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REVIEW

Role of Renin-Angiotensin System in Acute Lung Injury Caused by Viral Infection

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Abstract: The renin-angiotensin system (RAS) is the most important regulatory system of electrolyte homeostasis and blood pressure and acts through angiotensin-converting enzyme (ACE)/angiotensin II (Ang II)/Ang II type 1 (AT1) receptor axis and angiotensin-converting enzyme 2 (ACE2)/angiotensin (1-7)/MAS receptor axis. RAS dysfunction is related to the occurrence and development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) and causes a serious prognosis and even death. ALI/ARDS can be induced by various ways, one of which is viral infections, such as SARS-CoV, SARS-CoV-2, H5N1, H7N9, and EV71. This article reviews the specific mechanism on how RAS dysfunction affects ALI/ARDs caused by viral infections. SARS-CoV and SARS-CoV-2 enter the host cells by binding with ACE2. H5N1 and H7N9 avian influenza viruses reduce the ACE2 level in the body, and EV71 increases Ang II concentration. Treatment with angiotensin-converting enzyme inhibitor and angiotensin AT1 receptor blocker can alleviate ALI/ARDS symptoms. This review provides suggestions for the treatment of lung injury caused by viral infections.

Keywords: renin angiotensin system, acute lung injury and acute respiratory distress syndrome, viral infection

Introduction

The renin-angiotensin system (RAS) is important because it regulates blood pressure and maintains the water and electrolyte balance and cardiovascular homeostasis in organisms[1] and is related to the inflammation, oxidative stress, immunity, apoptosis, fibrosis, and other physiological activities.[2]

The main components of this system include angiotensinogen (AGT), renin, angiotensin I (Ang I), angiotensin II (Ang II), and various enzymes and receptors, such as angiotensin-converting enzyme (ACE), angiotensin-converting enzyme 2 (ACE2), MAS receptor, Ang II type 1 (AT1) receptor, and Ang II type 2 (AT2) receptor. RAS functions through ACE/Ang II/AT1 and ACE2/Ang I (1-7)/MAS axes with opposite effects. A new branch has recently been discovered. When alanine replaces the aspartate at the amino terminal of Ang I (1-7), Ala-Ang I (1-7) (alamandine) is produced, binds to the new receptor Mas-related G protein-coupled receptor D (MrgD), and protects against hypertension, hypertrophy, lung damage, and fibrosis.[3–5] The regulatory mechanisms of RAS are listed in Figure 1. RAS is distributed in many human tissues, including brain, heart, kidney, and lung, which has the largest amount.[6–8]

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Acute lung injury (ALI) is acute hypoxic respiratory insufficiency caused by non-cardiogenic pathogenic factors and may develop to acute respiratory distress
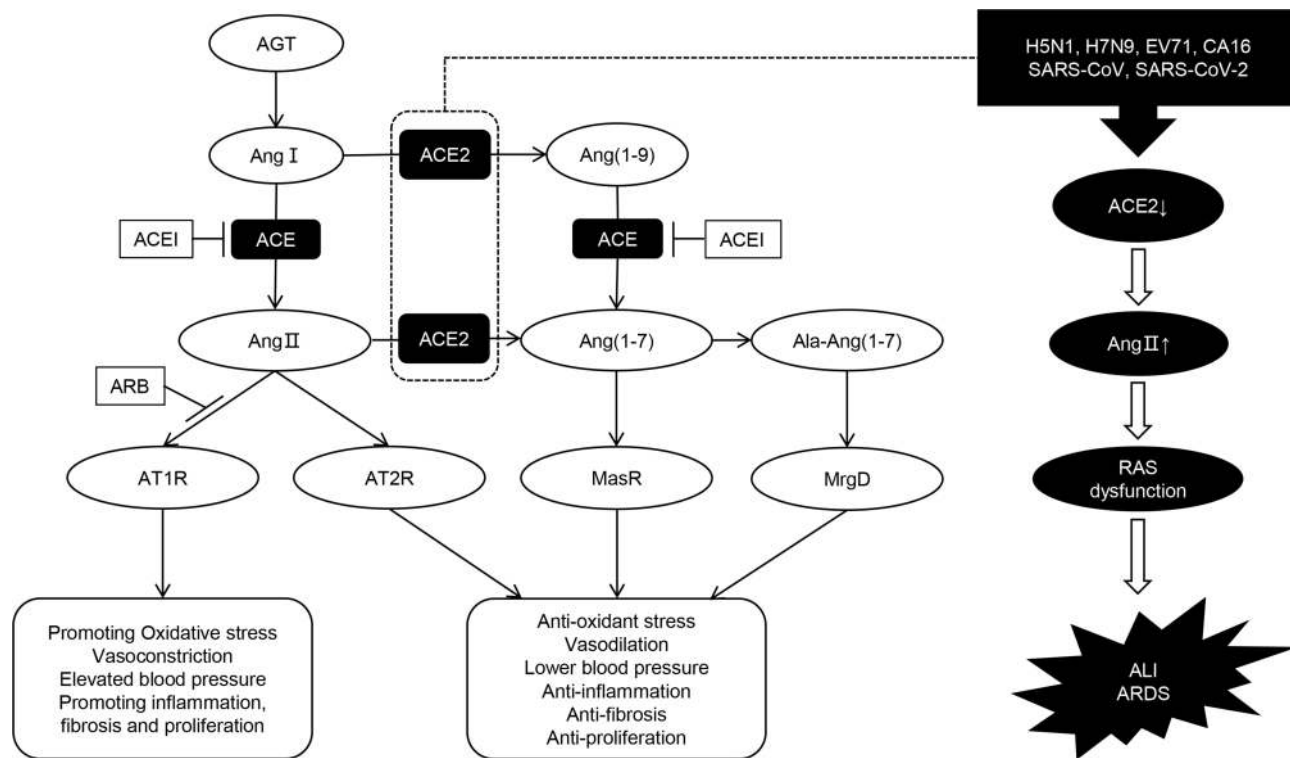
Figure 1 Diagram of regulatory mechanism of renin-angiotensin system (RAS). The classical RAS pathway begins with the conversion of angiotensinogen (AGT) to an inactive decapeptide precursor angiotensin I (Ang I) through the action of renin. Ang I is further recognized and cleaved by angiotensin converting enzyme (ACE) to produce active octapeptide angiotensin II (Ang II). Ang II is the key biological peptide of RAS which has various physiological regulatory effects. It acts mainly through the combination of type 1 angiotensin II receptor (AT1R) to constrict blood vessels, raise blood pressure, promote inflammation, and promote fibrosis and apoptosis. It can also bind to AT2, AT3, and AT4 receptors, and plays different physiological roles. In addition, angiotensin converting enzyme 2 (ACE2) can cleave Ang I C-terminal peptide to produce inactive Ang (1-9), then Ang (1-9) can be hydrolyzed by ACE and other peptidases to produce active Ang (1-7). ACE2 can also directly cleave Ang II to form Ang (1-7). Ang (1-7) binds to the Mas receptor (MasR) and exerts physiological functions that are contrary to Ang II, including vasodilation, lower blood pressure, anti-inflammation, anti-oxidative stress, anti-fibrosis, etc. These form two main functional axes of RAS. Ala-Ang (1-7) is produced when the aspartate at the amino terminal of Ang (1-7) is replaced by alanine. It can bind to the new receptor Mas-related G protein-coupled receptor D (MrgD) and protect against hypertension, inflammation, and lung damage. Furthermore, ACEI and ARB can protect against RAS imbalance by inhibiting the conversion of Ang I to Ang II and the binding of Ang II to the AT1R, respectively. We also showed that some viral infections can interfere with the function of RAS, leading to acute lung injury (ALI) and even acute respiratory distress syndrome (ARDS).
Abbreviations: AGT, angiotensinogen; Ang, angiotensin; ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AT1R, type 1 angiotensin II receptor; AT2R, type 2 angiotensin II receptor; MasR, Mas receptor; MrgD, Mas-related G protein-coupled receptor D; EV71, enterovirus 71; CA16, coxsackie 16; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; RAS, renin-angiotensin system; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

syndrome (ARDS) in severe cases. The 28-day mortality rates of normal and critically ill patients with ARDS are 30% and over 40%, respectively.[9–11] One of the important causes of ALI is virus infection. When the virus invades the respiratory tract, the epithelial cells and vascular endothelial cells are first damaged, and protein-rich edema fluid then accumulates in the lung interstitium and alveoli,[12] and triggers various immune cells such as macrophages and neutrophils to release a large number of inflammatory factors. When RAS homeostasis is disrupted, a cytokine storm appears and eventually causes ALI or even ARDS.[11–13] Some viral infections can also directly regulate the expression of RAS components by accelerating the imbalance of RAS and the occurrence and development of ALI/ARDS. RAS dysfunction induces

ALI primarily by triggering a cascade of downstream reactions. Ang II is the main effective molecule of RAS and binds to AT1R to activate the NF-κB, AK2/STATs, and MAPK pathways and triggers inflammation, thus stimulating the production of reactive oxygen species (ROS) and promoting cell apoptosis.[14–18] When the concentration of Ang II in the lungs increases, a large number of cytokines, chemokines, and ROS are released and exacerbate the lung damage caused by viral invasion. Pulmonary edema, pulmonary fibrosis, and lung cell apoptosis are related to RAS.[19–22] ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB) can alleviate ALI, improve pulmonary capillary permeability, and reduce apoptosis.[14,23] Therefore, RAS imbalance can promote the development of ALI/ARDS.

This article focuses on the role of RAS in ALI/ARDS caused by viral infections, as shown in Figure 1. The three parts aimed to explain RAS's role in the progression of different viral infections causing lung injury.

Role of RAS in ALI Caused by Coronavirus Infections

SARS

In 2003, severe acute respiratory syndrome (SARS) was first reported in China and then spread worldwide.[24] By July 31, 2003, SARS had resulted in 8096 reported cases, including 774 deaths in 26 countries.[25] A new coronavirus named severe acute respiratory syndrome coronavirus (SARS-CoV) is the pathogen of this epidemic,[26,27] and binds to host cells via its surface Spike protein, particularly S1 domain, and then enters the body and causes severe lung injury.[28] SARS pathogenesis has been widely studied.

ACE2 protein is the functional receptor of SARS-CoV, and the combination of ACE2 and S protein of SARS-CoV is crucial in lung injury. Li et al[28] found that viral genome copies in ACE2-transfected cells increase by more than 100,000-fold in the first 48 hours. ACE2 contributes to the efficiency of SARS-CoV replication. When wild-type (WT) mice were infected with SARS-CoV, the lung ACE level did not change, whereas ACE2 was reduced substantially because of virus–receptor interaction. The type II transmembrane serine protease TMPRSS2 can cleave ACE2 and S protein to promote the S protein for membrane fusion and the entry of SARS-CoV into cells.[29] Therefore, the ACE2 concentration decreases in the membrane but increases in the cytoplasm in SARS-CoV infected cells. Meanwhile, Ang II level in lung tissues increases considerably in SARS-CoV-infected mice. ARB treatment for the mice with infected SARS-CoV can remarkably alleviate the pulmonary edema and severe ALI.[30] This finding suggests that SARS-CoV-mediated lung failure is caused by Ang II overexpression and excessive activation of the AT1 receptor.

ACE gene polymorphism, which is characterized by the insertion/deletion (I/D) of a 287-bp Alu repeat sequence in intron 16 of the ACE gene, is related to hypoxemia in patients with SARS.[31,32] A study reported that patients in the hypoxemic group had a high frequency of D allele and consequently had high serum ACE levels. I/D polymorphism affects the serum and tissue ACE levels in the general population.[33] The elevated ACE and decreased ACE2 levels in patients with SARS promote the huge expression of Ang II and AT1 receptor, thereby accelerating the lung injury and even leading to death.[31] Furthermore, the innate immunity response is activated, and the expression of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-8, IL-1β, interferon inducible protein-10 (IP-10), caspase 3 (CASP3), CASP9, and fibroblast growth factor-7 (FGF-7) increase in patients with SARS.[34–36] The inflammatory pathways, apoptosis, oxidative stress, and fibrosis are all activated in patients with SARS.[35,36]

SARS-CoV infects people through the combination of its S protein and lung ACE2, which reduces the ACE2 level in the lungs, increases Ang II expression, and over-activates AT1 receptor. The function of RAS is no longer balanced. Finally, plenty of cytokines, chemokines, and proteases are released, resulting in cytokine storm and eventually severe ALI/ARDS or even death. Figure 2 shows the graphic pathogenesis of SARS-CoV.

SARS-CoV-2

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection has spread in many countries and regions and is currently a major global health concern. Infected patients mainly show typical influenza-like symptoms. For severe cases, dyspnea or hypoxemia occurs 1 week after the disease onset and further develops into ARDS, septic shock, irreversible metabolic acidosis, and coagulopathy.[37]

Similar to SARS-CoV, the S protein of SARS-CoV-2 uses the cellular membrane ACE2 for entry, and is followed by employing TMPRSS2 for S protein priming to facilitate the fusion of viral and cellular membranes.[38–40] Virus infectivity studies showed that SARS-CoV-2 uses ACE2 as an entry receptor in the ACE2-expressing cells, such as Hela cells in Chinese horseshoe bats, civets, and pigs, but not Hela cells without ACE2. SARS-CoV-2 does not employ other coronavirus receptors such as DPP4 and APN entry host cells.[39] Virus entry in the host prompts two possible therapeutic targets for early-stage viral infection, including interference with the SARS-CoV-2 virus binding to the host and inhibition of serine protease TMPRSS2 activity. Another coronavirus, HNL63-CoV, also uses ACE2 protein as a receptor for cell entry, but its S protein has lower affinity for ACE2 than SARS-CoV and SARS-CoV-2. ACE2 is primarily distributed on the endothelial cells and smooth muscle cells of organs and tissues, including the oral and nasal mucosa, lung, small intestine, kidney, heart, and blood vessels; this condition is
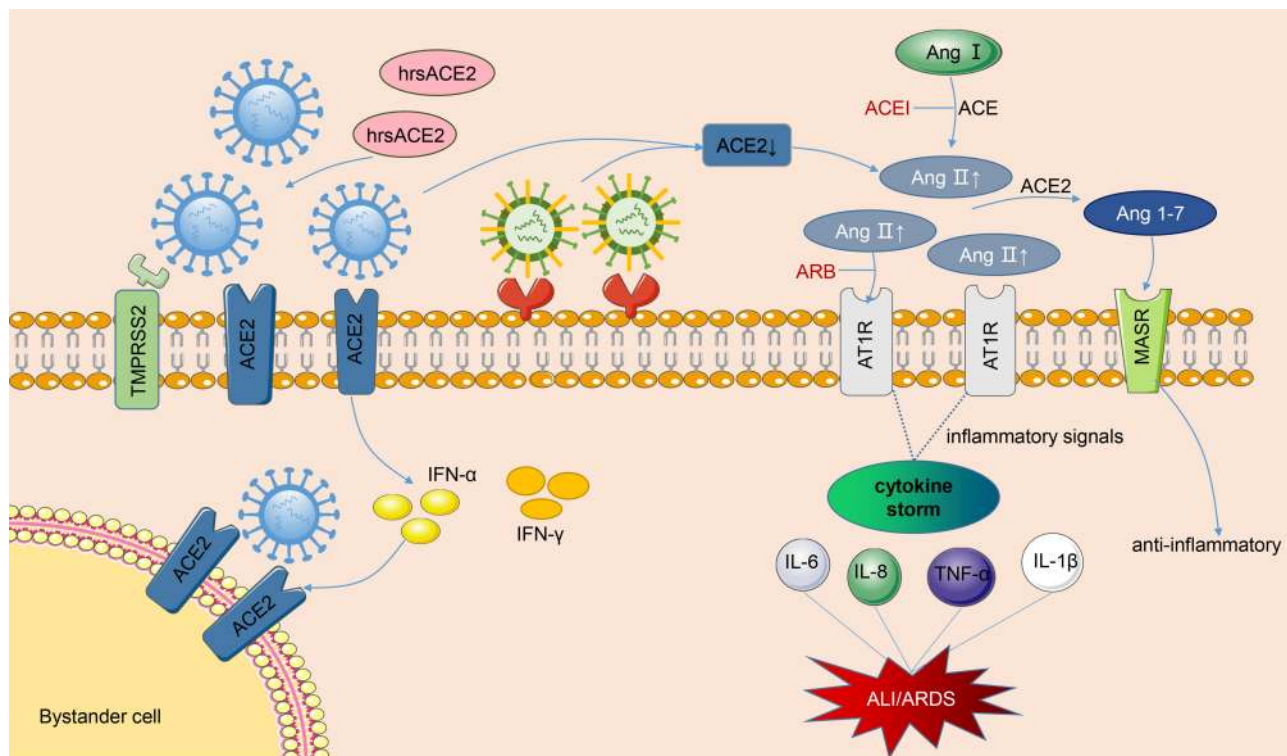
Figure 2 Pathogenesis of renin-angiotensin system in acute lung injury caused by viral infections. The SARS-CoV and SARS-CoV-2 bind to membranes angiotensin converting enzyme 2 (ACE2) of and employ type II transmembrane serine protease (TMPRSS2) for Spike protein priming, facilitating the fusion of viral and cellular membranes. After SARS-CoV-2 invades cells, it activates the natural antiviral pathway, prompts the infected cells to secrete interferon, stimulates bystanders to up-regulate ACE2 expression, and creates more targets for the entry of SARS-CoV-2. Occupation of ACE2 by the virus leads to the reduction of cell surface ACE2 levels. As the virus enters the cell, not limited to SARS-CoV and SARS-CoV-2, but also H5N1, H7N9 and EV71, the angiotensin II (Ang II) levels are significantly upregulated, a large amount of Ang II binds to the type 1 angiotensin II receptor (AT1R), then the inflammatory signaling pathways are overactivated, and then secrete various cytokines, resulting in cytokine storm and eventually lung injury. In the meantime, the ACE2 can cleave Ang II into Ang 1-7 which combines with Mas receptor (MasR) to fight against inflammation. ACEI and ARB can help restore the RAS balance after viral infections. Moreover, clinical-grade human soluble ACE2 (hrsACE2) can inhibit the coronavirus invasion by binding to coronavirus outside the cell. The blue virus in the figure represents coronaviruses, and the other one represents other viruses, such as H1N1, H7N9, and EV71.
Abbreviations: Ang, angiotensin; ACE2, angiotensin converting enzyme 2; hrsACE2, clinical-grade human soluble ACE2; TMPRSS2, type II transmembrane serine protease; AT1R, type 1 angiotensin II receptor; MasR, Mas receptor; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; INF, interferon; IL, interleukin; TNF, tumor necrosis factor; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

consistent with the multi-organ failure in patients with COVID-19.[40–43] Single-cell sequences showed that the alveolar type II cells (AT2) are the major cell type that express ACE2 in all human lung cells and exhibit viral replication and transmission functions compared with AT2 cells not expressing ACE2. This phenomenon may partly explain the severe alveolar damage of SARS-CoV-2 infection. However, the small sample size and individuals heterogeneity should be considered.[44]

In experimental models of acid-aspirating ALI, the Ang II level is upregulated markedly in lungs and plasma of mice, but is substantially downregulated by ACE inactivation. The acid-treated ACE2 knockout mice showed evident lung injury compared with wild-type mice, the injection of recombinant human ACE2 protein alleviated pulmonary edema, and the use of specific AT1 and AT2 receptor blockers rescued the ALI in *ACE2*-knockout

mice.[45] In other ALI animal models induced by lipopoly-saccharide or bleomycin, lung ACE2 level was severely decreased, and Ang II increased accordingly; ACE2 injection can weaken the lung pathological injury,[46,47] and RAS imbalance is accompanied by the upregulation of inflammatory injury.[47] These studies are limited to animal experimental models but can explain the mechanism of RAS systems to some extent. For the RAS imbalance caused by SARS-CoV and SAR-CoV-2 infections, the "abduction" effect of the virus on ACE2 must be considered.

In engineered extra pulmonary tissues, including engineered human blood vessel organoids and human kidney organoids, SARS-CoV-2 infection is inhibited by clinical-grade human soluble ACE2 (hrsACE2) – a decoy protein that has already been tested in phase I and II clinical trials. Vero E6 cells treated with hrsACE2 can dose-dependently

inhibit SARS-CoV-2,[48] suggesting that this protein can prevent early coronavirus from entering host cells. Additional clinical trials are needed to clarify the effects of hrsACE2 on RAS and clinical prognosis. Jose, Alex, and their colleagues found that ACE2 is a human interferon-stimulated gene (ISG). Interferon-α (IFN-α) and IFN-γ dose-dependently induce the upregulation of ACE2 in human primary basal epithelial cells. They also leveraged single cell RNA-seq and further screened the cells with enrichment for ACE2 and TMPRSS2 in non-infected controls and those infected with influenza A and B. The results showed that ACE2 is most upregulated in bystander goblet or squamous cells that are not directly infected by virus in the infected samples. This finding suggests that IFN produced by the virus-infected cells stimulates the surrounding uninfected cells and prompts the high ACE2 expression in bystander cells, thus providing additional invasive targets for SARS-CoV-2 infection. Individuals suffering from upper respiratory tract are highly susceptible to SARS-CoV-2.[49]

In addition to ACE2 as a viral receptor affecting viral entry, SARS-CoV-2 infection causes RAS disorders and systemic inflammatory response. Liu et al[50] found that the plasma Ang II level of patients with COVID-19 is substantially higher than that of healthy individuals and is linearly associated to viral load and lung injury, thus providing the contact between tissue ACE2 downregulation and RAS imbalance. A clinical descriptive study showed that cytokine storm syndrome (CSS) appears in patients with COVID-19 and severe pneumonia, and some cases may rapidly progress to ARDS or even multi-organ failure.[51] Inflammatory cytokines and chemokines, including IL-6, IL-2, IL-1β, IL-8, IL-17, IFN-γ, TNF-α, and monocyte chemoattractant protein-1 (MCP-1), are substantially upregulated in patients with COVID-19, especially IL-6, the key cytokine that triggers an inflammatory response and is correlated with mortality in these patients.[52,53] After the spike protein of SARS-CoV-2 binds to the ACE2 on the cell surface, the level of membrane ACE2 is down-regulated, Ang II cannot convert to Ang1-7 and thus increasingly binds to AT1 receptors. The uncontrolled ACE/Ang II/AT1R axis stimulates downstream inflammatory signaling pathways, resulting in an increased permeability of pulmonary capillaries, injury to lung endothelium and epithelial cells, and ultimately ALI or even ARDS. This finding is consistent with the above experimental model of artificially induced lung injury. In addition to CSS, viral replication in lung epithelial and endothelial cells is also a major cause of lung injury. The pathogenesis of RAS in ALI caused by SARS-CoV-2 is presented in Figure 2.

The association of ACE gene polymorphism with SARS-CoV-2 infection and mortality has been studied. According to the available data, the frequency of D allele is positively correlated with the number of SARS-CoV-2 infection cases in Asians and African Americans.[32,54] Owing to the combined effect of D allele and SARS-CoV-2 infection, the high ACE levels and decreased ACE2 levels lead to a high amount of Ang II in plasma and tissues and eventually result in severe lung injury and even death.

The possibility of using RAS inhibitors in COVID-19 treatment has become controversial. Patients with COVID-19 and hypertension, cardiovascular disease (CVD), diabetes, or chronic are advised to suspend the use of ACEIs or ARBs due to the possibility of upregulating ACE2, which may be conducive to viral invasion and may aggravate lung injury.[55] On the contrary, other researchers claimed discontinuing ACEIs and ARBs in COVID-19 patients may be harmful due to the superior effect in pneumonia prevention.[56–60] Some recent studies support this view, and population-based reports revealed that the use of ACEI and ARB inhibitors in patients with COVID-19 does not aggravate the severity of the disease, increase the risk of infection, improve prognosis, or reduce mortality.[61–66] In addition, a systematic review and meta-analysis of related research has reconfirmed this thesis.[67–71] Given that hypertension and CVD can increase the severity of the disease, dividing patients without hypertensive and CVD into a non-ACEI/ARB group may underestimate the favorable effects of ACEI/ARB drugs on affected patients. Limited by the retrospective design of most of these investigations, large-scale cohort studies are needed to confirm this view.

On the basis of existing evidence, ACE2 upregulation is limited only in animal experiments with the use of relatively high doses of ARBs and ACEIs. These results are inconsistent, and cannot be extrapolated to humans,[72–75] and the expression of ACEI/ARB-derived ACE2 on lungs and the respiratory epithelium remains unclear. Further mechanism studies are needed to illustrate the effects of RAS inhibitors on human ACE2 expression.

Role of RAS in ALI Caused by Avian Influenza Virus Infections

H5N1

Infections caused by avian influenza viruses often lead to severe ALI and can even progress to ARDS. In 1997, the first case of infection with highly pathogenic avian influenza with a high fatality rate of 33.3% was reported in Hong Kong.[76] In February 2020, two outbreaks of H5N1 and H5N6 avian influenza occurred in Hunan and Sichuan, China, suggesting that avian influenza virus is still one of the potential pathogens causing the global pandemic of viral infections.

The lung tissues of most dead patients exhibit the clinical features of ARDS and multiple organ dysfunction syndrome.[77,78] Some studies suggested that ALI caused by avian influenza virus is related to RAS. Zou et al[79] showed that the level of ACE2 protein in lung tissue decreases rapidly after H5N1 virus infection in mice, followed by a substantial increase in plasma Ang II concentration. However, no change is observed for ACE expression level. Compared with WT mice, *ACE2*-knockout mice infected with H5N1 show more severe lung injusy, and no matter before and after infection, and the injection of ACE2 protein can reduce the pathological damage caused by H5N1 infection. Yan et al[80] found that RAS is imbalanced after H5N1 infection, and the plasma Ang II level may be used as one of the clinical indicators to evaluate the fatality of H5N1 infection. With the increase in disease severity, the Ang II concentration in H5N1-infected patients also gradually increases, and the plasma concentration of Ang II is high in dead patients. The viral loads and final virus titers in the lung tissues of WT mice were substantially lower than those in *ACE2*-knockout mice. When the recombinant hACE2 protein was injected into H5N1-infected mice, the replication of H5N1 in the lungs decreased, and the survival duration was extended. Treatment with AT1 receptor inhibitor losartan can increase the survival rate of mice, but cannot reduce the viral load in lung tissues, suggesting that ACE2 protein may decrease plasma Ang II level by reducing virus replication to restore normal RAS function in ALI caused by H5N1.

The pathogenicity of H5N1 avian influenza is associated with cytokine storm. The levels of intercellular adhesion molecule-1 (ICAM-1), IL-1β, IL-6, IL-8, and TNF-α in the lung tissues and peripheral in the mice of H5N1 virus pneumonia model were substantially higher than those in the control group.[81] Other cytokines and chemokines, such as IL-8, MCP-1, and IP-10 were found in the serum of fatal cases infected by H5N1.[82] In vitro infection experiments have revealed that H5N1 virus has higher ability than H1N1 in inducing the release of cytokines and chemokines in epithelial cells and macrophages.[83]

In summary, H5N1 infection dysregulates lung RAS and increases Ang II expression to stimulate the AT1 receptor, thereby inducing the activation of downstream inflammatory signals, forming a cytokine storm, and eventually resulting in ALI, even ARDS (Figure 2).

H7N9

H7N9 avian influenza virus infection was first reported in humans in 2013.[84] Since then, H7N9 virus has spread continuously among humans and birds and had resulted in 1568 human infections and 615 deaths as of March 31, 2019.[85] H7N9 virus has dual-receptor binding tropism and binds to α-2, 6-linked sialic acid (human receptor), and α-2, 3-linked sialic acid (avian receptor).[86,87] Human upper respiratory tract and lung tissues contain α-2,6 glycans, and only lung tissues contain α-2,3 glycans.[88] In vitro experiment showed that the virus titer in lungs is higher than that in the trachea under H7N9 infection.[89] The epithelial cells of lower respiratory tract and type II alveolar cells are susceptible to the H7N9 virus.[89] Meanwhile, ACE2 is mainly expressed in the epithelial cells of lung tissues and type II alveolar cells.

When H7N9 virus infects the human respiratory tract and induces ALI, the ACE2 expression is decreased, whereas the Ang II level is elevated.[90] To understand the regulatory mechanism, researchers infected the WT mice and *ACE2*-knockout mice with H7N9 virus.[91] ACE2 expression was substantially down-regulated in the WT mice 3 days after infection, while the expression of ACE was similar between H7N9-infected mice and control mice. In addition, pulmonary edema was aggravated, and the viral titers in the lung increased in the H7N9-infected mice. All *ACE2*-knockout mice that were infected with H7N9 virus died quickly, and 20% of WT mice survived. Pulmonary edema and lung injury were more severe in *ACE2*-knockout mice than in WT mice. Therefore, ACE2 plays a protective role against lung injury. In addition, the Ang II levels in plasma and lung tissues of H7N9-infected mice increased substantially. In H7N9-infected patients, the plasma Ang II concentrations increased continuously and reached a peak when the patient was close to death.[90]

Meanwhile, the plasma Ang II concentrations of the patients who recovered within 28 days were remarkably lower in the second week than that in the first week. Therefore, plasma Ang II level is related to the viral load and the severity of lung injury. Treatment with an AT1 receptor blocker can seriously attenuate the symptoms of lung injury and reduce lung viral titers, whereas treatment with an AT2 receptor blocker does not attenuate the lung edema and lung injury.[91] In addition, the levels of IP-10, MIG, IL-6, IL-8, IFN-α, and IFN-γ are remarkably higher in H7N9-infected patients than in healthy subjects.[89] Dysfunctions in chemokine and cytokine are responsible for the severe lung injury in human H7N9 infection.

In summary, H7N9 virus enters human lungs by binding to α-2,6-linked sialic acid and α-2,3-linked sialic acid, and then reduces ACE2 expression in lung tissues, and finally increases the plasma Ang II level. Ang II combined with AT1 receptor activates NF-κB and JAK/STATs inflammatory pathways,[89,92] and promotes the release of various cytokines and inflammatory mediators (Figure 2). Dysfunctions of RAS and cytokine storm lead to ALI and ARDS in H7N9-infected patients.

Role of RAS in ALI Caused by Another Virus
Hand, Foot, and Mouth Disease

Hand, foot, and mouth disease (HFMD) is an infectious disease mainly caused by coxsackie 16 (CA16) and enterovirus 71 (EV71). Most HFMD cases are wild and limited to fever, oral ulcers, and vesicular rashes on the hands, feet, and buttocks. Some patients may rapidly progress to severe HFMD with serious complications, including brainstem encephalitis, encephalomyelitis, meningitis, neurogenic pulmonary edema (NPE), and cardiopulmonary failure.[93] NPE and pulmonary hemorrhage are the main causes of ALI caused by HFMD.

RAS is involved in the systemic inflammatory response induced by HFMD virus infection.[94] A clinical research study found that the serum Ang II concentrations of critically ill children with HFMD are substantially higher than those in the mild or severe group; this finding indicates that RAS plays a key role in the occurrence and development of pre-cardiopulmonary failure of HFMD, and its activation may eventually lead to NPE and ALI.[95] Time-series analysis showed Ang II level is positively related to noradrenaline (NA) in mild and severe cases. NA secretion is induced by the combination of Ang II and AT1R and

can induce the water and sodium storage and associate with pulmonary edema.[96] Animal experiments suggested that EV71 infection can induce Ang II and NA expression in the brains, skeletal muscle, and lungs of mice.[97] Therefore, RAS participates in the development of HFMD, and the elevated Ang II may be one of the early warning indicators of disease progression into cardiopulmonary failure. In addition, the increased Ang II facilitates its binding to the receptor, activates the downstream signals, increases water and sodium retention, promotes capillary contraction, and increases blood pressure, all of which are important in the development of HFMD to NPE and induce the lung injury.

HFMD viral infections can induce excessive immune response.[98–103] During this process, lymphocytes and macrophages are continuously activated and expanded, thus aggravating the injury of lung endothelial cells and epithelial cells and inducing the release of inflammatory cytokines such as IL-1, IL-4, IL-6, IL-10, IL-13, IL-17, TNF-α, and INF-γ and the formation of a cytokine storm (Figure 2). In addition, large amounts of nitric oxide are expressed, thus further diluting blood, destroying blood vessels, and leading to ARDS and cardiopulmonary failure.

Summary and Outlook

Pneumonia caused by viral infection is one of the major threats to human health. RAS plays an important role in lung injury caused by viral infection, and RAS dysfunction is the key to the occurrence and development of ALI/ARDS in patients with viral infections. As a key member of RAS, ACE2 can be used as a receptor for SARS-CoV, SARS-CoV-2, and HCoV-NL63 to assist the viruses to enter the body, decrease the level of ACE2, and cause RAS dysfunction. Viral infections such as H5N1, H7N9, and EV71 can inhibit the expression of ACE2 and increase the level of Ang II after entering the bodies by binding to other receptors, thus forcing the imbalance of RAS. Inflammatory pathways and innate immunity are then activated, and plenty of cytokines, chemokines, and proteases act together to induce ALI or even ARDS. ACEI, ARB, and hrsACE2 may alleviate the severity of ALI by acting on RAS, thereby lowering the release of inflammatory molecules, and inhibiting the viral replication. However, the investigations on ACEI, ARB, and hrsACE2 as treatment for pneumonia caused by viral infection are limited to experimental studies and a few population-based studies.[104–106] This must be further confirmed by more

basic research and clinical studies. And this review could be a stimulus.

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Disclosure

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