested that MMP-9 plays an important role in secondary brain damage and vasogenic brain edema, while MMP-2 is involved in tissue repair and nerve regeneration.

Previous studies also suggested that MMP-9 may also related to the hemorrhage translation after tPA or urokinase thrombolysis<sup>[24]</sup>.

#### **4.3 MMPs and cerebral ischemia reperfusion**

Animal model studies showed that 3 hours and 48 hours of reperfusion occurred after cerebral ischemia, BBB was opened and the opening reached to the peak in the 48th hour; The first opening was related to the increased level of MMP-2 while the second opening occurred in the stage when the level of MMP-9 was significantly higher; the content of MMP-2 reached to the peak 5 days after reperfusion and the repair process began at the same time; the content of TIMP-1 significantly increased in the 48th hour while that of TIMP-2 increased to the maximum on day 5<sup>[12]</sup>. These results suggested that reperfusion may affect MMPs and TIMPs, while MMPs and TIMPs promoted the reperfusion injury by complex ways. When the synthetic inhibitors of MMPs (BB-1101 ) was applied to inhibit MMPs, both the BBB's first opening and cerebral edema after reperfusion were prevented, suggesting that BBB's opening and brain edema after reperfusion were related to MMPs.

## 5. Effect of inhibiting matrix metalloproteinase on cerebral ischemia

Matrix metalloproteinase inhibitors have been used to treat cancer metastasis. Currently, many MMP inhibitors are also used in experimental models of neurological diseases<sup>[6]</sup>, such as bacterial meningitis, cerebral infarction and experimental allergic meningitis. Studies have shown that the content of MMPs increased after cerebral ischemia and reperfusion, exogenous inhibitors could reduce the ischemic and reperfusion injury<sup>[12,13]</sup>. Thus, MMPs may become a new potential target for stroke therapy and matrix metalloproteinase inhibitors can be used for treatment of cerebrovascular diseases<sup>[2]</sup>.

### 5.1 Matrix metalloproteinase inhibitors and cerebral ischemia

Previous studies have showed that the activated leukocytes could increase the reperfusion injury in the central nervous system. So, the drugs which can inhibit the leukocyte adhesion (including the intracellular adherence factor antibodies) have a neuroprotective effect. Matrix metalloproteinase inhibitors can combine with the divalent cation *in vitro*, inhibit the leukocytes function, and reduce the reperfusion injury.

Lee' et al<sup>[3]</sup> have shown that MMP inhibitors could inhibit the MMP-9 production in brain after stimulated and parenchymal angiogenesis. Horstmann<sup>[27]</sup> found that MMP-1 not only had the direct proteolytic capacity, but also played a role in the activation cascade of MMPs. It could crack collagen types I, II, III and be involved in the activation of MMP-2, MMP-9. Non-specific matrix metalloproteinase inhibitors are clustered in atherosclerosis tissues and inhibit the activity of MMP-9 in the carotid artery plaques, thereby stabilizing the easily broken atherosclerotic plaques. Matrix metalloproteinase inhibitors can also reduce the incidence of acute plaque rupture by reducing MMP-9 activity. The content of TIMPs is significantly higher in cerebral ischemia-reperfusion. They combine with the corresponding MMPs and prevent the activation of MMPs. They inhibit the function of MMPs, stabilize the ECM, significantly reduce the blood-brain barrier damage and the brain edema after ischemia<sup>[12]</sup>.

### 5.2 Matrix metalloproteinase inhibitors and therapies for cerebral ischemia

Previous studies suggested that MMP-9 monoclonal antibody may significantly reduce the infarction volume in a rat model of ischemia<sup>[13]</sup>. Clinical studies have also confirmed that MMP-9 is related to the total infarction volume. It is reported that matrix metalloproteinase inhibitors and MMPs neutralizing antibodies can reduce the vasogenic brain edema and infarction volume<sup>[26]</sup>. In addition, MMPs inhibitors are also effective in preventing atherosclerosis and the ischemic brain damage.

rt-PA and urokinase are effective drugs for acute ischemic stroke. However, the clinical application of thrombolytics is limited by the narrow therapeutic time window and the complication of bleeding after thrombolysis. But if we combine rt-PA or urokinase with the MMP inhibitors (BB-94 or doxycycline) in thrombolysis treatment, the incidence of hemorrhage and the amount of hemorrhage after thrombolysis may be decreased and the thrombolytic time window will be prolonged<sup>[28,29]</sup>. This is because that if MMPs inhibitors are used before the application of rt-PA or urokinase, MMP-2, MMP-3 and MMP-9 (which have the potential damage for BBB) would be inhibited. BBB would be closed and the integrity of blood vessels would be maintained, thus might increase the safety of the thrombolytic therapy<sup>[6,30]</sup>.



## 6. Conclusion

MMPs may play an important role in the brain ischemia and reperfusion by degrading the ECM and destroying the blood-brain barrier which can lead to the vasogenic brain edema and secondary brain injury. The matrix metalloproteinase inhibitors and MMPs neutralizing antibodies can reduce the vasogenic brain edema and infarction volume. In addition, MMPs inhibitors are also effective in preventing atherosclerosis and the ischemic brain damage. Thus, MMPs may become a new potential target for stroke therapy and matrix metalloproteinase inhibitors can be used for the treatment of cerebrovascular diseases.

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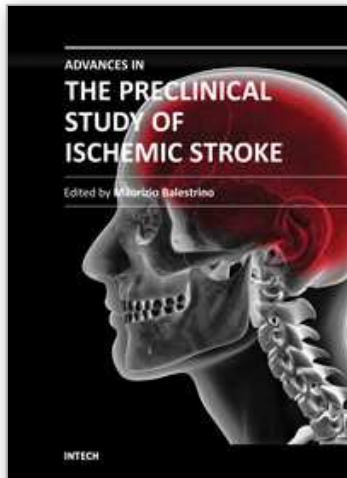
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## **Advances in the Preclinical Study of Ischemic Stroke**

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This book reports innovations in the preclinical study of stroke, including - novel tools and findings in animal models of stroke, - novel biochemical mechanisms through which ischemic damage may be both generated and limited, - novel pathways to neuroprotection. Although hypothermia has been so far the sole "neuroprotection" treatment that has survived the translation from preclinical to clinical studies, progress in both preclinical studies and in the design of clinical trials will hopefully provide more and better treatments for ischemic stroke. This book aims at providing the preclinical scientist with innovative knowledge and tools to investigate novel mechanisms of, and treatments for, ischemic brain damage.

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