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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 responsible for degradation and remodeling of extracellular matrix proteins. The activity of MMPs is tightly regulated at several levels including cleavage of prodomain, allosteric activation, compartmentalization 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 development, 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 accumulating 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 neuroinflammation, apoptosis and degradation of α-synuclein and DJ-1. MMP inhibitors could represent potential 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-enzymes. Currently, 24 MMP genes and 23 MMP proteins have been reported because two identical 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 including 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 PRG (V/N)PD amino acid sequence. The cysteine contained within this sequence interacts with zinc
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 proteolytic 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 transcriptional regulation; 2) activation of proenzyme by removing the propeptide domain; 3) the interaction with tissue inhibitor of metalloproteinases (TIMPs); 4) pericellular or intracellular compartmentalization; 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, oncogene products and interestingly, cell-cell or cell-ECM interaction (Ries and Petrides, 1995; Vincenti and Brinckerhoff, 2007). Their gene expression also can be suppressed by other factors such as TGF-β, retinoic acids and glucocorticoids (Osteen et al., 1996; Li et al., 2011; Ye et al., 2011). These external effectors trigger the var-ious intracellular signal transduction 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” structure (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 have the only 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.
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 Brinkerhoff, 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<sup>2+</sup> interaction, which renders pro-MMPs partially active. Then, the partially active enzyme auto-catalyzes the pro-peptide 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 secreted as their pro-domain. Proteolytic cleavage of pro-MMPs by furin-activated MMPs is realized covalently through the mechanism of catalytic auto-processing (Yan and Boyd, 2007). Only at extremely high activity, furin can cleave large amounts of pro-MMPs, but in the case of furin inhibition, the MMPs remain as pro-MMPs.

Tissue inhibitors of metalloproteinases (TIMPs) are the endogenous regulators of MMP activities in the tissue (Vincenti, 2002). Following activation, the activities of MMPs are regulated by endogenous regulators in the tissue (Vincenti, 2002). TIMPs are able to regulate the activities of MMPs by forming non-covalent complexes with TIMPs. Four homologous TIMPs have been identified so far by their amino acid sequences (Yong et al., 2002). They are MMP-1, MMP-2, MMP-3 and MMP-9. Some MMPs have unique motifs in their pro-domains that can interact with TIMPs. TIMP-2 and TIMP-3 have a unique motif, PHCGVPD, that is assumed to increase autophosphorylation of TIMPs. TIMP-1 and TIMP-3 inhibit MMPs through the formation of non-covalent complexes with TIMPs. Four homologous TIMPs have been identified at the early stage of MMPs to be involved in the regulation of MMPs. TIMP-1 and TIMP-2 are able to form complexes with MMPs, and TIMP-3 is able to form complexes with MMP-2. TIMP-4 inhibits MMPs by forming complexes with MMPs.

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 transcriptional 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 nuclei 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 (Tnl), 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 be important in the maintenance of normal physiologic conditions.
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 myelination (Cafete 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 (Forshy et al., 1999; Lorenz et al., 2002; Lorenz et al., 2003; Yong et al., 2007; Candelario-Jalil et al., 2009; Choi et al., 2011; 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) (Yuschenko 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 Sorensen, 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: propagating 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 knock-out 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 neurons and apop-totic 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 (Forshy et al., 1999). In contrast to MMPs, the expression of TIMP-1 and -2 is decreased, sug-gest ing 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 charact-eric 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., 2007). 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 over-expressed in AD brain tissue compared to controls and it can degrade synthetic 40-residue long Aβ protein in vitro (Backstrom et al., 1992; Rohrer et al., 1994). MMP-2 has also been shown to degrade 40- to 42-residue long Aβ purified from AD brain tissue (Rohrer et al., 1994). In AD brains, MMP-3 is ex-pressed predominantly in brain white matter. Double immuno-staining 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 P38K-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 neu- rodegenerative disorders characterized by motor symptoms including resting tremor, rigidity, bradykinesia and postural in-stability resulting from selective degeneration of dopaminergic neurons in the substantia nigra pars compacta. Accumulating evidence suggests MMPs as a major culprit in the pathogen-esis 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 postmor-tem PD brain tissue was first reported by Lorenzi et al. showing alterations in MMP-2 and TIMP-1 in the SN of PD patients (Lorenzi et al., 2002). Since then, a number of studies includ-ing 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 pathol-ogy 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 concentra-tion 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 de-generation 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 re-lease 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. In-crease in MMP-3 expression in the SN was observed in ro-dent 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 dopa-minergic neurons in the SN of mice administered with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a selective dopa-minergic 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 dopamine-ergic 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 in-jection (McCain 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 mecha-nism 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 component in Lewy bodies, 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. MMP-3-cleaved species (N-terminal) in extracellular 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 increase 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 aggregation 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 into several fragments by C-terminal truncation. These fragmented peptides are prone to aggregate and result in increased cytotoxicity. MMP-3 could also degrade DJ-1 and impair 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 degeneration. 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 result in increased oxidative stress. Intracellular actMMP-3 is directly linked apoptotic pathway in dopaminergic cells as well.
the pathogenesis of PD is illustrated in Fig. 2. 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, epigallocatechin gallate (EGCG) extracted from green tea and flavonoids also belong to natural MMP inhibitors. Since the first endeavor to develop small molecule 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 studied most widely. A ZBG of hydroxamate 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 highly selective 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. Muscu loskeletal 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 inhibitors 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 inhibitors (Romainic 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 characterized by progressive white matter damage caused 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 generation 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, regul ation and functions of MMPs and sublitize 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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