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Matrix Metalloproteinases, New Insights into the Understanding of Neurodegenerative Disorders

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Abstract

Matrix metalloproteinases (MMPs) are a subfamily of zinc-dependent proteases that are re-sponsible for degradation and remodeling of extracellular matrix proteins. The activity of MMPs is tightly regulated at several levels including cleavage of prodomain, allosteric activation, com-partmentalization and complex formation with tissue inhibitor of metalloproteinases (TIMPs). In the central nervous system (CNS), MMPs play a wide variety of roles ranging from brain devel-opment, synaptic plasticity and repair after injury to the pathogenesis of various brain disorders. Following general discussion on the domain structure and the regulation of activity of MMPs, we emphasize their implication in various brain disorder conditions such as Alzheimer's disease, multiple sclerosis, ischemia/reperfusion and Parkinson's disease. We further highlight accumu-lating evidence that MMPs might be the culprit in Parkinson's disease (PD). Among them, MMP-3 appears to be involved in a range of pathogenesis processes in PD including neuroinflamma-tion, apoptosis and degradation of α-synuclein and DJ-1. MMP inhibitors could represent poten-tial novel therapeutic strategies for treatments of neurodegenerative diseases.

Key Words: Matrix metalloproteinases, MMP-3, Parkinson's disease, Microglia, Neurodegenerative disorders

The matrix metalloproteinases (MMPs) are zinc and calcium-dependent endopeptidases which belong to the metzincin superfamily like the astacins, serralysins, reprolysins, and adamalysins or disintegrin metalloproteinases (ADAMs). Since its first discovery by Jerome Gross and Charles Lapiere in 1962 (Gross and Lapiere, 1962), MMPs have constituted a large family of pro-teases. Currently, 24 MMP genes and 23 MMP proteins have been reported because two iden-tical genes in chromosome 1 encode MMP-23. They are a group of proteolytic enzymes that are involved in degradation and remodeling of extracellular matrix (ECM) and basement membrane proteins. Accumulating evidence, however, suggests that MMPs are also participating in a range of physiological processes such as inflammation, immunity, neurite growth and bone remodeling through processing bioactive molecules including cell surface receptors, apoptotic ligands, pro-neurotrophic factors and chemokines/cytokines (Yamamoto *et al.*, 1999; Lee *et al.*, 2001; Van Lint and Libert, 2007).

In the central nervous system (CNS), MMPs play a fundamental role in CNS development in-cluding neurogenesis, myelogenesis, and axonal guidance as well as maintaining normal brain functions such as synaptic plasticity, learning and memory. The basic biology and roles of MMPs in the CNS have been extensively discussed by recent reviews (Yong, 2005; Agrawal *et al.*, 2008). In this review, we provide an overview of the basic biochemical characteristics, regulation of activation and biological functions of MMPs, and then discuss their role in the CNS mainly focusing on brain pathologic conditions including neurodegeneration, neuroinflammation and ischemia.

MODULAR DOMAIN STRUCTURE AND SUBFAMILIES

The MMP members share structural homologies including common N-terminal propeptide and catalytic domains. In addition, subfamilies are categorized by other domains such as fibro-nectin-like repeats, C-terminal hemopexin-like domains, Ig-like domain and transmembrane domains (Fig. 1). All MMPs have an N-terminal signal peptide directing them to the secretory pathway. Except membrane-type MMPs (MT-MMPs), all MMPs are destined to be released into the extracellular space as inactive pro-enzyme forms called zymogens. The propeptide domain, consisting of about 80 amino acids, has a conserved PRCG (V/N)PD amino acid sequence. The cysteine contained within this sequence interacts with zinc

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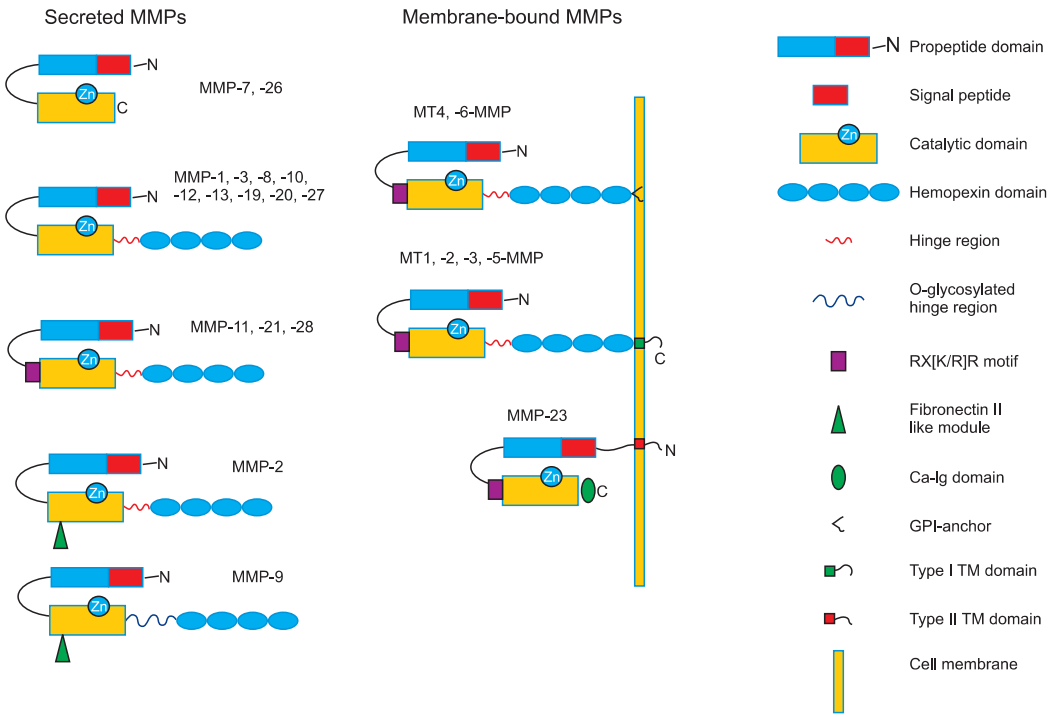

Fig. 1. Domain structure of matrix metalloproteinases family. All MMPs consist of a N-terminal signal peptide and a propeptide domain followed by a C-terminal catalytic domain. A propeptide domain contains a cysteine switch which forms complex with catalytic zinc in a catalytic domain inhibiting their enzymatic activity. MMP-7 and -26 have only the minimal domain. Most of MMPs have a linker (hinge-region) and hemopexin like do-main at the C-terminal to a catalytic domain. MMP-11, -21 and -28 have a furin-activating motif, RX[K/R]R, at the C-terminal end of their propeptide domains. Two gelatinases, MMP-2 and -9, contain three fibronectin II like repeats in the catalytic domains. MMP-9 is the only MMP which has a heavily O-glycosylated hinge region. All membrane-anchored MMPs contain a furin-activating motif. MT4, -6-MMPs are anchored to the plasma membrane through GPI-anchor. MT1, -2, -3 and-5-MMPs are bound to the cell membrane through type I transmembrane domain while MMP-23 is through type II transmembrane domain. The C-terminal of MMP-23 contains cysteine array (Ca) and immunoglobulin (Ig)-like domain replacing hemopexin domain.

in the catalytic domain to suppress its own proteolytic activity (Cysteine-switch) (Van Wart and Birkedal-Hansen, 1990; Becker *et al.*, 1995). The catalytic domain consisting of about 160-170 amino acids has a HEXXHXXGXXH, catalytic zinc-binding motif and a conserved methionine, which form a unique “Met-turn” struc-ture (Bode *et al.*, 1993). The catalytic domain also requires an additional structural zinc and 2 to 3 calcium ions for the stability and the enzymatic activity. MMP-7 and -26 consist of this minimal domain, propeptide and catalytic domains. C-terminal structures after catalytic domains are much more variable conferring MMPs substrate specificity and the interface for interaction with TIMPs (tissue inhibitor of metalloproteinases). Most MMPs have a linker (hinge region) and a hemopexin-like domain in addition to a minimal domain. The hinge region of most MMPs consists of 10-30 amino acids that connects a catalytic domain and a hemopexin-like domain. C-terminus hemopexin domain in collagenase (MMP-1, interstitial collagenase) is crucial for cleavage of triple helical interstitial collagen (Bode, 1995). The two gelatinases (MMP-2 and MMP-9) have additional three fibronectin-like repeats in their catalytic domain that interact with collagens and gelatins, respectively (Allan *et al.*, 1995; Steffensen *et al.*, 1995). Additionally, MMP-9 has a heavily O-glycosylated hinge region that is responsible for fine tuning its bioavailability (Van den Steen *et al.*, 2006). The membrane-type MMP subfamily has a transmembrane domain that anc-hors MMPs to the cell surface. MT1 through 6-MMPs and MMP23 belong to this subfamily. Three secreted MMPs (MMP-11, -21, -28) and all MT-MMPs have a basic RX[K/R]R motif at the C-terminal end of propeptide domain which can be cleaved by intracellular furin.

Regulation of MMPs

Since MMPs are able to degrade all the protein constituents in the extracellular matrix, their pro-teolytic activity has to be tightly controlled under normal conditions to prevent tissue destruction (Yong *et al.*, 1998). There are the following ways to regulate the activity of MMPs: 1) gene tran-scriptional regulation; 2) activation of proenzyme by removing the propeptide domain; 3) the in-teraction with tissue inhibitor of metalloproteinases (TIMPs); 4) pericellular or intracellular com-partmentalization; 5) allosteric activation; 6) oxidative modification. Many MMP genes are inducible by a wide variety of effectors including growth factors, cytokines such as TNF-α and IL-1β, chemical agents, physical stress, oncogen products and interestingly, cell-cell or cell-ECM inte-raction (Ries and Petrides, 1995; Vincenti, 2001; Vincenti and Brinckerhoff, 2007). Their gene ex-pression also can be suppressed by other factors such as TGF-β, retinoic acids and glucocorti-coids (Osteen *et al.*, 1996; Li *et al.*, 2011; Ye *et al.*, 2011). These external effectors trigger the var-ious intracellular signal transduction

pathways including MAPKs, JAK-STAT or NF-κB pathways leading to the induction of MMP genes (Korzus *et al.*, 1997; Kheradmand *et al.*, 1998; Reunanen *et al.*, 1998). Although the activator protein-1 (AP-1) binding site in the MMP promoters has been considered as a main transcriptional regulator in most MMPs (Auble and Brinckerhoff, 1991; Kim *et al.*, 2008; Liu *et al.*, 2010; Singh *et al.*, 2010), MMP-8, -11 and -21 are lack of AP-1 cis-element in their promoter. Another group of promoters of MMP-2, -14, and -28 does not have TATA box and are mainly regulated by ubiquitous Sp-1 family of transcriptional factor (Yan and Boyd, 2007).

The MMPs are initially expressed as inactive zymogens in which a zinc atom in the catalytic domain interacts with a cysteine residue (Cysteine switch) (Van Wart and Birkedal-Hansen, 1990). Activating factors cause the disruption of the Cys-Zn^{2+} interaction, which renders pro-MMPs par-tially active. Then, the partially active enzyme auto-catalyzes the propeptide region and make the enzyme fully active (Van Wart and Birkedal-Hansen, 1990). Activation of all MT-MMPs and furin-activated MMPs is well characterized intracellular event which leads to immediate catalytic activation of MMPs upon appearing on the cell surface or secretion. This process is achieved by serine proteinase, furin that is localized in the *trans*-Golgi network. Remaining MMPs are se-creted as inactive zymogens and activated by serine proteinases like plasmin or other MMPs (MMP-3 and -14). Plasmin that is activated from plasminogen by the action of tissue- or urokinase-plasminogen activator is an important physiologic activator of pro-MMPs. Activation of proMMP could be achieved without involving proteolytic cleavage of prodomain by the mechanism called allosteric activation. Both proMMP-9 and -2 could be activated upon binding to their substrates, gelatin or collagen IV and α2 chain of collagen VI, respectively (Bannikov *et al.*, 2002; Freise *et al.*, 2009). Reactive oxygen species (ROS), peroxynitrite, glutathione could activate MMPs without removal of prodomains through modification of thiol in their catalytic core which lead to disruption of thiol-zinc interaction (Okamoto *et al.*, 2001; Gu *et al.*, 2002; McCarthy *et al.*, 2008).

Tissue inhibitors of metalloproteinases (TIMPs) are the endogenous regulators of MMP activ-ities in the tissue (Vincenti, 2001). Following activation, the activities of MMPs are regulated by the formation of non-covalent complexes with TIMPs. Four homologous TIMPs have been iden-tified to date (Yong *et al.*, 1998). They have about 190 amino acids with longer N-terminal and shorter C-terminal domain. N-terminal domain itself is fully functional in terms of inhibition of MMPs by chelating their catalytic zinc atom. The expression of TIMPs is also regulated at the transcriptional level. For example, TIMP-1 contains AP-1 site in its promoter (Ulisse *et al.*, 1994). This implies that the expression of MMPs and TIMPs can be regulated coordinately by the same signal. However, the MMPs and TIMPs can also be regulated in opposite patterns. It has been shown that TGF-β induces the increased expression of TIMP-1 and suppresses collagenase and stromelysin (MMP-3) expression in fibroblasts and endothelial cells (Edwards *et al.*, 1987). Since a number of studies have demonstrated that excessive production of MMPs are involved in the pathology of many inflammatory and malignant diseases, the balance between the MMPs and their inhibitors is thought to be important in the maintenance of normal physiologic conditions.

Subcellular localization and regulation

Accumulating evidence suggests that they are localized to various intracellular sites including nucleus, cytoplasm and mitochondria. Recent studies have identified diverse intracellular sub-strates for MMPs and its novel biological roles. Although the molecular mechanisms are poorly understood, nuclear localization of MMPs has been widely observed in various types of cells including cardiac myocytes, fibroblasts, neuronal cells, pulmonary artery endothelial cells and hepatocytes. Currently nuclear localization of MMP-2, -3, -9, -13 and MT1-MMP has been reported. MMP-2 and -3 have nuclear localization sequence (NLS) in the C-terminus and catalytic domain, respectively (Kwan *et al.*, 2004; Si-Tayeb *et al.*, 2006). Nuclear localization of MMP-2 in cardiac myocytes has been observed, highlighting its role in degradation of Poly (ADP-ribose) polymerase (PARP) (Kwan *et al.*, 2004). More recently, it has been reported that cigarette-smoke induced MMP-2 expression in the nucleus of pulmonary artery endothelial cells, causing apoptosis (Aldonyte *et al.*, 2009). In the ischemic neurons, increased proteolytic activity of MMP-2 and -9 in the ischemic neuronal nuclei at the early phase is responsible for DNA fragmentation after reperfusion. This is caused by MMP-mediated degradation of PARP-1 and X-ray cross-complementary factor 1 (XRCC1) (Yang *et al.*, 2010). Exclusive expression of cleaved active MMP-3 in the nucleus was demonstrated, suggesting removal of prodomain is crucial for nuclear translocation of MMP-3 (Si-Tayeb *et al.*, 2006). Interestingly, transcription factor-like function of MMP-3 was shown in chondrocytes. Binding of nuclear MMP-3 to a transcription enhance sequence in the connective tissue growth factor (CCN2/CTGF) enhances transcriptional activity CCN2/CTGF (Eguchi *et al.*, 2008). Extensive analysis of nuclear MMP-3 associated proteins (NuMAPs) identified several candidates such as HP1γ and NCoR1 whose function on transcrip-tional regulation of CCN2/CTGF could be modulated by MMP-3. Nuclear localization of MMP-13 was also reported in oxygen and glucose deprived neuronal cells and after cerebral ischemia of rats and humans (Cuadrado *et al.*, 2009). Both MMP-2 and MT1-MMP was observed in the nuc-leus of hepatocellular carcinoma (HCC) and aggressiveness of HCC including poor prognosis and large tumor expands was associated with nuclear localization of MT1-MMP (Ip *et al.*, 2007).

Increasing number of studies indicate that various MMPs have been also found in the cytosol. We have recently demonstrated that active MMP-3 is expressed in the cytosol of dopaminergic cells and plays role in apoptosis and is involved in cleavage of α-synuclein and DJ-1, modulating their functions (Choi *et al.*, 2008; Choi *et al.*, 2011a; Choi *et al.*, 2011b). This will be discussed more in detail later in this review. Mitochondrial localization and perinuclear accumulation of MMP-1 was shown in epithelial cells conferring resistance to apoptosis (Limb *et al.*, 2005). Intra-cellular role of MMP-2 has been highlighted in acute myocardial ischemia and reperfusion model demonstrating that MMP-2 is responsible for cleavage of troponin I (TnI), the contractile protein regulatory element, and the cytoskeletal protein α-actinin. Peroxynitrite is a key mediator for the activation of MMP-2 in this model (Wang *et al.*, 2002a; Wang *et al.*, 2002b; Sung *et al.*, 2007). Another example is MMP-26 which is mainly retained inside cells despite of its N-terminal signal peptide. Prodomain of MMP-26 contains a unique motif, PHCGVPD, that is assumed to in-crease au-

tocatalytic activity leading intracellular activation (Marchenko *et al.*, 2004).

MMPs in the Central Nervous System (CNS)

A range of MMPs play multiple roles in the development of the CNS, maintaining normal physiological functions, recovery after injury and the pathogenesis of brain diseases. During development of the CNS, various MMPs and TIMPs are expressed in various types of cells including neurons, astrocytes, oligodendrocytes and microglia, being involved in neurogenesis, axonal guidance, angiogenesis and myelinogenesis (Cañete Soler *et al.*, 1995; Vaillant *et al.*, 2003; Larsen *et al.*, 2006). In the adult brain, MMPs are likely involved in a range of pivotal processes like migration of neurons and glia, synaptic plasticity, learning and memory, myelin turnover and angiogenesis through extracellular matrix (ECM) remodeling (Szklarczyk *et al.*, 2002; Meighan *et al.*, 2006; Ogier *et al.*, 2006; Bozdagi *et al.*, 2007). They are also important in the repair of adult brain after injuries such as spinal cord injury and stroke (Larsen *et al.*, 2003; Lee *et al.*, 2006). The normal functions of MMPs in the CNS were extensively discussed in the recent review by Agrawal *et al.* (2008).

MMPs in Neurodegenerative diseases

Recently, an increasing amount of evidence suggests that MMPs may play an crucial role in the pathogenesis of several neurodegenerative disorders including multiple sclerosis, Alzheimer's disease, Parkinson's disease, malignant glioma, neuroinflammation and ischemia (Forsyth *et al.*, 1999; Lorenzl *et al.*, 2002; Lorenzl *et al.*, 2003; Yong *et al.*, 2007; Candelario-Jalil *et al.*, 2009; Choi *et al.*, 2011b; Shin *et al.*, 2012).

The roles for MMPs in the pathogenesis of multiple sclerosis (MS) have been widely studied. MS is a brain inflammatory disorder demonstrating destruction of myelin sheath in the brain and spinal cord. Infiltration of various types of peripheral immune cells such as T cell, dendritic cells and monocyte/macrophages into the brain parenchyma accompanied with breakdown of blood-brain barrier (BBB) are major pathologic characteristics of MS. Upon entering in the CNS, they result in severe destruction of myelin and axon in cooperation with parenchymal resident cells including astrocytes and microglia. Alterations of various MMPs like MMP-1, -2, -3, -7, -9, -12, -13, -14 and -19 have been reported in MS. The MMPs were detected in the cerebrospinal fluid (CSF) of patients with MS or its animal model, experimental allergic encephalomyelitis (EAE) (Yushchenko *et al.*, 2000; Fainardi *et al.*, 2009). MMP-9 has been most extensively studied among them. Enhanced expression of both MMP-7 and -9 in parenchymal macrophages and small blood vessels were demonstrated in postmortem human MS brain (Cossins *et al.*, 1997). The ratio of MMP-9/TIMP-1 in serum was elevated in relapsing-remitting MS patients and is cor-related with increase in positive MRI lesions (Waubant *et al.*, 1999). In EAE model, it has been shown that MMP-9 plays a key role in BBB disruption and trafficking of leukocytes into the brain parenchyma (Agrawal *et al.*, 2006). Higher level of MMP-2 in serum and CSF of MS patients was also reported (Avolio *et al.*, 2003; Benesová *et al.*, 2009). The increased expressions of MMPs were shown in microglia and astrocytes in the brain lesions of MS patients (Cuzner *et al.*, 1996; Maeda and Sobel, 1996). In animal studies, the application of several MMP inhibitors elicit reduced symptoms and severity of EAE (Hewson *et al.*, 1995). The molecular mechanisms of MMPs in the pathogenesis of MS include the direct destruction of myelin protein, BBB disruption and chemokine/cytokine activation. Myelin protein could be a direct proteolytic substrate for MMPs. Activated leukocytes from peripheral blood or CNS resident cells could release MMPs which target myelin protein resulting in fragments. Fragmented myelin protein further activate neighboring immune cells releasing MMPs. This forms a vicious loop for activation/destruction leading to demyelinated axons (Starckx *et al.*, 2003; Opdenakker *et al.*, 2006; Candelario-Jalil *et al.*, 2009). MMP-mediated cleavage of cytokines/chemokines and its role in immune modulation have been investigated in MS patients and EAE model (Sellebjerg and Sørensen, 2003). MMPs are also involved in the conversion of pro-TNF-α to mature secreted protein and blood-brain barrier (BBB) disruption (Gearing *et al.*, 1994; Gasche *et al.*, 2001).

The role of MMPs in cerebral ischemia and stroke was also investigated both in animal mod-els and human stroke. Dual roles of MMPs have been observed after brain ischemia: propagat-ing neuronal death and apoptosis at the early phase of injury through disruption of ECM and opening the BBB; late-phase repairing by promoting angiogenesis and neurogenesis. At the early stage after stroke, transient activity of MMP-2 which is responsible for reversible opening of the BBB has been reported in rodent and non-human primates (Chang *et al.*, 2003; Yang *et al.*, 2007). Tight junction protein, claudin-5 is degraded by MMP-2. MMP-9 is activated and implicated in more extensive cerebral vascular damage at the later phase. Thus, early intervention within 3 h post reperfusion with MMP inhibitors showed the prevention of BBB disruption (Yang *et al.*, 2007). In addition, cerebral infarct size was significantly reduced by treatment with MMP inhibitors or in MMP-9 knockout but not in MMP-2 knockout mice (Asahi *et al.*, 2000; Asahi *et al.*, 2001). Interestingly, NO produced in cerebral ischemia and reperfusion can activate pro-MMP-9 by S-nitrosylation which in turn, causes direct neuronal apoptosis (Gu *et al.*, 2002). In reperfusion injury following ischemia in rat brain, the expression of MMP-3 is induced in both microglia and apoptotic neurons and it is suggested that MMP-3 may play an important role in disrupting the BBB together with other MMPs such as MMP-2 and -9 (Rosenberg *et al.*, 2001).

Malignant gliomas are the most common malignant brain tumors that are extremely invasive. The strong correlation between the invasiveness of glioma cells and MMPs such as MMP-2, MMP-9 and MT-MMPs has been shown both *in vitro* and *in vivo* (Rao *et al.*, 1996; Uhm *et al.*, 1996; Yamamoto *et al.*, 1996). The expression of MMPs are up-regulated in many gliomas (Forsyth *et al.*, 1999). In contrast to MMPs, the expression of TIMP-1 and -2 is decreased, sug-gesting disruption of the balance between MMPs and their inhibitors may contribute to pathology of malignant gliomas (Mohanam *et al.*, 1995). It was also shown that MMPs inhibitor induces apoptosis of malignant gliomas (Yoshida *et al.*, 2003). MMP-9 plays a key role in regulating in-vasiveness of malignant glioma cells and invasiveness is largely attributed to the poor prognosis. Recent study indentified miRNAs, miR-491-5p, as a direct regulator of MMP-9 expression in U251 and U87 glioma cells, demonstrating that miR-491-5p reduces MMP-9 expression

and inhibits cellular invasion (Yan *et al.*, 2011). Recently, other MMPs like MMP-1, -11 and -19 were appeared to be of importance for the development of high-grade astrocytic tumor and may be promising targets for therapy (Stojic *et al.*, 2008).

Alzheimer's disease (AD) is the most common neurodegenerative disease that accounts for 50-80% of dementia. Pathologically, AD is characterized by gross atrophy of affected cerebral cortex resulted from neuronal loss and synaptic degeneration. The temporal, parietal lobe and parts of the frontal cortex and cingulate gyrus are most widely affected (Wenk, 2003). The presence of extracellular amyloid plaques and intracellular neurofibrillary tangles is the most charac-teristic pathologic feature of AD (Tiraboschi *et al.*, 2004). Extracellular plaques consist of about 40 amino-acid long small peptides called beta-amyloid (Aβ). Aβ is generated by enzymatic cleavage of amyloid precursor protein (APP), a transmembrane protein. The process involved in proteolytic cleavage of APP is still waiting for elucidation. One of these fragments, Aβ1-42, gives rise to fibrils of Aβ, which further aggregates outside neurons in dense masses of protein known as senile plaques (Ohnishi and Takano, 2004; Tiraboschi *et al.*, 2004). It has been shown that MMPs play a dual role in the pathogenesis of AD. MMPs may directly de-grade Aβ resulting in reduction in Aβ deposit (Yan *et al.*, 2006; Miners *et al.*, 2008). On the other hand, MMPs such as MMP-2, -3 and -9 could be induced by Aβ in microglia, astrocytes or vas-cular smooth muscle cells contributing to brain parenchymal destruction. MMP-9 is overexpressed in AD brain tissue compared to controls and it can degrade synthetic 40-residue long Aβ protein *in vitro* (Backstrom *et al.*, 1992; Roher *et al.*, 1994). MMP-2 has also been shown to degrade 40- to 42-residue long Aβ purified from AD brain tissue (Roher *et al.*, 1994). In AD brains, MMP-3 is expressed predominantly in brain white matter. Double immunostaining of MMP-3 and GFAP in the white matter suggests that astrocytes may be a major source of MMP-3 in AD brain (Yoshiyama *et al.*, 2000). MMP-3 immunoreactivity was also detected in the interstitium between myelinated axons and senile plaques of patients with AD (Yoshiyama *et al.*, 2000). It has been also demonstrated that Aβ1-42 induces MMP-3, -12 and -13 expressions in microglia in PI3K-dependent manner (Ito *et al.*, 2007). Recent analysis of CSF from AD patients indicated that MMP-3 is significantly elevated while MMP-2 is decreased (Horstmann *et al.*, 2010). These data suggest that MMPs may be involved in the processing of APP and the pathogenesis of AD.

Parkinson's disease (PD) is the second most common neurodegenerative disorders characterized by motor symptoms including resting tremor, rigidity, bradykinesia and postural instability resulting from selective degeneration of dopaminergic neurons in the substantia nigra pars compacta. Accumulating evidence suggests MMPs as a major culprit in the pathogenesis of PD. Expression of MMPs such as MMP-1, -2 and -9 as well as TIMP-1 and -2 in the substantia nigra (SN) of postmortem PD brain tissue was first reported by Lorenzl *et al.* showing alterations in MMP-2 and TIMP-1 in the SN of PD patients (Lorenzl *et al.*, 2002). Since then, a number of studies including our own have demonstrated that MMPs are implicated in a range of pathophysiological processes of PD such as microglial activation, inflammation, direct dopaminergic apopto-sis, disruption of the BBB and modulation of α-synuclein pathology by cleavage (Kim *et al.*, 2005; Choi *et al.*, 2008; Joo *et al.*, 2010; Kim and Hwang, 2011).

MMP-3 AND PARKINSON'S DISEASE

MMP-3 was first noted as a neutral proteinase in human cartilage in 1974 (Sapolsky *et al.*, 1974) and in rabbit bone fibroblast culture (Werb and Reynolds, 1974). The name 'stromelysin' was introduced by Chin *et al.* (1985), but it has also been named 'transin' and 'collagenase activating protein' (Chin *et al.*, 1985; Matrisian *et al.*, 1985; Treadwell *et al.*, 1986). MMP-3 has a broad spectrum of substrates such as collagens, gelatin, elastin, laminin, casein, fibronectin, α1-AT, MBP and TNF-α precursor (Chandler *et al.*, 1997). In addition, MMP-3 also can play a central role in the cleavage of other pro-form of MMPs including MMP-1, -2, -7, -8, -9, -13 leading to active forms (Chandler *et al.*, 1997). MMP-3 has been implicated in inflammatory dis-orders including rheumatoid arthritis (RA), multiple sclerosis and AD (Zucker *et al.*, 1994; Maeda and Sobel, 1996; Yoshiyama *et al.*, 2000). MMP-3 levels are significantly in-creased both in serum and synovial fluid in RA patients (Zucker *et al.*, 1994; Ishiguro *et al.*, 1996). Serum MMP-3 levels are decreased by anti-TNF-α therapy in RA, suggesting that TNF-α may induce MMP-3 expression (Catrina *et al.*, 2002). It has also been shown that MMP-3 levels in synovial fluid (SF) are significantly related with the concentration of soluble FasL (sFasL) in SF of patients with RA, which indicates that MMP-3 may regulate the shedding of FasL (Matsuno *et al.*, 2001). The role of MMP-3 as a mediator of neuroinflammation responsible for dopaminergic neuronal degeneration was demonstrated. Active MMP-3 is released from neurons undergoing apoptosis after stress. Then it activates microglia to secrete pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 as well as reactive oxygen species (ROS) that subsequently cause neighboring neuronal death. NNGH, a specific inhibitor of MMP-3, largely attenuates microglial activation and neuronal death (Kim *et al.*, 2005). MMP-3 is also involved in LPS-mediated microglial activation. MMP-3 and -9 are responsible for mitogen-activated protein kinases (MAPKs)- and NF-κB-mediated proinflammatory cytokines release from LPS-stimulated microglia (Woo *et al.*, 2008).

Expression and activity of MMP-3 have been shown in a range of rodent PD models and postmortem PD brain. Increase in MMP-3 expression in the SN was observed in rodent model of PD, rats injected with 6-hydroxydopamine (6-OHDA) (Sung *et al.*, 2005). Recent study showed that MMP-3 is expressed in Lewy bodies (LBs), a pathologic hallmark of PD (Choi *et al.*, 2011b). Increased immunoreactivity of MMP-3 was also observed in tyrosine hydroxylase (TH)-positive dopaminergic neurons in the SN of mice administered with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a selective dopaminergic neurotoxin. In this study, significant reductions in MPTP-mediated dopaminergic neuronal degeneration as well as microglial activation were observed in MMP-3 knockout mice suggesting that MMP-3 is a key player in dopaminergic neuronal degeneration (Kim *et al.*, 2007). Rat injected with LPS in the SN shows microglial acti-vation and dopaminergic neuronal degeneration. In this model, *MMP*-3 expression in the SN was significantly increased 24 h and 48 h after LPS injection (McClain *et al.*, 2009). In contrary to the general belief that the inactive proform of MMP3 is activated in extracellular space, emerging evidence implies the existence of a mechanism of intracellular activation of MMP-3. Under apoptotic stress, MMP-3 is induced and generates the proform which is subsequently cleaved to the catalytically active MMP-3 by a

serine protease other than furin. Intracellular enzymatic activity of MMP-3 is directly responsible for apoptosis of dopaminergic cells (Choi *et al.*, 2008). Recently, intracellular targets for MMP-3 that are clearly linked to the pathogenesis of PD have been investigated (Sung *et al.*, 2005; Choi *et al.*, 2011a; Choi *et al.*, 2011b). Mutations in SNCA that encodes α-synuclein were the first reported genetic cause in familiar forms of PD (Polymeropoulos *et al.*, 1997). Later, α-synuclein aggregates were identified as the major com-ponent in Lewy bodies (LB), intracellular protein inclusions, a pathologic hallmark of PD (Spillantini *et al.*, 1997). α-synuclein is cleaved by MMP-3 generating fragmented peptides that forms more toxic aggregates than the intact α-synuclein. MMP3-cleaved species (N-terminal) in extra-cellular space were cytotoxic when they were added to the cell culture media (Sung *et al.*, 2005). The presence of C-terminally truncated α-synuclein has been reported in Lewy bodies of sporadic PD and Lewy body dementia (Baba *et al.*, 1998; Liu *et al.*, 2005). C-terminal truncation is also observed preferentially in A53T transgenic mice showing motor symptoms (Lee *et al.*, 2002). Various lengths of the truncated forms of α-synuclein were reported (Li *et al.*, 2005; Liu *et al.*, 2005). About 15% of α-synuclein in Lewy bodies is truncated forms and incomplete degradation produced highly amyloidogenic fragments (Baba *et al.*, 1998; Campbell *et al.*, 2001). More recently, it has been shown that MMP-3 cleaves WT and mutant α-synuclein generating slightly different fragmented peptide profiles. MMP-3 gives rise to C-terminally truncated peptides of amino acids 1-78, 1-91, and 1-93 and that A53T mutant α-synuclein generates significant in-crease of these peptides. Both *in vivo* and *in vitro* experiments shows that these peptides cause stronger dopaminergic neuronal death compared to the intact α-synuclein despite less aggregation formation (Choi *et al.*, 2011b). The results suggest that MMP-3 could modulate the aggrega-tion property of α-synuclein contributing to the pathogenesis of PD. In addition, DJ-1 is also fragmented by MMP-3. DJ-1 is a protein belonging to ThiJ/PfpI/DJ-1 superfamily. Two mutations were identified within the *DJ*-1 gene in two families linked to the recessive PD PARK7 locus (Bonifati *et al.*, 2003). One is a chromosomal deletion of 4 kb leading to the absence of DJ-1 expression, while the other is a L166P point mutation in which a highly conserved leucine was substituted for a proline. The latter destabilizes DJ-1 protein and promotes its degradation through the ubiquitin-proteasomal system (Miller *et al.*, 2003). Active MMP-3 cleaves DJ-1 caus-ing impairment of its antioxidant function. While MPTP administration significantly diminished

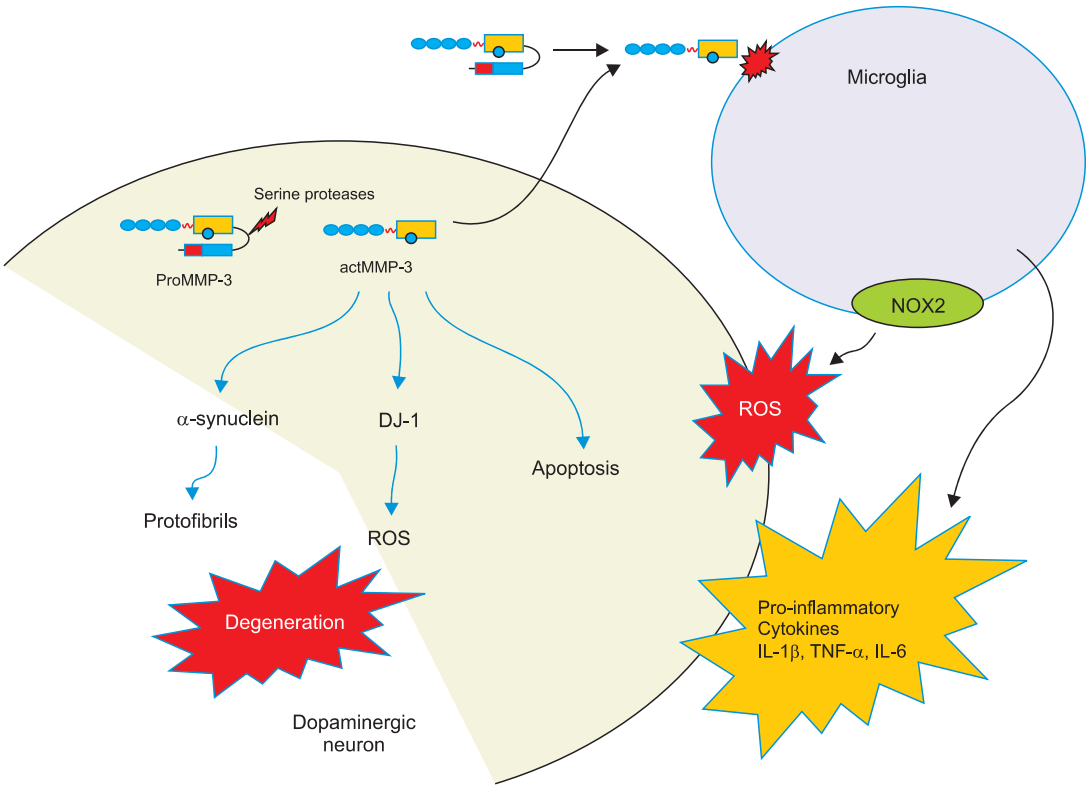

Fig. 2. The role of MMP-3 in the pathogenesis of Parkinson's disease. Emerging evidence suggests that MMP-3 plays a key role in dopaminergic neuronal degenera-tion. Under stress conditions, MMP-3 is induced in dopaminergic neurons generating proMMP-3. Activation of MMP-3 might be achieved in cytoplasm as well as extracellular space. Catalytically active MMP-3 (actMMP-3) triggers microglial activation resulting in release of proinflammatory cytokine such as IL-1β, TNF-α and IL-6. Microglial substrates for act MMP-3 and signaling event leading to microglial activation are yet to be elucidated. NADPH oxidase (NOX2)-mediated ROS generation was also observed in microglia treated with actMMP-3. In addition, MMP-3 could be also activated intracellularly by unknown serine proteases upon stress such as 6-OHDA or MPP+, a selective dopaminergic toxin. Activated MMP-3 could cleave α-synuclein into several fragments by C-terminal truncation. These fragmented peptides are prone to aggregate and re-sult in increased cytotoxicity. MMP-3 could also degrade DJ-1 and impair its antioxidant function resulting in increased oxidative stress. Intracellular actMMP-3 is directly linked apoptotic path-way in dopaminergic cells as well.

DJ-1 expression in the SN of mice, its degradation was largely attenuated in MMP-3 knockout mice. This study suggests that cleavage of DJ-1 by the intracellular MMP-3 in response to cell stress impairs the protective role of DJ-1 against oxidative damage (Choi *et al.*, 2011a). The proposed roles of MMP-3 in the pathogenesis of PD is illustrated in Fig. 2.

MMP inhibitors and Neuronal disorders

As emerging evidence indicates MMPs as a major culprit for a number of disease conditions including cancers, inflammation and neurodegenerative disorders, the importance of MMPs as a therapeutic target has been highlighted. MMP inhibitors could be categorized into two groups, macromolecular inhibitors such as TIMPs and monoclonal antibodies and small molecules including natural and synthetic inhibitors (Sang *et al.*, 2006; Hu *et al.*, 2007). TIMPs are the most thoroughly studied natural MMP inhibitors. Physiological balance between MMPs and TIMPs are considered important to prevent multiple disease conditions. Long-chain fatty acids, epigal-locatechin gallate (EGCG) extracted from green tea and flavonoids also belong to natural MMP inhibitors. Since the first endeavor to develop smallmolecule MMP inhibitors for the treatment of arthritis, a number of synthetic MMP inhibitors have been tested for various diseases over the past three decades. The first generation of synthetic MMP inhibitors was designed based on mimicking natural peptide substrates, thus so called peptidomimetic MMP inhibitors. Later on, structure-based MMP inhibitors with a zinc-binding group (ZBG), a backbone that chelates zinc ion in the catalytic core of MMPs, have been extensively developed and tested. Four major ZBGs have been exploited for the development of MMP inhibitors: carboxylates, thiolates, phosphinyls and hydroxamates. Of these, hydroxamates-based MMP inhibitors have been stu-died most widely. A ZBG of hyroxamate acts as a bidentate ligand with the catalytic zinc ion and it also forms hydrogen bonds with enzyme backbones, resulting in potent inhibitory effect. Batimastat is one of the first generation of broad-spectrum hydroxamates inhibitors. Because of the similarity of catalytic core structure between MMPs, it has been challenging to develop highlyselective MMP inhibitors. As crystallographic structures of more MMPs were revealed, the nextgeneration MMP inhibitors with greater target selectivity were designed. Prinomastat is a second-generation hydroxamates MMP inhibitor that has much higher IC50 value against MMP-1 and -7 (Sang *et al.*, 2006). Due to their numerous normal physiological functions including tissue remodeling, repression of tumor angiogenesis and inactivation of chemokines, therapeutic inhi-bitions of MMPs have potential to accompany side effects. Musculoskeletal syndrome (MSS) is the most common side effect caused by many MMP inhibitors, which is characterized by joint pain, stiffness and tendinitis (Cho *et al.*, 2006). Despite the effort toward developing MMP inhibi-tors with high selectivity and therapeutic efficacy, tetracycline derivative, doxycycline, remains the only FDA approved MMP inhibitor (Hu *et al.*, 2007). In spite of their low potency, non-hydroxamates MMP inhibitors containing other ZBGs such as carboxylates with greater target specificity have been developed (Walker and Rosenberg, 2010).

It has been reported that MMP inhibitors bring about beneficial effects in animal studies of multiple sclerosis, vascular dementia, meningitis, Guillain-Barre syndrome and stroke. Of these, MMP inhibitors have been most intensively tested in acute cerebral ischemia. Studies on mo-noclonal antibodies against MMPs and broad spectrum MMP inhibitors such as GM-6001, BB-94 and BB-1101 demonstrate that BBB damage, infarct volume and neuronal death are significantly reduced by MMP inhibitions (Romanic *et al.*, 1998; Gu *et al.*, 2005). As discussed, MMPs have a dual role after stroke, aggravating neuronal damage at the early phase and tissue repair at the later stage, suggesting that short-term administration during the early stage would be effective. Patients with MS treated with minocycline, tetracycline derivative, demonstrate reduced number of gadolinium-enhancing lesions on MRI (Metz *et al.*, 2004). In EAE, MMP inhibitors reduce damage to the BBB and low-dose tetracycline administration with interferon-beta effectively reduces inflammation (Giuliani *et al.*, 2005). In vascular cognitive impairment which is charac-terized by progressive white matter damage cause by ischemic injury or hypoxic hypoperfusion, MMP inhibitors reduce white matter damage (Cho *et al.*, 2006; Walker and Rosenberg, 2010). Use of MMP inhibitors in the treatment of AD is controversial since they are involved in the genera-tion of Aβ from APP as well as clearance of Aβ As discussed earlier, a couple of MMPs, especially MMP-3, play crucial roles in the pathogenesis of PD, suggesting that MMP inhibitors might ameliorate dopaminergic neuronal degeneration.

CONCLUSION

In this review, we discuss general structure, activation, regulation and functions of MMPs and subtilize their roles in the CNS. Finally, we emphasize on the implication of MMPs in a range of neurodegenerative conditions. Based on an increasing number of studies, we further discuss the link between MMP-3 and the pathogenesis of PD. Lastly, current status on development of MMP inhibitors for treatment of neurodegenerative diseases is discussed. We are anticipating much more exciting works that potentially lead to therapeutic interventions for various brain disorders.

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