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Review

The role of matrix metalloproteinase in infectious diseases

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Abstract: Matrix metalloproteinases are involved in extracellular matrix remodeling through the degradation of extracellular matrix components and are involved in the inflammatory response by regulating the activities of TNF-alpha and IL-1beta, which are pro-inflammatory cytokines, in addition to extracellular matrix components. Since the regulation of inflammatory response and changes in the extracellular matrix by MMPs are related to the development of various diseases including lung and cardiovascular diseases, many studies have been conducted on the role of MMPs in pathogenesis. In addition, various studies have demonstrated that MMPs are involved in the pathogenesis of infectious diseases by regulating the expression and activity of MMPs by infection with pathogens. In this review, we discuss the role of MMPs in infectious diseases and the role of MMPs in inflammatory responses and present their potential as therapeutic targets in infectious diseases.

Keywords: Influenza A virus; SARS-COV-2; matrix metalloproteinases; infectious diseases

1. Introduction

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidase belonging to metzicin superfamily and are involved in the degradation and remodeling of extracellular matrix (ECM) components such as fibronectin, laminin, collagens, elastin, and basement membrane glycoproteins. MMPs are known to play important role in physiological processes such as wound healing, angiogenesis, embryonic development, synaptic plasticity, cell polarity, cell migration, and proliferation. In particular, various studies have been conducted on the role of MMPs in mechanisms related to angiogenesis and tumor invasion and metastasis, and it has been shown that the expression of MMPs by tumors is closely related to cancer metastasis and their proliferation. Based on molecular biological studies, cancer researchers thought that MMP inhibitors would be effective as an invasive cancer treatment by inhibiting the spread of cancer, and several clinical studies using various drug candidates were conducted [1, 2]. Unfortunately, several clinical trials for metastatic cancer have failed because severe side effects have been observed. The results of clinical trials have led to re-recognize the various functions of MMPs. MMPs cleave ECM components, but also signaling molecules and receptors to regulate cytokine signaling, disruption of the tissue-blood vessel barrier (TBB), and influx of infectious agents and immune cells during inflammation and infectious diseases. In this review, we will overview the role of MMPs in infection-associated pathology and discuss the therapeutic potential of MMP inhibitors in infectious diseases.

2. Matrix Metalloproteinase and inflammatory diseases

More than 24 MMP members identified in vertebrates are classified as collagenases, gelatinases, stromelysins, elastases, and membrane-type MMPs (MT-MMPs) according to their substrates and structural differences. The MMPs have multiple domains: a pre-domain (signal peptide), a pro-domain, a catalytic domain, and C-terminal-hemopexin-like (HPX) domain. Some MMPs have a specific structure. For example, gelatinase (MMP-2

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and MMP-9) contain a fibronectin type II (FN) motif before zinc-binding motif in the catalytic domain and the FN motif allows binding to gelatin and collagen. Matrilysin (MMP-7 and MMP-26) and MMP-23 do not have a HPX domain, and MMP-23 has a signal anchor with a transmembrane domain at the N terminus. MT-MMPs have a glycosylphosphatidylinositol (GPI) anchor or a transmembrane domain. The pro-domain contains a cysteine thiol group that interacts with zinc bound by three histidines in the zinc-binding motif, and this interaction keeps the inactive state of MMPs (ProMMPs). Proteolytic cleavage of pro-domain or modification of cysteine thiol group led to activation of MMPs. The reactive oxygen species (ROS) can activate MMPs through the oxidation of cysteine thiol groups of pro-domain under inflammation [3, 4]. Generally, activated MMPs are regulated by the four natural tissue inhibitors of metalloproteinases (TIMPs) that bind to catalytic domain in a 1:1 non-covalent manner. An imbalance between MMPs and TIMPs often leads to inflammation and immune responses. Catalytic domain contains a zinc-binding motif and an active site and determines substrate specificity. HPX domain regulates substrate binding and TIMPs binding. TIMP-1 and TIMP-2 were bound to the HPX domain of MMP-9 and MMP-2, respectively. In addition, proMMP-9 exhibits catalytic activity by binding to substrates, and the HPX domain of proMMP-9 has a higher substrate binding affinity than the HPX domain of active MMP-9 [5, 6]. The HPX domain of MMP2 binds to monocyte chemotactic protein 3 (MCP-3, also known as CC-chemokine ligand 7, CCL7) and cleaves MCP-3. Cleaved MCP-3 acts like a chemokine antagonist, modulating the inflammatory response [7]. In addition, CXC-chemokine ligand 12 (CXCL12, also known as SDF-1α) is also cleaved by MMPs and lost its binding affinity to CXCR4 [8]. MMP-1, -3, and -13 can cleave the CCL2 (also known as MCP-1), CCL8 (MCP-2), and CCL-13(MCP-3) and cause them to act like chemokine antagonist [9]. On the other hand, CXCL5 and CXCL8 are processed by MMP-9 to increase their chemoattractive properties, resulting in more efficient recruitment of neutrophils [10]. MMP-7 is involved in syndecan-1 cleavage and releases CXCL1 to recruit neutrophils to the site of injury [11]. MMPs regulate the activation and inactivation of the pro-inflammatory cytokine, interleukin 1 beta (IL-1β). MMP-7 and MMP-12 also act as tumor necrosis factor (TNF) converter that processes proTNF-alpha to release active TNF from macrophages [12, 13]. These studies showed that MMPs are involved in acute and chronic inflammation through cytokine and chemokine modulations, and can act as a switch in inflammation-related diseases and their regenerative phase.

2.1. Matrix Metalloproteinase and lung diseases

MMPs play an important role in the development of chronic inflammatory diseases, including pulmonary fibrosis (PF), chronic obstructive pulmonary disease (COPD), and coronary heart disease such as atherosclerosis. The development of emphysema-associated COPD and PF was associated with deposition of ECM in the lung. In the clinical research, the expression of MMP-1, MMP-2, MMP-8, MMP-9, MMP-12, and MT1-MMP in the lung was increased in COPD patients [14-19]. MMP-12 and other MMPs cleave elastin and other ECM components, causing the lung to lose its elastic recoil. Also, cleaved elastin fragment and collagen-derived peptide Pro-Gly-Pro mediate monocyte infiltration and promote inflammation, prolonging the inflammatory response and ECM disruption. Interestingly, MMP-12 deficient mice exposed to cigarette smoke do not develop emphysema and reduced macrophage recruitment to the lung [20-23]. MMP-12 is rarely detected in healthy macrophages, whereas its expression is increased in alveolar macrophages of smokers. These findings indicated that MMP-12 plays a pivotal role in emphysema-associated COPD. The increase in MMP-1, MMP-2, MMP-8, and MMP-9 were found in sputum and bronchoalveolar lavage (BAL) from asthma patients as well as COPD patients [24]. In the BAL of idiopathic pulmonary fibrosis (IPF), MMP-2, MMP-3, MMP-7, MMP-8, and MMP-9 are significantly increased compared to normal control [25]. MMP-3 deficient mice are protected against bleomycin-induced PF, and overexpression of recombinant MMP-3 in the rat lung leads to myofibroblast accumulation and PF [26]. In addition, Wnt/beta-catenin signaling, which is important in the pathogenesis of IPF, is activated by

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MMP-3 [27-29]. In damaged lung epithelial cells, MMP-7 induces the release of the syndecan-1/CXCL-1 complex to promote fibrosis development through neutrophil influx and later acts as an anti-fibrotic mediator to induce immunosuppressive leukocyte influx to resolve the fibrotic condition [30]. A decrease in PF and an increase in macrophage inflammatory protein-1 alpha (MIP-1α) and CXCL10 (also known as IP-10) were observed in MMP-8 deficient mice [31]. CXCL10 exhibits anti-fibrotic activity through inhibition of fibroblast chemotaxis. MMP-9 expression was found to be elevated in both humans and experimental lung fibrosis [32, 33], but animal studies using knockout mice showed conflicting results for the role of MMP-9, making it difficult to demonstrate a clear role [34, 35]. Although the role of some MMPs is controversial to establish clearly, clinical and in vitro studies can confirm the association of MMPs with chronic lung disease.

2.2. Matrix Metalloproteinase and cardiovascular diseases

In cardiovascular diseases, MMPs are activated through a variety of pathways to influence the process of atherosclerotic lesion formation. Thrombin exerts a potent pro-inflammatory effect on vascular cells, upregulates MMP-10, and promotes MMP-2 activation [36, 37]. MMPs activity, including MMP-1, MMP-2, and MMP-9, is induced by cathepsins present in atherosclerotic lesions [38-42]. Hormonal stimulation such as angiotensin II (Ang II) and estrogen also activates vascular MMPs, including MMP-2, MMP-8, MMP-9, MMP-13, and MT1-MMP [43-48]. In addition, oxidative stress and inflammatory cytokines such as TNF-alpha and ILs activate MMPs and are involved in vascular remodeling [49-51]. Several studies shown elevated plasma levels of MMP1, MMP-7, MMP-8, MMP-9, and MMP-10 in patients with coronary artery disease (CAD), whereas MMP-2 and MMP-3 levels were decreased [52-54]. In addition, the expression and activity of MMP-1, MMP-8, and MMP-13 were increased in human atherosclerotic plaques, resulting in plaque instability by collagen degradation [55-59]. Studies of inhibitor-treated or MMP-13-deficient mice showed that MMP-13 had no effect on plaque size, but was involved in collagen degradation in plaques [56, 60]. MMP-12 is expressed on macrophages present in advanced plaques and contributes to necrotic core expansion by promoting macrophage apoptosis [61, 62]. MMP-14 is also most prominently expressed in foam cell macrophages of advanced plaques, promoting plaque progression and instability [63, 64]. MMP-1, MMP-8, MMP-12, MMP-13, and MMP-14 not only degrade the extracellular matrix proteins present in the fibrous cap but also recruit monocytes/macrophages to the plaque region to promote foam cell formation and death. As a result, it was demonstrated that plaque instability was increased by enhancing lipid core expansion, plaque thrombus formation, and thinning of the fibrous cap by these MMPs. On the other hand, MMP-2, MMP-3 and MMP-9 are involved in promoting plaque stability [65]. An increase in the fibrous layer and an increase in plaque size were observed in MMP-3 deficient apoe knockout mice, demonstrating that MMP-3 is involved in plaque stability [66]. Increased expression of MMP-2 and MMP-9 was confirmed in the expansively remodeled plaques of patients who died from coronary artery disease [52, 67-69]. These results demonstrated that MMP-2, MMP-3, and MMP-9 can promote plaque stability by migrating vascular smooth muscle cells (VSMC) to developing atherosclerotic plaques. Furthermore, the absence of TIMP-1 in mice was observed to increase neointimal formation [70]. More recently, studies have reported that regulating MMPs and TIMP expression via specific microRNAs has a direct effect on plaque progression. In atherosclerosis, MMPs act as regulators that can control plaque stability and progression, and the expression of these MMPs is regulated by cytokines, oxidative stress, smoking, and pathogen infection. Acute inflammation is triggered by a variety of factor, including pathogens, tissue injury and toxic compounds. The inflammatory response eliminates inflammatory factors, including pathogens, and then restores damaged tissue and homeostasis.

3. Matrix metalloproteinase and infectious diseases

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Infectious diseases are diseases caused by infection by various microorganisms such as bacteria, viruses, protozoa, and fungi, and exhibit various symptoms. Excessive activity of MMPs induced by infection has been implicated in the pathogenesis of infectious diseases such as sepsis, meningitis, tuberculosis, Lyme disease, and pneumonia.

3.1. Bacterial pneumonia

Pneumonia is an infection of the lungs caused by pathogen, including *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus*, influenza viruses, adenoviruses, and respiratory syncytial viruses. Epithelial cells not only act as a physical barrier, but also regulate inflammation by secreting MMPs and cytokines to recruit inflammatory cells to attack invasive pathogens. MMP-7, MMP-10, and MMP-28 are upregulated in bronchial epithelial cells by bacterial infection [71-73]. MMP-28 is observed to regulate neutrophil recruitment to the lung in viral infection. MMP-8 and MMP-9 were increased in patients with hospital-acquired pneumonia (HAP) and correlated with clinical severity [74]. In HAP patients infected with high-risk pathogens, MMP-8 and MMP-9 levels were increased in the lungs and MMP-9 activity was also increased compared to control and low-risk pathogen-infected patients [75]. MMP-8 and MMP-9 are produced by neutrophils or macrophages, and MMP-8 is involved in neutrophil migration. MMP-9 and MMP-2 are known to play an important role in the migration of various leukocytes, and MMP-9 increases the influx of immune cells through destruction of basement membrane components. However, Rosendahl et al. suggested that bacteria could utilize MMP-9 to self-propagate at local sites of infection by increasing TBB permeability [76]. The increase in the permeability of TBB by MMPs including MMP-9 is thought to affect the two aspects of inflammatory cell influx and pathogen dissemination in the pathology of pneumonia. MMP-9 increase is observed not only in HAP but also in patients with community-acquired pneumonia (CAP) and ventilator-associated pneumonia [77, 78]. MMP-9/TIMP-1 ratio was significantly increased in CAP patients, and TIMP-1 level was positively correlated with CAP severity [79]. The balance of MMP-9/TIMP-1 and the activity of MMP-9 appear to play an important role in the pathology of bacterial pneumonia. The role of MMP in pneumonia caused by viral infection including influenza A virus (IAV) will be described later.

3.2. Bacterial sepsis

Sepsis is a disease in which pathogens or endotoxins cause an inflammatory response throughout the body through blood vessels, indicating major organ abnormalities. Various clinical studies have shown increased concentrations of MMPs and TIMPs including MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, TIMP-1, TIMP-2, and TIMP-3, in the plasma of sepsis patient. However, as a result of statistical studies on the association between an increase in MMP and disease severity, MMP-7 and MMP-9 were negatively correlated with disease severity, and MMP-3 and TIMP-1 concentrations were associated with mortality [80-82]. Other research groups described serum levels of MMP-8 and TIMP-1 were correlated with mortality in sepsis patients [83, 84]. Various animal and *in vitro* studies were performed to demonstrate the role of MMPs clinically associated with the severity of sepsis. In animal model of sepsis, MMP-2 and MMP-9 are activated, blood-brain barrier (BBB) permeability increase, and BBB permeability was reversed by MMP inhibitor [85]. Additionally, studies of abdominal sepsis using MMP-9 deficient mice have shown that MMP-9 deficiency reduces leukocyte recruitment [86]. Tressel and colleagues reported that proMMP-1 and active MMP-1 are increased in plasm of sepsis patients and that active MMP-1 level directly correlate with death [87]. In addition, MMP-1 is considered to be an important activator of PAR1, and blockage of MMP-1 activity inhibited endothelial barrier disruption, lung vascular permeability, and cytokine storm. Through a study of the cecal ligation and puncture-induced sepsis mouse model, Solan et al. reported that MMP-8 deficiency improved the survival of mice and decreased early lung neutrophil

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infiltration, cytokine and chemokine expression [84]. It was suggested that the inflammatory response by MMP-8 is directly related to NF-kB activity. In studies of other MMPs, it has been recently reported that MMP-13 is an important mediator regulating intestinal epithelial barrier integrity by TNF activity in sepsis and inflammatory bowel disease [88]. These studies are evidence that MMPs increased by sepsis are involved in increasing inflammation and disease severity. Unlike these MMPs, MMP-7 expression in the small intestine is involved in antimicrobial and homeostasis maintenance through α-defensin activation. In mice, MMP-7 deficiency impairs defense against gut pathogens such as *Salmonella typhimurium* and *E. coli* [89]. In clinical and animal studies, MMP-7 is considered to be more important in eliminating infectious agents through immune activation in sepsis patients, but there are some controversies. A study reported in 2014 showed that the absence of MMP-7 protects mice from LPS-induced lethality due to a decrease in α-defensin activation and the subsequent reduction in stimulation of IL-6 secretion by macrophages [90]. This finding indicated that MMP-7 can exhibit pro-inflammation activity through α-defensins activity in acute inflammation.

3.3. Other bacterial infectious diseases

Borrelia burgdorferi, which causes Lyme disease, upregulates MMP-9 and MMP-1 in human monocytes, and activated MMPs may be play in the transmission of the Lyme disease spirochete [91, 92]. In the study of bacteria-induced periodontitis, MMP-13 expression is increased by infection and inhibition of MMP-13 expression decreased the production of inflammatory mediators and bone resorption [93-95]. In neuroinflammatory diseases such as bacterial meningitis, MMP is known to be involved in the pathology through the influx of blood-derived immune cells by opening the neural barrier. In particular, high levels of MMP-8 and MMP-9 are found in the cerebrospinal fluid of patients with bacterial meningitis.

These studies prove that bacterial infection is involved in various pathologies by regulating the expression of MMPs involved in host immune responses. In particular, many results have reported that it is involved in the inflammatory response and removal of pathogen through the process of regulating the permeability of the TBB involved in the influx of immune cells and the movement of pathogen due to the regulation of the expression of MMPs by infection. In addition, these results are not limited to bacterial infections, but are also confirmed in viral infections. Recently, associations of MMPs with viral pathologies, including IAV, zika virus, dengue virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported.

4. Virus-induced matrix metalloproteinases expression and pathogenesis

4.1. Zika virus infection

Zika virus (ZIKV) is a virus belonging to the flavivirus family, which includes dengue virus (DENV), Japanese encephalitis virus (JEV), and west nail virus, and is transmitted through insects including mosquitoes and ticks. ZIKV was discovered in 1947, but recently, the virus spread significantly in South America in 2015, and was pointed out as the cause of microcephaly and Guillain-Barré syndrome, and various studies have been conducted to elucidate these causes and mechanisms. In a study examining the concentrations of cytokines, MMP-2, and MMP-9 in semen and plasma from ZIKV-infected patients, MMP-2 and MMP-9 levels remained high even after the virus was cleared [96]. Another study suggested that MMP-2 and MMP-9, which are increased in the placenta of ZIKV-infected patients, may induce collagen degradation, leading to placental villi immaturity [97]. In mouse and *in vitro* studies, it has been reported that MMP-9 increased during ZIKV infection and that the NS1 protein of ZIKV was involved in MMP-9 ubiquitination, which increase stability and consequently increases the blood-testis barrier (BTB) permeability, leading to the entry of ZIKV into the testis [98, 99]. In addition, it was reported that the activity of MMP-10 and MMP-13 were increased upon ZIKV infection of

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HUVEC cells, a human umbilical vein endothelial cell line [100]. These results are insufficient to prove whether the ZIKV-induced changes in MMPs are involved in the induction of microcephaly, but suggest that MMPs may be involved in infection-induced placental damage and sexual contact infection.

In particular, it has been reported that MMP-2 and MMP-9 are increased by ZIKV as well as DENV and JEV infection to induce vascular leakage as well as increase in BBB permeability [101, 102, 103]. In a recent review on the role of MMPs in the pathogenesis of DENV, it was also noted that there is a correlation between the disease severity caused by DENV infection and MMP-2 and MMP-9 [104]. In the study of the association of MMPs with various diseases such as vascular disease, lung disease, and cancer, MMP-2 and MMP-9 have been heavily studied due to their broad substrate specificity. In a recent COVID-19 study, it was reported that MMPs, including MMP-2 and MMP-9, are altered in patients with COVID-19.

4.2. Severe acute respiratory syndrome coronavirus 2 infection

COVID-19, a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection through the respiratory tract, has symptoms similar to influenza and pneumonia, mainly causing respiratory symptoms, but also affects other parts of the body. In addition, sequelae may appear for a long time after recovery from COVID-19. One of the causes of COVID-19 sequelae is lung injury and multiple organ failure due to cytokine storm, and MMPs play an important role in lung physiology. In a recent study, it was confirmed that MMP-2, MMP-3, and MMP-9 were correlated with the COVID-19 severity [105, 106]. Interestingly, MMP-2 was decreased in the plasma of COVID-19 patients compared to the control group [105]. Additionally, MMP-2 was upregulated in COVID-19 patients with hypertension, although still downregulated compared to healthy controls. Elevation of MMP-2 in hypertension is known from several studies, but studies on the mechanism of MMP-2 decrease in COVID-19 patients are needed. MMP-9 is known to induce leukocyte recruitment by increasing expression in lung diseases including COPD and Asthma. Circulating leukocyte count, IL-6, and myeloperoxidase levels were correlated with MMP-9 concentration in COVID-19 patients [106], and these results prove that MMP-9 is associated with inflammation in COVID-19 patients. MMP-3 plays a role in the pathogenesis of acute inflammation-induced lung injury, as evidenced by a reduction in the extent of lung injury by inhibition of MMP3 in animal models [107, 108]. The increase in MMP-3 in the serum of COVID-19 patients was not confirmed after 1 week of hospitalization, which is evidence that the major contribution of MMP3 activity in the early stages of lung inflammation caused by COVID-19 [106]. Recently, the results of a study on the expression of MMPs in the lung biopsy samples of COVID-19 patients and the mechanism of lung disease pathogenesis were reported [109]. Unlike the studies using serum from COVID-19 patients, MMP-2, MMP-7, MMP-8, and MT1-MMP were increased in the lung of COVID-19 patients. In particular, MMP-2 and MMP-8 were significantly increased, indicating a positive correlation with soluble HLA-G and soluble TREM-1 levels, which regulate an innate immune response. Also, a significant relationship was confirmed between MMP-2 expression and malondialdehyde (MDA) level, an oxidative stress marker. MMP-2/MMP-8 activity is involved in the lung pathogenesis of COVID-19 patients by increasing the influx of immune cells into the lung, secreting HLA-G, and regulating the immune response through oxidative stress. Consequently, they suggested that MMP-2/MMP-8 activity is involved in the lung pathogenesis of severe COVID-19 patients by increasing the influx of immune cells into the lung, and regulating the immune response through secreting HLA-G and oxidative stress [106].

There are opinions that the pathological features of COVID-19, including severe lung disease and excessive inflammatory response, may be related to MMPs, and thus MMPs inhibitors have the potential as effective COVID-19 treatment agents. Although there are no studies yet that specific MMP inhibitors have alleviated the severity of COVID-19, there are reports that doxycycline, a non-specific MMP inhibitor, can reduce the need for

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intensive care unit hospitalization for COVID-19 patients [110]. However, doxycycline is a broad-spectrum tetracycline antibiotic used for the treatment of bacterial and parasitic infections, and it is difficult to regard it as an MMP-specific inhibitory effect.

4.3. Influenza A virus infection

In the case of respiratory syncytial virus (RSV) and influenza A viruses (IAV), which cause lung disease through respiratory infection, there are studies that MMPs inhibition can reduce the severity of viral pathology [111 - 114]. In particular, IAV infection causes lung damage and increases the risk of various diseases such as bacterial pneumonia, sepsis, and exacerbation of cardiovascular diseases. Various studies have demonstrated the mechanisms by which MMPs, particularly MMP-9, increase the risk of disease caused by IAV infection [113, 115-118]. The most well-known mechanisms are: First, viral infection increases the pro-inflammatory cytokines such as TNF-alpha, IL-6, and IL-1 beta, and increases activity of AP-1, NF-kb, and MAPK signals. After that, proteases including MMPs and trypsin are upregulated, resulting in increased permeability and immune response. In particular, cytokine storms, in which inflammatory cytokines are explosively increased in the early stages of IAV infection, are often induced by the uncontrolled neutrophil influx and alveolar macrophage activation. TNF-alpha, which is increased due to IAV infection, induces MMP-9 secretion in neutrophils, and ECM collapse occurs due to the secreted MMP-9 and increases the influx of immune cells to the site of infection, increasing the severity of IAV infection. The role of MMP-9 in lung diseases caused by IAV infection was also demonstrated in studies using MMP-9 deficient mice [118]. According to the results of these studies, lung injury was reduced in MMP-9 deficient mice due to decreased immune cell influx and type I IFN levels compared to WT mice during H1N1 infection. Interestingly, studies on lung damage caused by secondary bacterial infection after influenza virus infection also found that the MMPs inhibitor batimastat reduced the inflammatory response and lung damage in the infected mice. In addition, Talmi-Frank et al reported that the combination therapy of anti-MT1-MMP and the antiviral agent Tamiflu significantly increased ECM protection and survival rate from sepsis caused by *S. pneumoniae* [119]. These results demonstrate that MMP-9 as well as MT1-MMP play an important role in sepsis or pneumonia, secondary bacterial infection caused by influenza virus infection.

IAV infection increases the risk of underlying diseases, including cardiovascular disease and hypertension, as well as lung disease. In particular, acute cardiovascular disease exacerbation due to influenza virus infection has been proven through many studies and it is known that vaccination can effectively reduce the risk. Cardiovascular disease exacerbation caused by influenza virus is known to be caused by increased immune cell influx and thrombosis due to viral infection [120], but the mechanism is not clear. We predicted that MMPs may play an important role in the mechanism of IAV-induced cardiovascular disease exacerbation, and we demonstrated that IAV-induced MMP-13 expression in atherosclerosis plaques reduced plaque stability [121]. Cellular sources of MMPs in atherosclerosis plaques are known as endothelial cells, vascular smooth muscle cells, and macrophages. In particular, macrophages are known to be related to the secretion of various MMPs. We confirmed that MMP-13 was significantly increased in IAV-infected macrophages *in vitro* and *in vivo*. MMP-13 is mainly involved in plaque stability through collagen degradation. MMP-9 and MT1-MMP not only increase the influx of immune cells by increasing permeability in IAV-infected lungs, but also may induce IAV-exposed macrophages to flow into atherosclerotic plaques. Virus-exposed macrophages increase MMP-13, contributing to decreased plaque stability and risk of rupture. Some studies have suggested a relationship between other MMPs and IAV, but it is necessary to prove it through additional studies [122-124]. Additionally, MMP inhibitor study showed that treatment of doxycycline to IAV-infected mice reduced acute lung injury and decreased MMP2/MMP-9, but did not change viral concentrations [125]. In this study, it was suggested that the pulmonary injury was reduced due to the MMPs inhibitor effect by doxycycline.

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Other studies have identified that altered MMP expression and activity in cells infected with viruses, including tick-borne encephalitis virus or varicella zoster virus (Table 1). Additional verification is needed to prove the regulatory mechanism caused by viral infection and its role in pathological mechanisms, but previous studies can confirm that MMPs expression is increased in various viruses and that MMPs expression is involved in pathological mechanisms.

Table 1. Viral infections in which matrix metalloproteinases activity is associated with pathology.

Virus	MMPs regulation	Reference
Human Immunodeficiency Virus (HIV)	MMP-2 ↑ , MMP-9 ↑ , TIMP-1 ↓	[126-130]
Human T-Lymphotropic Virus type 1 (HTLV-1)	MMP-3 ↑ , MMP-9 ↑	[131-133]
Hepatitis B Virus (HBV)	MMP-2 ↑ , MMP-9 ↑ , MT1-MMP ↑	[134-136]
Hepatitis C Virus (HCV)	MMP-2 ↑ , MMP-9 ↑	[137, 138]
Dengue Virus (DENV)	MMP-2 ↑ , MMP-9 ↑	[104, 139, 140]
Japanese Encephalitis Virus (JEV)	MMP-2 ↑ , MMP-7 ↑ , MMP-9 ↑ , TIMP-1 ↑ ↓ , TIMP-2 ↑ , TIMP-3 ↑	[102, 141, 142]
Respiratory Syncytial Virus (RSV)	MMP-2 ↑ , MMP-9 ↑ , MMP-10 ↑ , MMP-12 ↑	[114, 143-145]

MMPs; matrix metalloproteinases

5. Conclusions and Future Directions

Microbial infection induces inflammation at the site of infection, leading to various diseases, such as pneumonia, meningitis, hepatitis, and cardiovascular disease. Various studies have demonstrated the involvement of MMPs in the development of these diseases. MMP-8 and MMP-9 levels are increased in pneumonia patients, and an increase in MMP-8 and MMP-9 in lung tissue induces neutrophil influx, contributing to the elimination of infectious agents. However, the increase in TBB permeability by MMP-9 may contribute to the spread of infectious agents as well as neutrophil influx. MMP-9 is significantly increasesd by infection with respiratory viruses including IAV, SARS-COV-2, human rhinovirus, and RSV, and correlated to the severity of infectious diseases. Furthermore, IAV infection in MMP-9 deficient mice decreased the virus burden, lung injury, and increased adaptive immune response, which is evidence of the pathological function of MMP-9 [118]. According to a recent report, it was confirmed that MT1-MMP inhibition reduced mortality and tissue damage caused by IAV infection, and also reduced secondary bacterial infection [119]. MT1-MMP is known to activate proMMP-9, suggesting that proMMP-9 activity may be reduced by MT1-MMP inhibition. In addition, increased BBB permeability by MMP-9 was confirmed to play a pivotal role in infectious encephalitis and meningitis [102, 103, 116]. The symptoms caused by SARS-COV-2 and IAV infection were alleviated by doxycycline and batimastat, which are broad-spectrum MMPs inhibitors [110, 118, 125]. Several studies have confirmed that MMPs, including MMP-2, MMP-3, and MMP-8, are involved in the pathogenesis of infectious diseases. In addition to MMP-9 and MT1-MMP, which have proven therapeutic effects in animal models, studies on the therapeutic effect on infectious diseases targeting other MMPs are needed.

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In conclusion, MMPs are regulated by pathogen infection and involved in the pathogenesis of infection, and it is considered that disease can be alleviated through the regulation of over-activated MMPs. Although there have been various clinical studies on MMP inhibitors, most MMP inhibitors have been clinically tested for cancer, and clinical trials have failed due to side effects. Alleviation of pathological mechanisms through MMP inhibition in infectious diseases has been confirmed in some animal experiments, providing a proof-of-concept for MMP inhibitors. Although the therapeutic potential of MMP inhibitors in infectious diseases has been suggested, further studies including identification of specific targets and demonstration of effectiveness in clinical trials are needed.

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