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Role of the extracellular matrix in COVID-19

Jia-Jia Huang, Chu-Wen Wang, Ying Liu, Ying-Ying Zhang, Nai-Bin Yang, Yu-Chun Yu, Qi Jiang, Qi-Fa Song, Guo-Qing Qian

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Abstract

An outbreak of coronavirus disease 2019 (COVID-19) has spread globally, with over 500 million cases and 6 million deaths to date. COVID-19 is associated with a systemic inflammatory response and abnormalities of the extracellular matrix (ECM), which is also involved in inflammatory storms. Upon viral infection, ECM proteins are involved in the recruitment of inflammatory cells and interference with target organ metabolism, including in the lungs. Additionally, serum biomarkers of ECM turnover are associated with the severity of COVID-19 and may serve as potential targets. Consequently, understanding the expression and function of ECM, particularly of the lung, during severe acute respiratory syndrome of the coronavirus 2 infection would provide valuable insights into the mechanisms of COVID-19 progression. In this review, we summarize the current findings on ECM, such as hyaluronic acid, matrix metalloproteinases, and collagen, which are linked to the severity and inflammation of COVID-19. Some drugs targeting the extracellular surface have been effective. In the future, these ECM findings could provide novel perspectives on the pathogenesis and treatment of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Extracellular Matrix; Inflammation

Core Tip: Coronavirus disease 2019 (COVID-19) shows abnormal expression of the extracellular matrix (ECM). The ECM is a type of macromolecular network secreted by cells into the extracellular stroma, which is also the major component of connective tissue. It can trigger various activities biologically essential for tissue homeostasis and normal organ development. Upon severe acute respiratory syndrome coronavirus 2 infection, ECM proteins are involved in the recruitment of inflammatory cells and interference with target organ metabolism, including that of the lung. The manuscript addresses the current findings of ECM, which are linked to the severity and inflammation of COVID-19, and the roles of ECM in COVID-19.

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INTRODUCTION

In December 2019, an outbreak of novel coronavirus-infected pneumonia, called coronavirus disease 2019 (COVID-19), led to a global pandemic. It has a high incidence rate with a rapid rate of transmission and has spread worldwide[1]. Up to now, World Health Organization statistics indicate that more than 600 million people have been infected with COVID-19 (Source: <https://covid19.who.int>. Last accessed date October 10, 2022). With further evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the Omicron variant has emerged as the dominant strain[2]. Therefore, the development of effective countermeasures is important to combat COVID-19.

COVID-19 shows a systemic inflammatory response and abnormal expression of the extracellular matrix (ECM), which regulates homeostasis and injury repair responses[3,4], has a crucial structure with a dynamic and complicated organization, and can trigger various activities biologically essential for tissue homeostasis and normal organ development[5]. For instance, the tissue architecture of the lung forms during embryonic development by epithelial branching and is determined by the pulmonary ECM, which changes in composition and distribution over time and provides mechanical stability and elasticity to the tissue. The ECM comprises the interstitial connective tissue matrix and basement membrane separating the epithelium from the surrounding matrix. Hynes *et al*[6] reported the most integrated list of proteins, constituting approximately 300 proteins, which form the core matrix and include 36 proteoglycans, 43 collagen subunits, and 200 complex glycoproteins. The interstitial connective tissue matrix contains collagen type I, fibronectin, proteoglycans, glycosaminoglycans, tenascin C, and elastin and provides a structural scaffold for the tissue. Among the components of the basement membrane are laminins, collagen type IV, heparan sulphate proteoglycans (HSPGs), entactin, nidogen and glycoproteins, such as integrins and hemidesmosomes, that bind to ECM proteins[7]. Among these, proteoglycans, glycosaminoglycans, collagens, and elastin are the main molecules of the ECM. During normal development, elements of the ECM interact with epithelial cells constantly *via* ligands as cell receptors, such as integrins and hemidesmosomes. Thus, ECM can deliver signals that regulate adhesion, migration, proliferation, differentiation, survival, and apoptosis[8]. It can also seal and release local growth factors, such as transforming growth factor (TGF)- β , epidermal growth factor, fibroblast growth factor, and other signalling molecules. However, its components change dynamically. Cleavage of ECM components regulates ECM abundance, composition, and structure, thereby influencing cell behaviour[9]. ECM can be cleaved by different families of proteases, such as matrix metalloproteinases (MMPs), adamalysins (ADAMs and ADAMTS), meprins, MMP inhibitors, and other enzymes (*e.g.*, Ser proteases). Cells constantly reconstruct and remodel the ECM through synthesis, degradation, reassembly, and chemical modifications, which are complex and firmly regulated to maintain tissue homeostasis. ECM is also involved in inflammatory storms. ECM proteins help recruit inflammatory cells. However, their characteristics and functional mechanisms in COVID-19 remain obscure. Here, we review the roles of the ECM in COVID-19 with underlying regulatory mechanisms and application prospects and challenges.

ALTERATIONS IN ECM MOLECULES IN COVID-19

Hyaluronan (HA) is a key ECM compound in every vital organ system that plays a crucial role in pulmonary biological functions. Respiratory abnormalities can be triggered by HA when production

and degradation are imbalanced[10]. HA is produced by three HA synthases (HAS1, HAS2, and HAS3); in particular, HAS2 generates HASs of a molecular mass greater than that of HAS1 and HAS3[11]. HA functions as a scaffold in ECM and contributes to the thickness of the endothelial glycocalyx under normal conditions. Furthermore, HA, particularly high-molecular-weight HA (HMW-HA), promotes the self-renewal survival activity of alveolar macrophages and type II alveolar epithelial cells. It is responsible for permeability selectivity and is involved in the mechanosensory effect of the endothelial glycocalyx in blood vessels upon blood folding[12].

In deceased COVID-19 patients, lungs at autopsy confirmed that HA obstructs alveoli with a presence in the exudate and plugs, as well as in thickened perialveolar interstitium compared with staining in normal lung tissue[13]. The pathophysiology of HA elevation in COVID-19 should be understood. Infection with SARS-CoV-2 causes a cytokine storm and releases abundant proinflammatory cytokines, such as interleukin-1 β and tumour necrosis factor- α , which leads to HAS2 overexpression[14]. Therefore, HMW-HA production increases remarkably and can absorb abundant water molecules owing to their hygroscopic properties. Hellman *et al*[13] reported that fatal cases of COVID-19 were associated with the accumulation of hyaluronic acid in the alveolar spaces of the lungs and occurrences of hypoxemia and respiratory failure. A mouse model has also been shown to develop lesions in the lungs due to HA[15]. In a prospective study, the authors found that the COVID-19 cytokine milieu stimulates aberrant synthesis and degradation of HA, and HA fragments present at elevated levels in COVID-19 patient plasma directly induce endothelial barrier dysfunction[16]. This finding was corroborated by other studies[17,18]. Therefore, HA storms are likely to occur during the progression of COVID-19. Hällgren *et al*[19] demonstrated that HA levels in both bronchoalveolar lavage fluid and serum increased in adults with severe acute respiratory distress syndrome (ARDS). SARS-CoV-2 infection leads to the accumulation of HA, similar to severe influenza[20]. In severe lung inflammation, HA is destroyed by the reactive oxygen species produced from neutrophils that can breakdown HMW-HA into small fragments, including low-molecular-weight HA and oligo-HA[21]. This could further boost the release of cytokines and be a feedback link of the HA storm. Thus, HA storms increase the severity and lead to a poor prognosis of COVID-19.

MMP

MMPs are a family of zinc-dependent enzymes that can degrade most extracellular matrix proteins[5]. They can be derived from several cell types, including epithelial cells, fibroblasts, and endothelial cells in the lungs, and they play important roles in several vital mechanisms and pathways, such as tumour infiltration and metastasis, regulation of inflammatory and immune responses, ECM degradation, normal tissue repair and remodelling, and proliferation and signalling pathways. To date, 23 MMPs have been identified in humans[22], all of which are released as inactive zymogens (preproenzymes) secreted from cells into the extracellular space. Subsequently, MMPs are processed proteolytically or by modifying the thiol group by oxidation for activation[7]. The development and progression of many acute and chronic lung disorders are associated with excessive MMP synthesis and degradation, which can result in cell injury and pulmonary fibrosis.

This paper summarizes the involvement of MMPs in regulating SARS-CoV-2 (Table 1). MMPs are differentially expressed in patients with COVID-19 in association with the occurrence and development of the disease. Syed *et al*[23] found that MMP-1 and vascular endothelial growth factor (VEGF)-A are excessively elevated in COVID-19 and associated with the severity of COVID-19. MMP-1 is an interstitial collagenase capable of degrading collagen types I, II, and III and plays a crucial role in vascular remodelling and diseases[24]. It is necessary for tissue development and maintenance, but its overexpression promotes hyperactivation of MMP-1/PAR1 signalling, which can increase the expression of VEGF receptor 2, decrease vascular endothelial cell function and lead to excessive recruitment and activation of inflammatory cells[25]. Furthermore, in idiopathic pulmonary fibrosis (IPF), it is described as a prospective peripheral blood biomarker[26]. The 6-mo follow-up after hospital discharge of patients with COVID-19 revealed that approximately half of the patients with moderate or severe COVID-19 developed impaired pulmonary diffusion and early fibrotic changes in association with elevated MMP-1[27]. According to a comparative study of COVID-19 and influenza A patients, elevated MMP-1 and MMP-3 Levels were found only among COVID-19 patients[28]. Thus, MMP-1 may play a role in tissue damage associated with SARS-CoV-2 infection, and MMP-1 Levels may be a prognostic biomarker of COVID-19.

Gelatinases, including gelatinases A (MMP-2) and B (MMP-9), whose expression increases during inflammation, cleave several types of collagens, such as types IV and V[29]. MMP-2 and MMP-9 are significantly elevated in asthma, acute lung injury, ARDS, and IPF. MMP2, a constitutively expressed MMP in the brain, is involved in central nervous system pathology, and MMP9 is a major inducible MMP released in neuroinflammatory responses. MMP-2 and MMP-9 levels are significantly elevated in the cerebrospinal fluid of patients with COVID-19 who have neurological syndrome compared to those without neurological syndrome[30]. In addition, patients with respiratory failure due to COVID-19 have elevated MMP-9 in the circulation. D Avila-Mesquita *et al*[31] reported compared to patients with mild

Table 1 Dysregulation of the extracellular matrix in coronavirus disease 2019

ECM	Alterations in COVID-19	Suggested ECM role in disease	In other inflammatory and fibrotic lung disorders
MMP-1	Increased MMP-1 levels have been detected in the serum of patients, which correlated with the severity of COVID-19 and early fibrosis with this condition[23]	Drive endothelial cell destruction, such as by over-activating the mmp-1/PAR1 pathway, increasing VEGF-2 receptor expression, and causing endothelial damage. Involved in collagen deposition in IPF	Emphysema, Asthma: MMP-1 levels raised
MMP-2	Increased MMP-2 levels have been detected in the CSF samples of COVID-19 patients with neurological syndrome[30]. Downregulated MMP-2 levels have been detected in the plasma samples with this condition, which correlated with the mortality rate of COVID-19[31]	Involved in disruption of the blood-brain barrier. Being Involved in the regulation of angiogenesis may lead to vascular remodeling. Play an anti-inflammatory effect in the endothelial dysfunction	Asthma, Idiopathic Pneumonia: MMP-2 levels raised. pulmonary fibrosis (IPF): Disproportionate extracellular matrix degradation
MMP-3	Increased MMP-3 levels have been detected in serum of individuals with this condition[37,40]	Associated with activation of MMP-9 and enhanced synthesis of procollagen	Asthma: MMP-3 levels raised
MMP-7	Increased MMP-7 levels have been detected in the serum of obese-diabetic patients with novel coronavirus pneumonia-infected[36]. Elevated in COVID-19 patients with early fibrotic changes[27]	Contribute to airway epithelial damage and inflammation as well as Play a profibrotic effect	Asthma, Cystic fibrosis (CF), ARDS: MMP-7 levels raised
MMP-8	/	/	COPD, Emphysema, Asthma: MMP-8 levels raised
MMP-9	Increased MMP-9 levels have been detected in the circulation of COVID-19 patients with respiratory failure and with obese-diabetic[36]	Associated with respiratory failure. Linked to inflammation-induced tissue remodeling. Contributes to the disruption of alveolar epithelial basement membrane	COPD, Emphysema, Asthma, IPF, UIP, ALI, ARDS: MMP-9 levels raised
MMP-10	The CSF levels of MMP-10 correlated with the degree of neurologic dysfunction exhibited[41]	Associated with neurodegeneration	/
MMP-12	/	/	COPD, Emphysema: MMP-12 levels raised
MMP-14	Increased MMP-14 levels in lung tissue have been detected COVID-19 patients[32]	Implicated in COVID-19 pathogenesis	COPD: MMP-14 levels raised
HA	Increased HA levels have been detected in lungs of deceased COVID-19 patients[13]. HA fragments present at elevated levels in COVID-19 patient plasma [16]	Induce endothelial barrier dysfunction	ARDS: HA levels raised
Proteoglycans	/	/	COPD, IPF, Asthma, Bronchiolitis obliterans syndrome: Versican levels raised
Collagen	16 collagens are downregulated or diminished in COVID-19[52]. Collagen deposits on Lung Samples of deceased COVID-19 patients[51]	Damage of mechanical characteristics of lungs	Asthma, COPD, IPF: Display differing collagen deposition
ADAMs	Increased ADAM12 and ADAM17 levels have been detected in serum of COVID-19 patients[56-58]	ADAM17 may be associated with viral entry. ADAM12 plays a role in inflammation and endothelial cell permeability	/
ADAMTS	ADAMTS13 decreased significantly with increasing COVID-19 severity[59,60]	Associated with vascular microthrombotic disease	/

COVID-19: Coronavirus disease 2019; ALI: Acute lung injury; ARDS: Adult respiratory distress syndrome; COPD: Chronic obstructive pulmonary disease; ECM: Extracellular matrix; HA: Hyaluronan; MMP: Matrix metalloproteinase; IPF: Idiopathic pulmonary fibrosis; UIP: Usual interstitial pneumonia; VEGF-2: Vascular endothelial growth factor 2.

COVID-19, patients with severe COVID-19 had lowered plasma MMP-2 levels and highly elevated plasma MMP-9 levels. Furthermore, compared to COVID-19 survivors, COVID-19 nonsurvivors had higher MMP-2 and MMP-8 levels in the lung[32]. Pedro V suggested that overexpression of MMP-2 and MMP-8 caused lipid peroxidation, which resulted in intensive destruction of lung tissue in severe COVID-19 cases[32]. Regulation of MMP expression and activity is complex. Mmp2^{-/-} mice display more pronounced interstitial and perivascular fibrosis in response to angiotensin II[33]. SARS-CoV-2 binds to angiotensin converting enzyme 2 for intracellular invasion, thereby increasing vasoconstriction and inflammation. An MMP-2 deficiency leads to inflammation, and low levels are just as harmful to the cardiovascular system as high levels[34]. Taken together, when MMP-2 activity falls below baseline, the bioavailability of proinflammatory cytokines could be normally cleaved and inactivated by MMP-2 elevation, leading to the production of cytokines in the circulation, which stimulates systemic inflam-

mation. MMP-9 is secreted by many cells, such as neutrophils and macrophages, and is correlated with inflammation. When activated by cytokines and lipopolysaccharides, macrophages can produce MMPs at sites of inflammation. To determine whether MMP concentrations are increased in COVID-19, two studies measured plasma concentrations in patients with COVID-19[35]. Studies have shown that patients with obesity, diabetes, and COVID-19 have elevated alveolar M2 macrophages and produce more MMP-7 and MMP-9, which promote fibrogenesis and lead to lung stiffening[35,36]. Therefore, MMP-9 may be an early indicator of respiratory failure in COVID-19, consistent with the results of Gelzo *et al*[37]. MMP-7, or fibrotic genes, is overexpressed in the lung tissue of patients with IPF and ARDS compared to normal lung tissue[38]. Recently, an observational and prospective study showed a significant increase in the detection of MMP-7 and MMP-14 in lung tissue from COVID-19 patients compared to that from non-COVID-19 subjects[32]. Another MMP in BALF that is upregulated during the initial phases of ARDS is MMP-28, which is associated with increased alveolar neutrophils[39].

MMP-3 plays a role in the pathogenesis of acute inflammation-induced lung injury. Shi *et al*[40] suggested that MMP-3, which activates other MMPs in the family, may be a valuable biomarker of COVID-19. It is elevated in COVID-19 in the initial phase of lung inflammation, which is possibly related to the activation of MMP-9 and augmented synthesis of procollagen I[37]. Nevertheless, after one week of hospitalization, an increase in MMP-3 serum levels in patients with COVID-19 was not observed, indicating that MMP-3 activity contributes most in the early stages of lung inflammation caused by COVID-19[37]. The level of MMP-10 in cerebrospinal fluid of COVID-19-positive patients and healthy controls was related to their degree of neurologic dysfunction[41].

Many other MMPs are altered in respiratory diseases[42] but have not yet been discovered or reported in COVID-19. In addition to the aforementioned enzymes, MMP-12, MMP-15, MMP-11, and MMP-13 cause acute lung injury and ARDS[43].

PROTEOGLYCANS

Proteoglycans are the major component of the basement membrane, intracellular granules, and ECM. They influence multiple cellular events structurally and functionally, including proliferation, differentiation, and gene expression. Proteoglycans, such as decorin, versican, perlecan, and aggrecan, are a family of widely differing protein molecules whose structure is characterized by a core protein molecule with one or more attached glycosaminoglycan side chains interspersed among collagen fibrils[19].

Decorin is a proteoglycan molecule rich in leucine that plays a critical role in ECM assembly and regulates cell growth, proliferation, adhesion, inflammation, and fibrogenesis. Decorin and TGF- β have a strong relationship. Therefore, as decorin is an inhibitor of TGF- β , it reduces tissue fibrosis in the kidney and lung in various diseases[44]. Moreover, it strengthens the immune system and improves conditions mediated by oxidative stress. Therefore, it has anti-inflammatory and anti-fibrillogenic effects that make it a potential drug for COVID-19-related complications, particularly in cases of lung fibrosis, although without direct evidence currently[44,45].

Perlecan, or HSPG2, is a structurally conserved heparan sulphate-bearing proteoglycan. It is fully secreted into the extracellular space, where it is incorporated into the basement membrane and intertwined with collagen type IV, facilitating epithelial and endothelial cell attachments and regulating cellular behaviour[46]. Versican is a versatile molecule that plays roles in cell adhesion, migration, proliferation, and inflammatory responses, and its protein levels are increased in cytokine- and growth factor-stimulated lung fibroblasts[47]. It is involved in remodelling in inflammatory lung disorders, such as asthma, chronic obstructive pulmonary disease, IPF, and bronchiolitis obliterans syndrome[47]. It is a potential target for modulating the inflammatory response in COVID-19[48].

COLLAGEN

Collagen is a type of glycoprotein composed of distinct subunits that are the main structural proteins of the ECM and divided into fibrillar (collagens I-III, V, and XI) and nonfibrillar forms[19]. Its molecules polymerize to form fibrils by self-assembly, and nonfibronectin, such as type IV collagen and fibril-associated collagens, is associated with the formation of other forms of ECM. Collagen types I, II, and III are more frequently encountered and comprise approximately 80%-90% of all types. Collagen plays a clear structural role in mechanical support and dimensional stability, which provides tensile strength to the ECM, limiting the distensibility of tissues. Fibrosis is a dynamic process, and commonly, the continuous deposition and resorption of connective tissues and collagens are pivotal. During wound healing, collagen synthesis increases and ceases once it is deposited to sufficient levels in tissues. In contrast, during fibrosis, collagen synthesis is faster than absorption, and uncontrolled collagen deposition causes tissues to become stiff, resulting in scarring. Collagen types I, III, and VI predominate in the interstitium of the alveolar wall in both normal and fibrotic lungs[49]. Asthma, chronic obstructive pulmonary disease (COPD), and IPF display differing collagen deposition. Particularly, in active fibrosis in IPF, compared to healthy lung tissues, lung procollagen pro-peptides types I and III are

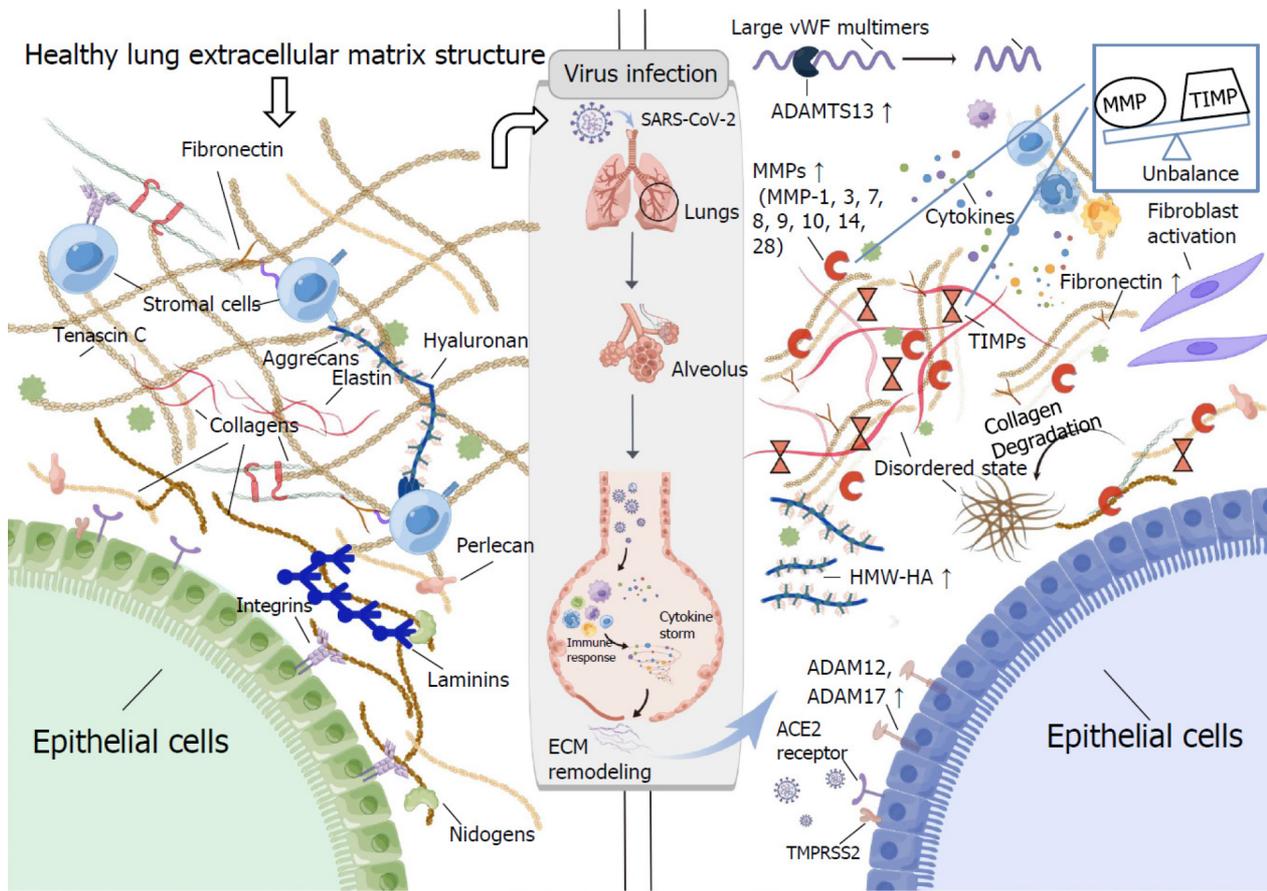
increased[50]. Furthermore, messenger RNA of type I collagen is increased and colocalised with its precursor protein (pro-collagen) in highly activated fibroblasts in IPF, reflecting active synthesis in different lung regions[49]. In COPD, type I and III procollagen expression profiles differ with disease severity. Postmortem studies have shown collagen deposits on lung samples of COVID-19 patients[51]. In contrast, the expression of many core ECM proteins, including 12 proteoglycans, 16 collagens and 56 glycoproteins, is diminished in COVID-19 using a proteomic approach[52]. In particular, COVID-19 patients lose the collagen that is predominant in lung tissue, resulting in fundamental mechanical damage to the lungs. The collagens that predominate lung tissue are lost in the lungs of patients with COVID-19, leading to fundamental damage to the mechanical characteristics of lungs with COVID-19. There is an imbalance in the ECM in the lung tissues caused by COVID-19, which characterizes the major symptoms of severely ill patients with COVID-19 at the molecular level[52].

ADAMALYSINS

Adamalysins have two subfamilies: Disintegrin and MMPs (ADAMs) and ADAMs with a thrombospondin domain (ADAMTS)[53]. ADAMs are disintegrins and MMPs that cleave transmembrane protein ectodomains, resulting in their shedding. Their key function is shedding of growth factors, cytokines, and adhesion molecules that identify these cell surface enzymes as key mediators of various pathophysiological processes. ADAMTS can cleave ECM proteins and procollagens I, II, and III to mature forms extracellularly, playing vital roles in tissue remodelling[54]. It has been shown that several adamalysin proteins play roles in COVID-19, particularly ADAM17, which plays an essential role in its pathogenesis[55,56]. ADAM17 cleavage results in biologically active soluble angiotensin converting enzyme-2 (ACE2), which blocks or promotes viral entry into SARS-CoV-2 by binding to it[56, 57]. The ADAM12 receptor and ephrin-A1, one of the ADAM12 substrates, play a role in inflammation and endothelial cell permeability. Among COVID-19 patients, some had significantly elevated concentrations of ADAM12 and ephrin-A1 in their blood serum, with critical patients having the highest levels [58]. Therefore, the inflammatory response mediated by Ephrin-A1 may be one of the major factors in the morbidity and mortality related to COVID-19. Levels of ADAMTS13, an antithrombotic metalloprotease that generates optimal-sized vWF proteins by cleaving large multimeric vWF precursor proteins, decreased significantly with increasing COVID-19 severity; the lower the activity of ADAMTS13, the higher the risk of mortality, which showed the best discriminatory ability to predict long-term mortality[17,59,60].

APPLICATION PROSPECTS OF ECM IN DIAGNOSIS AND TREATMENT

The COVID-19 pandemic is still underway, and most drugs available for COVID-19 are not specifically designed. The most effective way to combat pathogen infection is to design an effective pathogen-specific vaccine or antiviral agent. However, it is common for viruses to make errors during replication, and their proteins are constantly mutated. Each time a new pathogen emerges, the design of pathogen-specific therapies must be restarted. To date, therapeutic options are limited for COVID-19, and the treatment mitigates and repairs damage caused by pathogens, such as using corticosteroids, interleukin-6 receptor blockers, Janus kinase inhibitors, baricitinib, and sotrovimab. COVID-19 leads to lung damage and multiorgan failure that directly causes endothelial cell apoptosis, affects gas exchange and is the most refractory feature of respiratory diseases[61]. The composition and function of the pulmonary ECM is significantly disturbed in pathological tissue remodelling. Following SARS-CoV-2 infection, therapeutic approaches targeting ECM mediators are of interest, possibly preventing serious complications. Removing excess HA in patients with COVID-19 could reduce the severity of clinical morbidity[6]. Using 4-methylumbelliferone (4-MU), a competitive substrate inhibitor of UDP-glucosyltransferase, can reduce HA synthesis[62]. Hymecromone, a commercial drug containing 4-MU, has been shown through animal and clinical trials to improve lymphopenia and lung lesions in SARS-CoV-2-infected patients[15]. Moreover, decorin can treat lung fibrosis by direct application[63]. Therefore, it might be effective against pulmonary fibrosis associated with COVID-19. MMPs are imbalanced in lung diseases, such as asthma, COPD, pulmonary fibrosis, and ARDS, and inflammatory processes associated with COVID-19. Consequently, tissue inhibitors of MMPs (TIMPs) are secreted to maintain matrix equilibrium and regulate cytokine shedding. These inhibitors target MMPs to modulate their effects. TIMPs in a mouse model of lung injury reduce the inflammatory status and improve injury[64]. In particular, *Timp3*^{-/-} mice have spontaneous emphysema-like alveolar damage, suggesting a role for TIMP3 in the maintenance of lung homeostasis and remodelling[65]. Increasing the concentration and bioavailability of TIMP may be therapeutic. Hardy *et al*[43] suggested the possibility of using new cocktails of low-dose MMP inhibitors and AMP-activated protein kinase activators to increase host tolerance to pathologies through cooperative effects. Interestingly, in a mouse model of COVID-19, the administration of the ADAM17/MMP inhibitors apratastat and TMI-1 significantly improved lung histology and prevented leukocyte infiltration[66]. Similarly, in severe cases of COVID-19, the pan-



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Figure 1 The extracellular matrix of a healthy lung and its remodeling after infection with severe acute respiratory syndrome coronavirus

2. Tenascin C, collagen, elastin, integrins, laminins, perlecan, hyaluronan, aggrecan, and fibronectin are crucial components of the healthy lung matrix structure. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the cell via the effects of angiotensin converting enzyme-2 (ACE2) and transmembrane serine protease 2 (TMPRSS2). As a result of identifying the virus, immune cells, specifically macrophages, release proinflammatory mediators that activate more immune cells, creating an uncontrolled cycle of the inflammatory response “cytokine storm”. Extracellular matrix (ECM) remodeling occurs in response to lung injuries, including matrix metalloproteinase (MMP) overexpression and an imbalance between MMPs and tissue inhibitors of MMPs (TIMPs), increased deposition of ECM fragments and collagen, massive formation and deposition of fibronectin, and accumulation of hyaluronan (HA). Moreover, ADAM12, ADAM17, and ADAMTS13 expressions are elevated during SARS-CoV-2 infection. ACE2 angiotensin-converting enzyme 2, TMPRSS2 transmembrane protease serine 2, ADAM17 ADAM metalloprotease domain 17, ADAM12 ADAM metalloprotease domain 12, ADAMTS13 ADAMs with thrombospondin domain 12, HMW-HA high-molecular-weight hyaluronan, MMPs matrix metalloproteinases, TIMPs tissue inhibitors of matrix metalloproteinases. ACE2: Angiotensin converting enzyme-2; ECM: Extracellular matrix; HA: Hyaluronan; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitors of MMP; TMPRSS2: Transmembrane serine protease 2; HMW-HA: High-molecular-weight HA.

MMP inhibitor doxycycline has been preliminarily investigated[67]. Versican is a potential target for modulating the inflammatory response of COVID-19[48]. No therapeutic agents are available in clinical settings that target versican. This could also be a new direction for future research.

CONCLUSION

Extracellular matrix remodeling is broadly involved in several physiological, pathological, and homeostatic states. Its mediators can alter the fate of organs as they are present in and associated with cellular and circulating patterns. Furthermore, SARS-CoV-2 infection in the human body changes the matrix balance (Figure 1). For example, in patients with COVID-19, MMP-1[23,27], MMP-3[37,40], MMP-7[35,36], MMP-8[32], MMP-9[35-37], MMP-10[41], MMP-14[32], and MMP-28[39] secretion increases at sites of inflammation, which leads to pathological remodeling of the lung ECM. Among them, MMP-1 and MMP-9 have been implicated in pulmonary fibrosis[27,35]. It is possible, therefore, that COVID-19 results in endothelial cell damage through the upregulation of MMPs, which results in further inflammation and the spread of cytokines. ADAM17 mediates active ectodomain shedding of ACE2, which blocks or promotes viral entry into SARS-CoV-2 by binding to it[57]. On the other hand, increased ADAM17 expression in the majority of patients with severe COVID-19 demonstrated that ADAM17 activity itself may facilitate viral entry. ADAMTS13’s main role is cleaving vWF[60]. Reduced

activity of ADAMTS13 in COVID-19 patients results in aggregation of vWF platelets, vessel occlusion, and microvascular thrombosis[59].

As previously mentioned, the ECM is regulated by SARS-CoV-2 infection and is involved in the pathogenesis of infection. An overactive ECM can aggravate a disease, and regulation of overactive ECM can alleviate it. As the specific mechanisms targeting this aspect are unclear, the therapeutic course for ECM should be explored as possible targets for long-term therapy, as cured patients still develop sequelae. Studies have shown that multiple organ systems are affected to varying degrees by COVID-19 sequelae[68]. Patients with mild-to-moderate COVID-19 usually develop mild-to-moderate pulmonary fibrosis[69]. Severe or critical COVID-19 shows variable degrees of fibrosis, ranging from early interstitial to severe obliteration of alveolar structure[70]. Indicators of ECM could be used as tools for identification during the acute phase of disease in COVID-19 survivors who are risk of developing permanent pulmonary damage and fibrosis.

In conclusion, further work is required to better understand the underlying mechanisms of the extracellular matrix in COVID-19 and how the dysregulation of the different ECM components leads to disease manifestation.

FOOTNOTES

Author contributions: Huang JJ, Wang CW, Yang NB, Yu YC, Liu Y and Zhang YY designed the study and collected data; Huang JJ and Song QF analyzed the literature and wrote the manuscript; Jiang Q and Qian GQ funded and reviewed the manuscript; All authors read and agreed to the published version of the manuscript.

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