Multifaceted Role of Matrix Metalloproteases on Human Diseases

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Abstract

Matrix metalloproteases (MMPs) are important enzymes required in extracellular matrix (ECM) degradation for creating the cellular environments to maintain numerous physiological processes ranging from development to wound repair. However, MMP activity is strictly controlled and imbalance in the levels of MMP family members and its inhibitors has been implicated as an etiological factor in several diseases. Herein, involvement of MMPs and their natural inhibitors, tissue inhibitors of metalloproteases (TIMPs), in several disease processes have been considered for discussion.

Keywords

MMP · TIMP · AD · PD · ALS

1 Introduction

Matrix metalloproteases (MMPs) are zinc-containing endopeptidases capable of degrading various components of extracellular matrix (ECM) [1]. They are produced as latent zymogens (pro-MMPs). Once activated, they participate in the regulation of

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diverse physiological and pathological processes. Since its discovery about a few decades ago, MMPs have emerged as crucial mediators in defining interaction of cells with their surrounding microenvironment [2]. MMPs can be categorized into five major groups according to their substrate specificity: collagenases, gelatinases, membrane-type metalloproteases, stromelysins, and matrilysins [3].

MMP activity is tightly regulated at the transcriptional as well as at the post-translational level. MMPs enzymatic activities are controlled by tissue inhibitors of metalloproteases (TIMPs) after secretion in the extracellular milieu [4]. Among the four distinct TIMP molecules (TIMP-1, TIMP-2, TIMP-3, and TIMP-4), TIMP-1 is the major endogenous inhibitor of pro and active MMP-9 and inhibits their activity by forming a noncovalent complex [5].

The ECM is a three-dimensional, extracellular scaffold required for maintenance of life. Every tissue and organ is composed of ECM generated in early embryonic stages. The ECM provides structural support for organs, tissues, cell layers and for individual cells as substrates for cell motility. The function of ECM is much more than to provide physical support for tissues and organs; the ECM is constantly remodeled to provide a dynamic structure during tissue homeostasis [6]. MMPs can impact the development of several diseases through different pathophysiological mechanisms, mainly via tissue destruction and ECM degradation. Imbalance in MMP/TIMP ratio can cause a threat to mortality and severity of diseases. This chapter examines the detrimental role of MMPs and their endogenous inhibitors in the development of variety of pathological conditions, including neurodegenerative and lung diseases.

2 Structure and Function of MMPs

Members of the MMP family (Table 1) were initially grouped according to their preferred substrates, e.g., gelatinases, collagenases, matrilysins, and stromelysins. A sequential numbering system for MMPs was employed according to the chronology of their discovery when it became evident that more MMPs exist than was initially assumed and that the names based on substrate specificity were not sufficient. Some MMPs, like MMP-4, MMP-5 and MMP-6 are missing in the nomenclature as further studies showed that either the gene products did not exist or were identical to previously predicted MMP members [5]. MMPs are synthesized as pre proenzymes and secreted as latent pro-MMPs. The primary structures of vertebrate MMPs contain several domains. The propeptide domain consists of conserved PRCG(V/N)PD sequence. The conserved Cys within this sequence, called cysteine switch, coordinates with the catalytic zinc to prevent latent pro-MMPs from becoming inappropriately activated [7]. This sequence is missing in MMP-21 [8]. Stromelysin 3 (MMP-11) and *Xenopus* MMP possess a proprotein converting sequence R*X*(K/R)R at their C-terminal end. The catalytic domain possesses a zinc binding segment HE*XX*H*XX*G*XX*H and a unique methionine containing conserved stretch, called 'Met-turn' [9]. This domain is made up of three α-helices,

Table 1 Secreted MMPs and their substrates

MMP	Alternate names	Selected substrates
MMP-1	Collagenase-1	Collagen I, II, III, entactin, perlectan, IGFBP-2 and -3, proIL-1β, IL-1β
MMP-2	Gelatinase A	Gelatin, collagen IV, V, XI, laminin, aggrecan, proTGF-β, proTNF-α, IGFBP-3 and -5
MMP-3	Stromelysin-1	Aggrecan, laminin, fibronectin, fibrinogen, MCP-1 to -4, proMMP-1, -3, -7,-8, -9, -13
MMP-7	Matrilysin	Plasminogen, pro-α-defensin, FasL, proTNF-α, E-cadherin, syndecan, proMMPs
MMP-8	Collagenase-2	Collagen I-III, VII, X, aggrecan, fibronectin, proTNF-α, IGF-BP, MCP-1, angiotensin
MMP-9	Gelatinase B	Gelatin, collagen IV, V, XI, pro-IL-8, ProTNF-α, proTGF-β, proMMP-2, -9, -13
MMP-10	Stromelysin-2	Gelatins, fibronectin, proteoglycan, pro-MMP-1, -8, -10
MMP-11	Stromelysin-3	Fibronectin, laminin, aggrecan, IGFBP-1
MMP-12	Metalloelastase	Elastin, fibronectin, laminin, plasminogen, proTNF-α
MMP-13	Collagenase-3	Collagen I, II, III, entactin, aggrecan, tenascin, proTNF-α, proMMP-9, -13
MMP-14	MT1-MMP	Collagen I, II, III, laminin, fibronectin, proMMP-2, -13, CD44, tissue transglutaminase
MMP-15	MT2-MMP	Pro-MMP-2, pro-TNF-α, tissue transglutaminase 1
MMP-16	MT3-MMP	Collagen III, proMMP-2, proTNF-α, tissue transglutaminase
MMP-17	MT4-MMP	Gelatin, fibronectin, fibrin, proMMP-2, ADAMTS-4, TIMPs, proTNF-α
MMP-18	Collagenase-4	Collagen I, II, III
MMP-19	Stromelysin-4	Collagen IV, gelatin, laminin
MMP-20	Enamelysin	Amelogenin, aggrecan, cartilage oligomeric matrix protein (COMP)
MMP-21		Gelatin, α1-antitrypsin
MMP-24	MT5-MMP	ProMMP-2
MMP-25	MT6-MMP	Collagen IV, gelatin, fibrin, fironectin, proMMP-2 and -9, TIMPs, uPAR
MMP-26	Matrilysin-2	Collagen IV, fibronectin, fibrin, fibrinogen, proMMP-9 MMP-27 Gelatin, casein
MMP-28	Epilysin	Neural cell adhesion molecule (NCAM), casein

uPAR urokinase-type plasminogen activator receptor; *IGFBP-1* insulin-like growth factor binding protein

one five-stranded β-sheet and bridging loops [10]. This basic topology including the strictly conserved methionine containing 'Met-turn' is part of a larger metalloprotease family called metzincins, which include matrixins, adamalysin, astacins, and serralysins [9]. MMP catalytic domains are coordinated with zinc and calcium ions which are needed for their stability and enzymatic activity. Gelatinases (MMP-2 and MMP-9) contain three fibronectin-type II repeats which are located in the

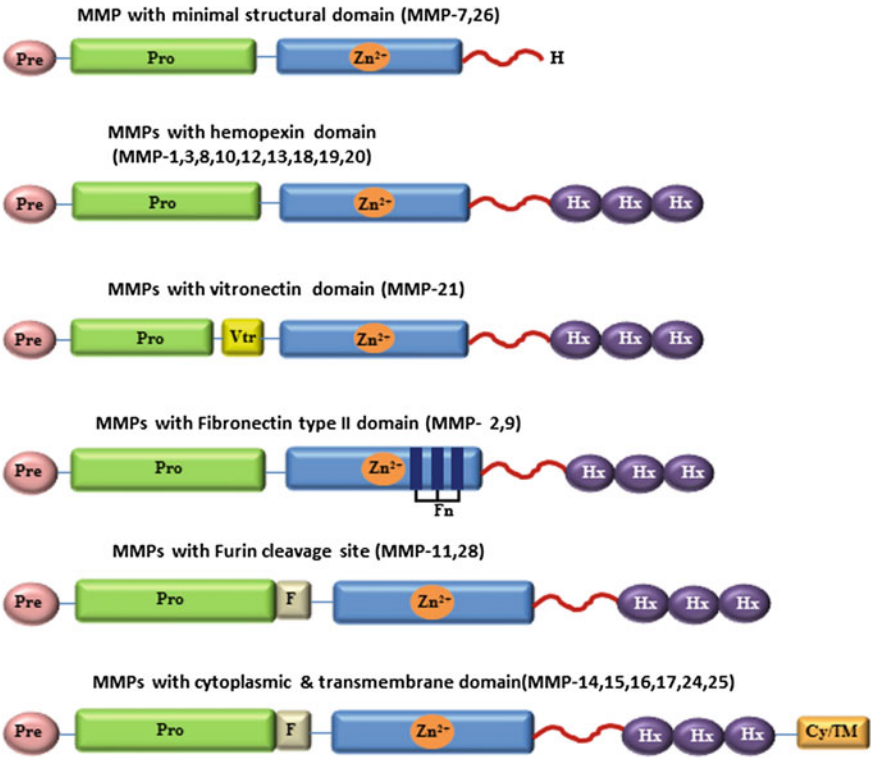

Fig. 1 Schematic representation of secreted MMP domain structure. The domain organization of MMPs is as indicated: *Pre* prepeptide; *Pro* propeptide; *Cat* catalytic domain; Zn^{2+} active-site zinc; *H* hinge region; *Hx* hemopexin domain; *Fn* fibronectin domain; *Vtr* vitronectin insert; *Cy/TM*, cytoplasmic/transmembrane domain

catalytic domain (Fig. 1). These repeats interact with collagens and gelatins [11, 12]. The C-terminal hemopexin-like domain has an ellipsoidal disk shape with a four bladed β-propeller structure; each blade comprising an α-helix and four antiparallel β-strands [13]. The hemopexin domain of collagenases is necessary for cleavage of triple helical interstitial collagens [14], although the proteolytic activity can be retained by the catalytic domains alone [15].

3 Role of MMPs in Neurodegenerative Diseases

3.1 Aging

Neurodegenerative diseases may be caused by multiple factors which include complex interactions of genetic elements and environmental factors. One of the

main features of aging is accumulation of advanced glycation end products (AGE). Activation of the receptor for AGE (RAGE) causes release of proinflammatory cytokines and free radicals which contributes to inflammatory processes [16]. A few reports suggest that vascular-derived insults could be a causal factor in propagating aging and to some of the age-related ailments, for instance, Alzheimer's disease (AD) [17, 18]. Age-related vascular diseases can indeed be triggered by dysregulation in the physiological balance between MMPs and TIMPs [19].

RNA profiling and DNA microarray analysis have shown TIMP-2, a potent inhibitor of MMP-2, to be a common biomarker of aging in heart and cerebellum of multiple mice strains, suggesting that an increase in the level of TIMP-2 may modulate impaired angiogenesis and fibrosis in aged tissues [20]. This study is corollary of the role of TIMPs in aging as transcription profiling data by Zahn et al. [21] indicates that TIMP-1 is the key gene product that exhibits maximum change in gene expression in several age-related human tissues. Elevated level of MMP-9 has been observed to be associated with aging and circulating MMP-9 and TIMP-1 levels in patients with brain ischemia and aging [22]. Moreover, Safciuc et al. [23] showed that microvessels in the brain of aged rats exhibit diminished MMP-2 activity and specific occurrence of MMP-9. Liu et al. [24] have suggested that an increase in MMP-12 could contribute to aging-associated neuroinflammation as they showed high level of MMP-12 in microglia in the brain of aging mice.

3.2 Alzheimer's Disease

Alzheimer's Disease (AD) is the commonest neurodegenerative disorder. Major characteristics of AD include neuronal cell death mediated brain atrophy, decreased dendritic arborization in the cerebral cortex and other subcortical areas. The hallmarks of AD include abundance of amyloid plaques in the nerve cells of the brain and neurofibrillary tangles, made up of misfolded proteins [25]. The relationship between MMPs and AD has been studied intensely. Using immunochemical methods Bjerke et al. [26] suggested that MMP-9 and TIMP-1 could be used as biomarkers of AD in addition to T-tau, P-tau, Aβ1–42, and white matter lesions. Another group proposed that high abundance of MMP-9 in a protease cascade, responsible for degradation of pronerve growth factor (proNGF) mature NGF (mNGF), resulting in degradation of mNGF which may cause the pathogenesis of cognitive deficits in AD [27] (Fig. 2). Lorenzl et al. [28] also documented higher levels of MMP-9 in serum of AD patients. MMP-9 expression was also demonstrated to be induced in neuronal cytoplasm, neurofibrillary tangles, amyloid plaques, and vascular tissue in AD patients [29], as well as in cultured rat astrocytes upon stimulation with Aβ [30]. Latent MMP-9 detected in pyramidal neurons of AD patients and near amyloid plaques by Backstrom et al. [31]. They also proposed that the lack of active MMP-9 contributes to the accumulation of insoluble beta-amyloid peptides in plaques. Yan et al. [32] demonstrated that MMP-9 can degrade Aβ fibrils in vitro, as well as amyloid plaques in brain of aged APP/PS1 (double-transgenic AD mouse model expressing variants of amyloid precursor

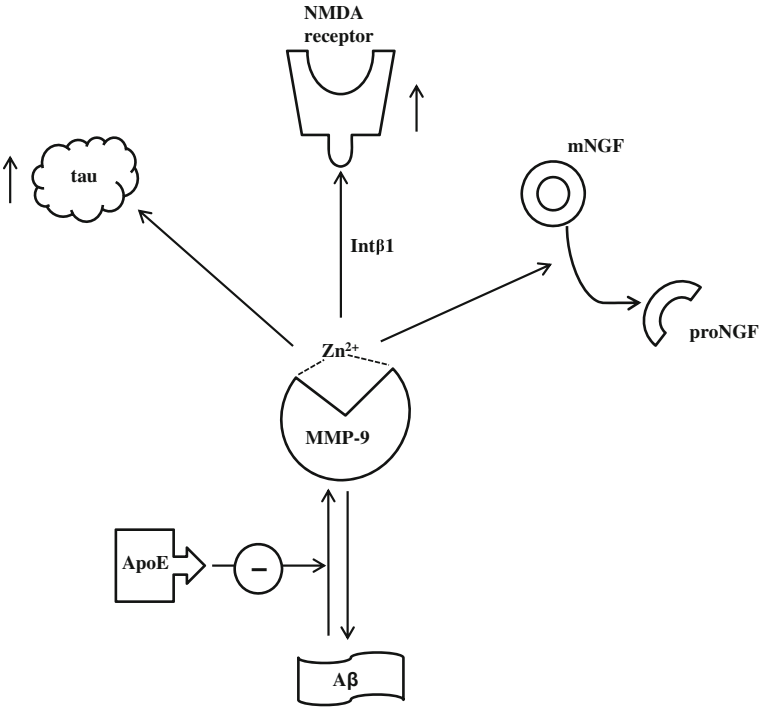

Fig. 2 MMP-9 in AD pathology: MMP-9 is responsible for degradation of pro nerve growth factor (proNGF) to mature NGF (mNGF) as well as Aβ fibrills. ApoE inbits Aβ induced MMP-9 synthesis. Activation of NMDA receptor is mediated by MMP-9 in integrin β1 (Intβ1) dependent manner which may facilitate AD. MMP-9 also mediates oligomeric deposition of tau protein in brain regions

protein (APP) and presenelin-1 (PS1) genes) and APPsw (APP gene bearing the Swedish mutation) mice, and increased MMP activity was selectively observed in compact Thioflavin S-positive plaques (a staining method to detect amyloid plaques). In rat primary astrocytes, treatment with oligomeric Aβ decreases MMP-2 expression and extracellular activity, whereas, in the brain of APP/PS1 AD mice, they found an increase in MMP-2 activity as well as mRNA level using immunohistochemistry and real time PCR, respectively. Furthermore, they suggested that Aβ can directly decrease the expression and activation of MMP-2 in astrocytes, while stimulates microglia to produce proinflammatory cytokines such as IL-1β and TGFβ, which in turn could induce MMP-2 expression and contribute to disease condition [33]. Liao et al. [34] using a transgenic mouse model of AD demonstrated expression of MMP-2 and membrane-type matrix metalloprotease (MT1-MMP), a potent activator of MMP-2, in reactive astrocytes around amyloid plaques and suggested their involvement in degradation of Aβ. In another finding, MMP-12 has been shown to exacerbate the proteolytic cascade by subsequent activation of other MMPs such as MMP-2 and MMP-3 [35]. By zymographic

study, Horstmann et al. [36] showed that MMP-3 levels were significantly elevated in plasma as well as in cerebrospinal fluid (CSF) of AD patients, whereas MMP-2 levels were significantly decreased. Interestingly in another study the levels of MMP-2 and MMP-3 were significantly down regulated in CSF of AD patients [37]. In a study, MMP-3 was demonstrated to express in astrocytes, microglia, and in endothelial cells in the brain as well as near-neuritic plaques in AD [38]. MMP-3 has also been shown to be induced in response to Aβ peptides in cultured astrocytes and neuronal cells [39]. A connection was found between MMP-3 and APOE 4 (apolipoprotein E) alleles and the presence of both is a risk factor for developing AD [40]. Furthermore, Aβ1–42 oligomers induce loss of barrier integrity at the blood–CSF barrier and were linked to increased MMP-3 expression and MMP activity [41]. Other MMPs, like MMP-1 has also been reported to be at increased level in brain of AD patients [42].

3.3 Parkinson's Disease

Parkinson's disease (PD) is a progressive movement disorder of the central nervous system that deteriorates over time mostly affecting middle- and old-aged people. Area of the brain called substantia nigra is mainly affected in PD. The exacerbated neurons emanate a chemical called dopamine that transmits signal to the brain to control movement and coordination of the body. With progression of PD, the amount of dopamine is downregulated in the brain, causing inability in controlling movement by the affected individual. Another hallmark of PD is the formation of Lewy bodies, an abnormal aggregate of proteins inside the nerve cells. These protein aggregates form fibrils and composed mainly of α-synuclein. The biological role of these protein aggregates is unclear [43]. Other symptoms of PD include mood and sleep disorders, dementia, and partial autonomic nervous system impairment [44]. It has been postulated that prolonged overactivation of microglia and production of proinflammatory cytokines could lead to neuronal degeneration in PD [45]. The hypothesis is supported by other studies which also predict involvement of active microglia in triggering neurodegeneration of dopaminergic neurons in the substantia nigra by lipopolysaccharide (LPS) [46, 47]. Initial neurotoxic insult to dopaminergic neurons could result in the release of certain factors that activate microglia to be damaging [48], however, the mechanism of this activation is largely unknown. MMP-3, produced by stress related dopaminergic neurons, could participate in microglial activation in the absence of any other inflammatory molecule as report suggests it could activate microglia, leading to the release of cytokines and receptors for phagocytosis of apoptotic cells [49]. In an in vitro study, Kim et al. [49] showed that MMP-3 could trigger microglia to produce proinflammatory cytokines, which in turn causes apoptosis of neuron, propagating further induction of apoptosis in neighboring dopaminergic neuronal cells. The presence of active microglia and extensive loss of dopaminergic neurons has been shown in a postmortem study by McGeer et al. [50] when they administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to monkeys for

5–14 years. In MMP-3 deficient mice using a broad spectrum MMP inhibitor, it has been shown that depletion of MMP-3 can significantly reduce MPTP induced degeneration of nigrostriatal dopaminergic neurons in the brain [51]. Involvement of MMP-9 was found in both striatum and substantia nigra after MPTP treatment and pharmacological MMP inhibitors protected against MPTP neurotoxicity [52]. The same group also demonstrated that post mortem analysis of brain tissue from PD patients did not display any change in the activities of MMP-9 and MMP-1 in substantia nigra, cortex or hippocampus, whereas MMP-2 was markedly down-regulated in the substantia nigra [53]. Additionally, they showed that MMP-9 was restricted predominantly in neurons and MMP-2 in astrocytes and microglia. In the same study, TIMP-2 levels were unaltered, whereas TIMP-1 was increased in substantia nigra but not in the hippocampus and cortex [53]. The increase in MMP-9 expression in substantia nigra and striatum in mice acutely injected with MPTP has been reported in reactive microglia and astrocytes, which indicates plausible role of MMP-9 in the onset of neuroinflammation in PD [54].

3.4 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is characterized by degeneration of motor neurons in the brain, brainstem, and spinal cord. In ALS all voluntary muscles are affected and manifested by muscular atrophy and weakness followed by paralysis and eventually respiratory failure and death [55]. Involvement of MMPs in this scenario was indicated by Lim et al. [56] when they studied brain and spinal cord specimens of ALS patients. They found MMP-2 in astrocytes and MMP-9 in pyramidal neurons in the spinal cord of ALS patient. In addition to that, MMP-2 activity was decreased in motor cortex, whereas MMP-9 activity was increased in spinal cord. Another group showed reduced MMP-9 activity during disease progression, with the peak at the onset of ALS and described a similar profile for MMP-2 [57]. Two separate groups have found elevated levels of both pro and active form of MMP-9 in the serum of ALS patients relative to healthy controls [58, 59]. In mild cases of ALS, expressions of MMP-2, MMP-9, TIMP-1 and MT-MMP-1 are elevated in serum compared to CSF, whereas MMP-2, MT-MMP-1 and TIMP-1 were either increased or remain unchanged with concomitant decrease in MMP-9 level [60]. Moreover, Fang et al. [61] found an increase in the levels of MMP-9 in CSF and skin in patients suffering from rapidly progressing ALS and suggested possible involvement of MMP-9 in progression of the disease, poor survival of the patients and neurodegeneration. Nevertheless, MMP-2 showed a slow but progressive decrease with the development of the disease [61]. In an ALS model with mice expressing mutant superoxide dismutase (SOD1), a reduction of MMP-9 function using gene ablation, viral gene therapy, or pharmacological inhibition has been shown to significantly delay muscle denervation, thereby assigning MMP-9 as a candidate therapeutic target for ALS [62]. Kaplan et al. [62] focused on the early stage of the disease and expression of MMP-9 by neurons, whereas another study by Kiaei et al. [63] at the later stages of

the disease revealed expression of MMP-9 by activated microglia, however, since the abrogation of MMP-9 gene does not rescue transgenic SOD1 mice from death, ALS indeed has complex background.

3.5 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, autoimmune disease of the brain and spinal cord (central nervous system). In MS, the body's immune system causes inflammation in the protective myelin sheath that surrounds nerve fibers and blocks messages between brain and the rest of the body. As the disease progresses the nerves start to deteriorate or become permanently damaged. MS can be categorized into four major groups. (1) Relapsing–remitting MS (RRMS) happens in majority of patients suffering from MS. Alternate periods of remission (improvement of symptom) and relapses (deterioration) are seen to occur in a patient the disease. (2) Secondary progressive MS (SPMS), which is characterized by progressive deterioration of the symptoms, affects some individuals affected by RRMS. (3) Primary progressive MS (PPMS). Individuals in this category display progressive worsening of the disease with no remissions or relapses. (4) Progressive relapsing MS (PRMS) is the rarest type. The condition is characterized by a progressive worsening of the situation from the beginning. However, there are occasional relapse periods.

Cuzner et al. [64] suggested presence of MMP-9 and its inhibitor in reactive astrocytes in the CNS of MS patients. Increased levels of MMP-9 were found in CSF of acute phase and primary progressive MS patients [65]. Maeda et al. [65] showed expression of MMP-1, MMP-2, MMP-3 and MMP-9 in macrophages in active MS and necrotic lesions and in small numbers in astrocytes in acute and chronic MS lesions. CSF samples from patients suffering from both RRMS and PPMS and demonstrated up regulation of MMP-9 in all the RRMS cases throughout both stages of the disease [66]. However, in PPMS patients, elevated MMP-9 was found only in about half of the samples and in smaller quantity than in the relapsing–remitting form and suggesting T-cells and macrophages are responsible for the secretion of MMP-9 in MS. Moreover, Lepert et al. [66] suggested that elevation in MMP-9 level throughout the progress of the disease may cause damage of neighboring tissue and neuronal cell loss. Employing MRI study Lee et al. [67] showed elevated levels of MMP-9 in serum of MS patients, along with an increase in TIMP-1 and TIMP-2 levels and proposed that an abnormality in the inhibitory response to metalloproteases might play an aetiological role in the chronicity of multiple sclerosis. However, in another MRI study, elevated levels of MMP-9, but not TIMP-1, in serum were observed in RRMS patients and this imbalance of MMP-9 and TIMP-1 was postulated to take part in new lesions in MS [68]. Analysis of mRNA also showed an increase in the levels of MMP-1, MMP-3, MMP-7, MMP-9 and TIMP-1 in blood monocytes of MS patients [69]. In an interesting study by Althoff et al. [70] using the encephalomyelitis model, mice that genetically modified to constitutively express TIMP-1 in the CNS had a

normal phenotype but had reduced symptoms of experimental autoimmune encephalomyelitis. MMP-9 deficient mice have been observed to be less susceptible to the development of experimental autoimmune encephalomyelitis [71].

3.6 Japanese Encephalitis

Japanese encephalitis (JE) that normally affects children is mediated by a single-stranded RNA virus, called JE virus (JEV) which results in severe neurological disorders [72, 73]. JE virus is from the genus *Flavivirus* and is closely related to West Nile and Saint Louis encephalitis viruses. Humans are infected by JE virus through the bite of infected mosquitos. It infects the central nervous system leading to acute encephalitis. JEV infection causes severe damage to neurons and in various parts of the brain such as thalamus, brainstem and striatum [74].

The exact mechanism of neuronal cell death in JE is not fully clear yet, however some studies indicate the role of MMPs in neuronal cell death. Recent study suggests that JEV infection causes upregulation in the expression of MMPs (MMP-2, -7, -9) and TIMPs (TIMP-1 and -3) and can contribute to the severity of the disease [75]. Pieces of evidence also suggests expression of MMP-9 is induced during JEV infection in rat brain astrocytes through generation of reactive oxygen species (ROS) during JEV infection [76, 77]. Higher concentrations of MMP-2, TIMP-2 and TIMP-3 have been demonstrated in cerebrospinal fluid (CSF) and in serum of JEV infected children compared with control [78]. Additionally, higher serum concentrations of MMP-9 and MMP-7 have also been detected in JEV patients compared with healthy control.

3.7 MMPs in Glaucoma

Glaucoma, a neurodegenerative disease, is related to a group of eye disorders that cause impairment to the optic nerve that transmits signal from the eye to the brain. Glaucoma normally has few or no early symptoms. Glaucoma can be categorized into two major divisions: open angle glaucoma and closed angle glaucoma. In open angle glaucoma the retinal ganglion cells (RGCs) degenerate slowly without any display of symptoms at the early stage while vision loss occurs quickly at later stage. The most predominant and major risk factor for glaucoma is amplification in intraocular pressure (IOP) mainly used to diagnose the disease. Glaucoma is associated with apoptosis of RGCs and optic nerve degeneration which may lead to vision loss [79].

The mechanism of RGC and optic nerve degeneration is unclear till date. However, role of MMPs in the pathophysiology of glaucoma has been reported by some authors. MMPs are involved in modulating the trabecular ECM to maintain stable aqueous humor outflow resistance and IOP [80]. MMP-9 was shown to have a role in glaucoma by promoting loss of laminin, RGC apoptosis, and elevated IOP [81]. In steroid-induced glaucoma (SIG), role of MMPs in the regulation of outflow

resistance has also been studied. SIG, a form of open angle glaucoma, results from continuous use of corticosteroid usage causes a decreased trabecular outflow leading to increased IOP [82]. Several MMPs (MMP-2, MMP-9, and MMP-13) have shown to be elevated in steroid induced mice model of glaucoma [83]. Gerometta et al. [84] has shown that mRNA expression of MMP-1 was elevated in steroid induced sheep model of glaucoma.

4 Role of MMPs in Lung Diseases

4.1 MMP in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a lung disease that causes difficulty in breathing. It is caused by injury to the lungs, usually from smoking. COPD is mainly referred to a mix of two diseases: Chronic bronchitis in which the bronchial tubes that carry air to the lungs are inflamed and increases mucus production. This results in narrowing and blockage in the airways, making it harder in the respiration process. Emphysema in which the tiny air sacs in the lungs are damaged and lose their flexibility, less air gets in and out of the lungs, which makes someone feel short of breath. COPD gets worse over time. The damage to the lung can't be undone. But preventive measures could be taken to check more damage and to feel better. Hallmark of COPD include elevated level of alveolar macrophages, neutrophils and cytotoxic T-lymphocytes and the release of multiple inflammatory mediators (lipids, chemokines, cytokines, growth factors). Worsening of inflammation may be caused by a high level of oxidative stress. There is also increased evidence for involvement of MMPs in this scenario [85].

Role of MMPs in COPD has been established by several studies on human subjects. Sputum of COPD patients demonstrated to have an increased MMP-2 and MMP-9 activity and higher levels of TIMP-1 [86]. Active MMP-9 was found in the sputum from 85% of COPD patients, whereas pro-MMP-2 (72 kDa) was found in 50% of COPD patients and in only 5% of controls [86]. COPD patients also showed higher levels of TIMP-1. This finding was substantiated by similar study done by Beeh et al. [87], who demonstrated an increase in MMP-9 and TIMP-1 levels in sputum from COPD patients, as well as an increased ratio of MMP-9 to TIMP-1. In bronchoalveolar lavage fluid (BAL) from COPD patients, there is an increase in collagenase activity (possibly due to elevated MMP-8 level) when compared with healthy controls. Additionally, MMP-9 has been observed to be present in the majority of COPD patients, whereas it was absent in control subjects matched for sex and smoking status [88]. In smokers with emphysema, MMP-8 and MMP-9 levels in BAL fluid were significantly upregulated compared to smokers without emphysema [89]. Russel et al. [90] found that cultured alveolar macrophages from COPD patients release higher amounts of MMP-9 than the alveolar macrophages from healthy smokers and nonsmokers.

Activity and expression of MMPs are up regulated in alveolar macrophages from COPD patients exposed with either tobacco smoke or wood smoke [91]. The study demonstrated increased macrophage elastolytic activity in COPD patients and suggested that the enzymatic activity is imparted by MMP-12. MMP-9 activity was increased in both COPD groups, whereas MMP-2 activity was higher in samples from wood smoke induced COPD than in those from COPD patients afflicted by tobacco smoking and in healthy controls. RT-PCR study revealed increased MMP-2 and MMP-12 expression in COPD patients. No significant difference has, however, been observed in alveolar macrophages from COPD patients when compared with healthy controls. However, earlier studies have shown up regulation in MMP-9 and MMP-1 mRNA levels in alveolar macrophages from emphysematous lung [92]. Immunohistochemical analysis on human lung tissue demonstrated elevated expression of MMP-1, -2, -8 and -9 in COPD patients [93]. MMP-1 and -2 were localized mainly in alveolar and interstitial macrophages and in epithelial cells, whereas MMP-8 and MMP-9 were primarily detected in neutrophils [93]. RT-PCR and ELISA studies revealed that mRNA and protein expression as well as MMP-1 activity were increased in the lung parenchyma of emphysema patients compared to control patients [94]. Studies of a group of researchers revealed an imbalance between MMP-9 and TIMP-1 levels in human lung tissue, which is associated with cigarette smoking [95]. They found positive correlation of MMP-9 level and the MMP-9/TIMP-1 ratio in the lung tissue extracts from cigarette smoking individual. However, MMP-9 levels were negatively correlated with FEV1 (forced expiratory volume; how much air a person can exhale during a forced breath), suggesting role of MMP-9 in the progression of airway obstruction in smokers. Genetic studies revealed that MMP-1 and MMP-12 polymorphisms are causal factors for worsening of lung function in smokers [96]. Polymorphism in the MMP-9 promoter region (-1562C/T) is responsible for the development of smoking-induced emphysema [97]. The allele frequency was greater in smokers with distinct emphysema compared with those without emphysema.

4.2 MMPs and Asthma

Asthma is a chronic disease of the airways that is manifested by inflammation resulting in narrowing of the air passage. Asthma causes repeated phases of wheezing (a high-pitched whistling sound made during breathing), shortness of breath, chest pain, and cough. The frequency of cough increases during night or early in the morning and it can be problematic as it hampers daily activities which may cause lethal asthma attack. Asthma cannot be cured completely, but its dangerous symptoms can be lessened by medication. Several reports indicate role of MMPs associated with asthma.

Zymographic analysis of sputum samples from patients with asthma revealed an increase in the activity of MMP-2 and MMP-9 and higher levels of TIMP-1 in their sputum [86]. Patients with severe asthma had increased MMP-9 levels and activity in their sputum than patients with mild asthma and normal individual.

Allergen challenge increases the MMP-9/TIMP-1 ratio and consequently an increase in MMP-9 activity. Moreover, Inhalation of budesonide (which reduces inflammation) had no effect on MMP-9 or TIMP-1 in patients with mild asthma [98]. Report suggests an increase in the MMP-9 levels, but not TIMP-1 level in allergen induced sputum of asthmatic patients [99]. Additionally, this study also indicates a significant correlation between MMP-9 levels at 6 h and the maximum percent fall in FEV1 (forced expiratory volume in 1 s; a parameter for the degree of airway obstruction in obstructive lung diseases) during the late response [99]. MMP-1 and MMP-2 are involved in IL-13 induced elastin, a protease known for its role in airway remodeling, expression in airway fibroblast in mild asthmatic subjects [100]. Inhibition of MMP expression reverses the effect of IL-13 induced suppression of elastin. Gelatin zymography and enzyme immunoassay of sputum samples revealed significantly increased activities of pro-MMP-9 in acute asthmatic patients than in stable asthmatic patients. [101]. Elevated MMP-9 activity significantly decreased after 7 and 28 days of therapy. Tenascin-C, an extracellular matrix protein increases MMP-1 expression in asthma derived airway smooth muscle cells and bronchial biopsies of asthmatic patients when compared with control [102]. Levels of MMP-9 in the sputum were significantly increased in patients with toluene diisocyanate (TDI)-induced asthma [103]. In a study in patients ventilated because of acute severe asthma, a 10- to 160-fold increase of MMP-9 and activated forms (46 and 26 kDa) of stromelysin-1 (MMP-3) in epithelial lining fluid was found [104]. About fourfold circadian increase in MMP-9 was found in bronchoalveolar lavage (BAL) fluid, and a twofold increase in MMP-9/TIMP-1 ratio in subjects with nocturnal asthma [105]. High molecular weight form of MMP-9 has been observed to be significantly higher in BAL fluid in patients with severe asthma, and MMP-9 level was correlated with BAL neutrophils [106]. A marked increase in MMP-9 production and activity has been observed in the plasma of patients with severe acute asthma following stimulation with Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) and phorbol-12-myristate-13-acetate (PMA) [107]. MMP-9 immunoreactivity was identified in endobronchial biopsy specimens from all the asthmatic subjects, but could not be identified in healthy controls. Immunoreactivity of MMP-9 was found in bronchial epithelium and extracellular matrix in submucosa [108]. Immunohistochemical analysis revealed that in a higher percentage of severe asthmatic patients MMP-9 staining of the subepithelial basement membrane is prominent compared to control subjects. MMP-9 levels in the BAL fluid were also increased in patients with severe asthma [109]. RT-PCR analysis demonstrated up regulation of mRNA transcripts for MMP-1 and TIMP-1 in cell pellets of induced sputum from asthmatic patients compared with control subjects [110]. The intensity of MMP-1 mRNA expression was inversely correlated with the FEV(1) in asthmatic patients. Vermaelen et al. [111] have shown that MMP-9 deficiency inhibits the development of allergic airway inflammation by impairing the recruitment of dendritic cells into the airways and the local production of dendritic cell-derived proallergic chemokines.

5 Conclusion and Future Perspective

An impaired pattern of MMPs and TIMPs is associated with an elevated risk in several human diseases. Currently there is no available clinical therapy to completely cure or postpone neurodegenerative diseases. Therefore, novel therapeutic approaches are needed to prevent the progression of the disease for a better and healthy lifespan of patients. More basic research is also required to fully understand the diverse roles of MMPs in the pathophysiology of neurodegenerative diseases in order to design plausible MMP inhibitors to set strategies for prevention or cure of chronic neurodegenerative diseases. The development of new inhibitors is also necessary and that may also alleviate the pain inflicted in patients with asthma and COPD. Targeted delivery of MMP inhibitors directly to the lung might result in fewer side effects, which needs to be explored.

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