REVIEW ARTICLE

The Remarkable Roles of the Receptor for Advanced Glycation End Products (RAGE) and Its Soluble Isoforms in COVID-19: The Importance of RAGE Pathway in the Lung Injuries

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Abstract The respiratory symptoms of acute respiratory distress syndrome (ARDS) in the coronavirus disease 2019 (COVID-19) patients is associated with accumulation of pre-inflammatory molecules such as advanced glycation end-products (AGES), calprotectin, high mobility group box family-1 (HMGB1), cytokines, angiotensin converting enzyme 2 (ACE2), and other molecules in the alveolar space of lungs and plasma. The receptor for advanced glycation end products (RAGEs), which is mediated by the mitogen-activated protein kinase (MAPK), plays a critical role in the severity of chronic inflammatory diseases such as diabetes mellitus (DM) and ARDS. The RAGE gene is most expressed in the alveolar epithelial cells (AECs) of the pulmonary system. Several clinical trials are now being conducted to determine the possible association between the levels of soluble isoforms of RAGE (sRAGE and esRAGE) and the severity of the disease in patients with ARDS and acute lung injury (ALI). In the current article, we reviewed the most recent studies on the RAGE/ligands axis and sRAGE/esRAGE levels in acute respiratory illness, with a focus on COVID-19–associated ARDS (CARDS) patients. According to the research conducted so far, sRAGE/esRAGE measurements in patients with CARDS can be used as a powerful chemical indicator among other biomarkers for assessment of early pulmonary involvement. Furthermore, inhibiting RAGE/MAPK and Angiotensin II receptor type 1 (ATR1) in CARDS patients can be a powerful strategy for diminishing cytokine storm and severe respiratory symptoms.

Keywords Receptor for advanced glycation end products · SARS-CoV- 2 · Respiratory distress syndrome · esRAGE · ACE2 protein

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Introduction

The largest pandemic of the twenty-first century is undoubtedly the outbreak of coronavirus diseases 2019 (COVID-19) which was initially reported in Wuhan, China, in December 2019 [1]. The pulmonary involvement is found in patients with COVID-19 in the form of severe pneumonia (15%) and acute respiratory distress syndrome (ARDS) (5%) [2]. According to studies, symptoms in infected children and young people are frequently moderate, manifesting in fever and a dry cough. However, in older people or those infected with comorbid conditions such

as high blood pressure, diabetes, and cancer, symptoms manifested in lung problems and rushes. The FDA has previously approved several therapies based on the severity of the disease: (1) Monoclonal antibodies are used to treat individuals with mild to moderate illness who do not require hospitalization but do require oxygen treatment [3], (2) To rehabilitate people who need to be hospitalized but don't require oxygen-therapy, Remdesivir is administered that can inhibit RNA polymerase of the coronavirus [4], (3) Dexamethasone is prescribed to manage patients who need non-invasive oxygen therapy (dexamethasone impedes the development of pulmonary damage). The WHO has also approved some COVID-19 vaccines with distinct immune technological advancement such as Pfizer-BioNTech, Moderna, AstraZeneca, Sinopharm, J&J/Janssen to control the pandemic globally [5].

To date, various clinical investigations on a variety of biomarkers have been conducted to identify the severity of the disease [6]. The receptor for advanced glycation end-products (RAGEs) is a 31 KDa protein, belongs to the immunoglobulins superfamily, and exists in two main types: membrane-bound RAGE (mRAGE) and soluble RAGE (sRAGE). Ligands such as advanced glycation end-products (AGEs) and S100 proteins lead to stimulation of intracellular signaling pathways when binding to RAGE. These signals activate viral inflammatory transcription factors and the nuclear factor kappa B (NF-κB) [7, 8]. After embryonic development, the expression of the RAGE gene decreases in all tissues except for lung tissue. Numerous studies have revealed that the inflammatory pathways associated with RAGE have played an essential role in the pathogenesis of lung tissue, and the regulation of these routes has led to a therapeutic advancement in chronic obstructive pulmonary disease (COPD) and ARDS [9]. RAGE may also play an important role in expediting the physiological age or aging process. The binding of ligands to RAGE, such as AGE, is part of this procedure. Inactivation of RAGE has been proven in multiple trials to be efficacious in lowering symptoms of pulmonary inflammation, particularly ARDS, based on this premise [2].

As a result, lowering the mortality rate of COVID-19 patients by targeting RAGE, particularly in the elderly, could be an effective strategy. The sRAGE is a sort of RAGE competitive inhibitor that comes in two isoforms: a membrane cleaved form (cRAGE) and an endogenous secretory form (esRAGE), both of which inhibit inflammatory responses in cells [10, 11]. The level of sRAGE in the blood depends on the amount of blood sugar and pathogens [12]. In cases of increasing blood glucose levels in diabetic patients, the sRAGE rate increases to prevent potential damage by AGE [13, 14]. According to several researches, the serum levels of sRAGE are also higher in young and healthy individuals [15]. Human

angiotensin converting enzyme II (ACE2) is a membrane-bound protein found in a variety of human cells, including the heart, kidney, and lung cells. It has been shown to be one of the main pathways for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into host cells. As a result, ACE2 receptor inhibitors can be used to minimize the occurrence of acute pulmonary symptoms [16, 17]. sRAGE has been reported to inhibit ACE2 expression in previous investigations. Thus, increasing the presence of sRAGE can contribute to reducing symptoms in SARS-CoV-2 infected patients. Based on a recent study, the serum levels of sRAGE are found to be higher following oxygen therapy in people with ARDS. Therefore, evaluating sRAGE serum levels can be helpful in studying the inflammations engendered by the virus entry into the pulmonary cells, the severity of damage to the lung tissue as well as a diagnostic criteria for hospital admission based on patients' clinical signs, along with measurements of other inflammatory factors such as IL-6, CRP, and D-dimer [6].

RAGE is involved in the SARS-CoV-2-induced acute respiratory distress syndrome. Diabetic individuals infected with SARS-CoV-2 are at a higher risk of developing acute respiratory problems, severe oxygen depletion, and death. In these patients, RAGE activity is a mechanism that raises the probability of a severe form of COVID-19. Higher levels of AGE and other ligands in people with diabetes may produce pro-inflammatory conditions, endothelial cell dysfunction, and vascular leakage, all of which contribute to the destruction caused by the novel coronavirus infection [18]. RAGE is triggered by a variety of ligands and activates several signaling pathways. NF-κB is one of these pathways, and as a consequence, several chemokines and cytokines are elevated. The activation of the angiotensin types I receptor and RAGE-dependent pathways results in a massive cytokine storm [19]. As an example, high mobility group box protein 1 (HMGB1) -a ligand for RAGE- has a variety of roles both inside and outside the cells. The extracellular HMGB1 released from the cells exhibits the potential pathogenic role in viral infectious diseases. Thus, HMGB1 inhibitors or antibodies against HMGB1 can be utilized to protect infected cells from infection-induced probable destruction [20, 21]. SARS-CoV-2 spike glycoprotein may bind to CD147 glycoprotein, a multi-ligand protein that is synthesized in cases of hyperglycemia and RAGE activation, in addition to the AGE primary receptor. CD147 is highly expressed in type II pneumonocytes and in a wide range of other cells, including immune cells, endothelial cells, and platelets, and also plays a significant role in COVID19-related pneumonia. The induction of CD147 glycosylation by AGEs in endothelial cells may increase matrix metalloproteinase (MMPs) activity and destabilize cellular junctions. The modulation of pulmonary inflammation with the help of controlling inflammatory pathways can be a

crucial step in the treatment of COVID-19 [22]. Therefore, in the present study, we have reviewed and explored the recent investigations conducted in the field of connections between RAGE and sRAGE with pulmonary inflammation development in patients with COVID-19 to provide a comprehensive response to this possible relationship.

The Structure of RAGE and Its Ligands

RAGE's structure is made up of three domains. Its extracellular domain is composed of the constant domain (C1 and C2) and a variable domain (V) linked together by an amino acid sequence. Its structure also includes a transmembrane and a cytoplasmic segment. According to the structural analysis of these regions, C1 and V domains are positively charged, whilst the C2 domain is negatively charged [23]. The charge of these domains is essential for binding a variety of particular ligands to RAGE. The involvement of numerous RAGE ligands activities in initiating inflammatory pathways in cells has been investigated so far [24]. RAGE-specific ligands are classified into three categories: endogenous, cytoplasmic, and exogenous ligands; as examples, AGEs, S100 family, amyloid-β peptide, and HMGB1, which bind to extracellular domains of RAGE (V, C1, and C2) [25] have a critical role in triggering chronic inflammatory conditions such as diabetes [26] and cardiovascular diseases [27], progression of numerous cancer cells [28, 29], pulmonary disorders [30], and neurodegeneration diseases such as Parkinson [31] and Huntington [32]. Of note, the monomeric form of RAGE in the cells' membrane has a low affinity for interacting with ligands compared to its dimeric form. As a result, RAGE dimerization is an essential phase in activating the cellular response in cells [24]. The mechanism by which RAGE-ligands impact associated signaling pathways in inflammation of cells, particularly lung cells, is described in the following sections (Fig. 1a).

RAGE and Its Isoforms

Regulating the expression of genes such as the RAGE gene (AGER) located on the major histocompatibility complex (MHC) region is a strategy to control inflammation in humans [33]. In human cells, alternative splicing on the RAGE mRNA results in generating different RAGE isoforms, including sRAGE and splice variant esRAGE [34]. These isoforms of RAGE have specific biological functions. Previous studies have suggested that sRAGE and other soluble isoforms of RAGE reduce the damaging effects of RAGE-ligands by inhibiting their binding capability in human cells (Fig. 1b). They have also proposed

that measuring the levels of sRAGE and esRAGE in body fluid could be used as a diagnostic for disorders such as diabetes [35], lung cancer [36, 37], cardiometabolic [38], renal disease [18, 39], pulmonary fibrosis [40], sepsis [41], and COVID-19 disease [42]. The breakage of the connection between RAGE's extracellular and transmembrane domains leads to the formation of cRAGE (causing its extracellular portion to be released) on the cell surface. This mechanism is stimulated via the binding of RAGE-ligands, including TNF-α, lipopolysaccharide (LPS), and HMGB1, to the extracellular domain of RAGE. The generation of cRAGE is related to the overexpression rate of MMP9 and ADAM10 in the stress conditions (increasing reactive oxygen species (ROS) level). Furthermore, by activation of ADAM10, upregulation of TNF- and induction of NF-κB in the RAS/MAPK signaling pathway promotes overproduction of cRAGE in the cells [43]. The serum/plasma levels of soluble isoforms of RAGE, especially sRAGE and esRAGE, significantly correlated with physical exercise [44], and genetic differences in individuals. The genetic variations among people are due to the highly polymorphic in the AGER gene [45].

Roles of RAGE/Ligands in the Inflammatory Disease

Calprotectin/S100 Family

S100 protein families are characterized by the presence of the EF-hand domain in the structure. They can bind to Ca^{2+} ions with the help of these domains. S100A8 and S100A9 are two main types of the S100 family, both of which can be found in heterodimer form on the cell surface in normal conditions. After neutrophil secretion, S100A9/S8 binds to RAGE and Toll-like receptor 4 (TLR4), causing inflammation and regulating critical processes in the cells such as cell proliferation, angiogenesis, Ca^{2+} homeostasis, and cellular energy. In individuals with a wide range of diseases, such as vascular inflammation and cardiovascular illnesses, the levels of S100A9/S8 in their blood are much higher than in healthy persons. Zhong et al. discovered that binding of S100A8/9 to RAGE on the surface of vein endothelial cells via the PI3K/Akt/mTOR (mammalian target of rapamycin complex 2) pathway increased angiogenesis in vivo and in vitro in intimal hyperplasia models [46].

Furthermore, the findings of Araki et al. showed that the levels of S100A9/S8 proteins are raised in pulmonary fibrosis in lung fibroblasts cells; they discovered that binding of these heterodimers to RAGEs on the surface of fibroblasts activated the NF-κB pathway, causing inflammation in the cells. According to these findings, inhibiting S100A9/S8 binding to RAGEs can help control and reduce inflammation

Fig. 1 Structure of RAGEs and roles of RAGE/ligand axis in pro-inflammatory pathways. **A** RAGE's extracellular domain structure is composed of the constant domain (C1 and C2) and a variable domain (V); RAGE ligands (endogenous and exogenous) bind to the extracellular domains of RAGE. Cytoplasmic ligands such as mDia1 bind to the cytoplasmic domain of the RAGE. **B** Soluble isoforms of RAGE (sRAGE) are included esRAGE and cRAGE; esRAGE is constructed through alternative splicing on the RAGE mRNA, and cRAGE is formed through ADAM10 activity in the extracellular space. **C** Binding of RAGE ligands (mDia1, AGEs, etc.) to RAGE and its dimerization have significant roles in the inflammatory response in cells through regulation of cellular pathways such as PI3K/Akt/mTOR, MAPK/P38, JAC2/STAT3, and other pointed pathways in the figure. Source The Authors
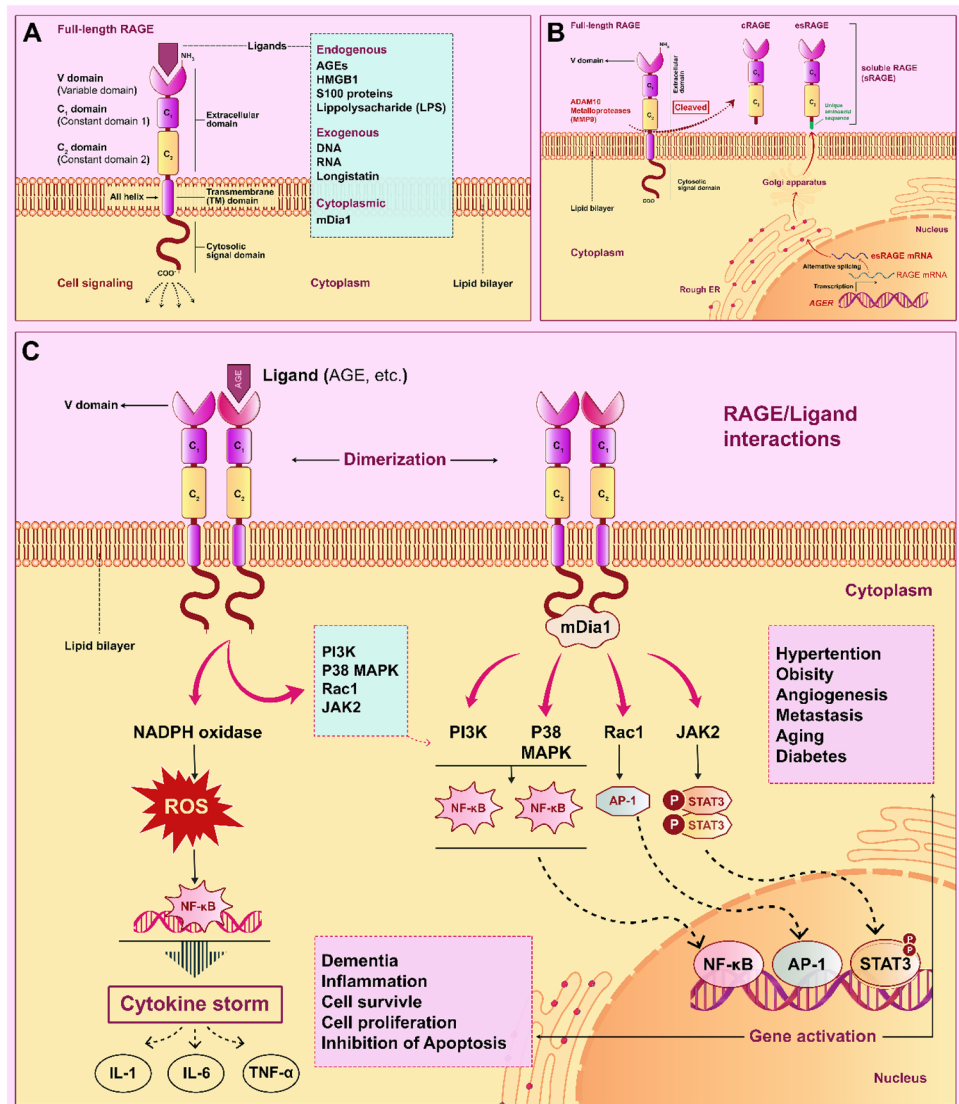
and inflammatory symptoms in lung complications such as Idiopathic pulmonary fibrosis (IPF), ARDS, and Acute lung injury (ALI) (Fig. 1c) [47].

Advanced Glycation End Products (AGES)

AGEs are one of RAGE's most important ligands; these ligands play an essential role in inflammation in neuron cells by increasing amyloid deposition, diabetes complications in chronic conditions, and cardiovascular disease. AGEs included oxidized compounds with reduced sugars in the blood through nonenzymatic reactions [48, 49]. Ren et al. looked into the possible effects of AGEs/RAGE signaling pathway in hepatic ischemia–reperfusion (HIR) after liver transplantation; various levels of ROS and cytokines are produced in the liver during HIR and released into the bloodstream; the presence of these inflammatory agents in liver cells and

other organs, particularly neuron cells, is detrimental to the hippocampus of the brain. Previous findings have shown that levels of AGEs and expression of the RAGE gene are raised in the body under oxidative stress circumstances in various inflammatory conditions. According to the findings of this research, the expression of the RAGE gene was significantly increased in the HIR. As a consequence, overexpression of the RAGE gene can be used as a proper biomarker for stress-induced oxidative damage in cells such as the hippocampus, and targeting RAGE and associated molecules such as NF-κB, ERK1/2, and PI3K in signaling pathways is also a valuable approach for preventing cell damage in stressful situations (Fig. 1c) [50]. Among various glycation end products in the serum, the presence of Nε-(carboxymethyl) lysine or CML in diabetic patients with retinopathy complications, cardiac ischemia, and cardiovascular are increased significantly [51]. The expression of RAGE is reported to

be a significant player in the occurrence of nephropathy, neuropathy, and retinopathy problems in diabetes patients with microvascular and macrovasecular issues [52]. Earlier findings have also demonstrated that reduced levels of sRAGE/esRAGE in the blood of obese and diabetic patients enhanced the incidence of steatosis in liver cells and cardiovascular diseases [53, 54]. Wang et al. showed that the concentration of sRAGE/esRAGE in blood was influenced by AGER gene mutations in prediabetes patients; they found that polymorphism in the T429C (T/C allele) hindered the associated mechanism that controls blood glucose concentration by lowering the concentration of soluble forms of RAGE [55]. Additionally, Sebeková K et al. observed that total sRAGE concertation was reduced in non-diabetic patients before the onset of metabolic syndrome symptoms [56].

High Mobility Group Box Family (HMGB)

The structure of HMGB1 is consists of a single amphipathic alpha-helix chain with two boxes (A and B), which are joined together by a basic domain. The presence of three cysteine amino acids in its box A (Cys23 and Cys45) and box B (Cys106) play a vital role in cell response to redox condition HMGB1 is involved in the control of gene expression via interacting with chromatin. Moreover, HMGB1 promotes inflammatory signaling pathways in necrotic cells, such as JAK/STAT1 and MAPK, and pathogen-induced immune cells via attaching to its receptors on the cell surface,

Table 1 Roles of RAGE/sRAGE/ligands in some inflammatory disease

Diseases	RAGE/sRAGE/ligands	Definitions	Study type	Refs.
T2DM	Increase sRAGE level	Increases sRAGE levels in patients with T2DM after aerobic exercise—Improvement the cardiometabolic risk factor	Randomized controlled trial	[44]
T2DM	Increase levels of sRAGE/esRAGE	Increases sRAGE/esRAGE levels in patients with T2DM after supplementation with pioglitazone and glimepiride	Randomized controlled trial	[59]
T2DM	Decrease levels of CML and LPS—Increase levels of sRAGE	Positive effects of resistant dextrin (a type of prebiotic supplementation) to decrease the inflammation in T2DM patients and improvement the cardiometabolic risk factor through increase the levels of sRAGE along with decrease the levels of CML and LPS	Randomized controlled trial	[60]
Lung cancer	Decrease level of sRAGE during lung cancer	Progression of lung cancer is correlated with level of sRAGE	Case control	[36]
BOS	Increase sRAGE level	Early increase of plasma sRAGE levels is proper marker of alveolar cells lung injury	Multi-center cohort study	[61]
Tuberculosis and pneumonia	Increase of serum sRAGE level—Increase of pleural sRAGE level	More increase of serum sRAGE level in tuberculosis than pneumonia- More Increase of pleural sRAGE level in pneumonia than tuberculosis	Case control	[62]
IPF	Increase of AGE/sRAGE ratio	Increase of sRAGE in the serum of IPF patients is a proper prognostic biomarker	Case control/Observational study	[63]
ARDS	Increase plasma sRAGE and S100A12 levels	Increase pulmonary injuries and inflammatory cytokines secretion in sepsis-induced ARDS	In vivo—Case control	[64]
ARDS	Increase plasma sRAGE levels	Increase ARDS risk	Cohort/Comparative Study	[65]
ALI	Decrease sRAGE level, Increase expression of RAGE/ NF-κB	Induce the lung injury, pulmonary edema, and oxidative stress	In vivo	[66]
SSc	Increase levels of sRAGE and HMGB-1	Association between concentration of sRAGE and HMGB-1 in the severity of SSc	In vivo—Case control	[67]

Type 2 Diabetes Mellitus; Bronchiolitis obliterans syndrome; Idiopathic pulmonary fibrosis; Acute lung injury; systemic sclerosis

particularly RAGE and TLRs (Fig. 1c) [57, 58]. Activation of RAGE/ligands and their concentration in the blood have been linked to various inflammatory disorders (see Table 1).

RAGE and Lung Injuries

Pulmonary Fibrosis

Progressive fibrosis in the parenchyma cells and lung alveolar epithelial cells is defined as idiopathic pulmonary fibrosis (IPF). Despite scientific advancements in the treatment of IPF with 'Nintedanib', existing medicines are insufficient to prevent mortality in this condition. Therefore, early detection of IPF by using appropriate biomarkers is critical for lowering death rates [68]. Earlier studies have shown that certain polymorphisms in the AGER gene enhance the incidence of progressive lung damage in people with IPF, particularly in individuals with severe IPF, by affecting the levels of sRAGE in the blood [69]. In 2020, Yamaguchi et al. evaluated the concentration of esRAGE in patients with IPF against healthy controls; they found that esRAGE levels in patients' blood and bronchoalveolar lavage (BALF) fluid were dramatically decreased [70]. Furthermore, the findings of Machahua C et al.'s investigations suggest that the accumulation of AGEs (CML) along with decreased expression of RAGE in lung samples from IPF patients (surgical lung biopsy) accelerates the fibrotic process in lung cells as compared to control groups [71].

Interestingly, studies have also demonstrated that the level of soluble forms of RAGE (sRAGE and esRAGE) in patients with COPD and IPF is correlated with single nucleotide polymorphism (SNP) of the AGER gene, which is involved in the severity of lung inflammation. Based on these findings, Kinjo T. proved that SNP (rs2070600) of AGER gene lowered the levels of sRAGE in Japanese patients (minor allele of rs2070600) with combined pulmonary fibrosis and emphysema (CPFE) and IPF [69, 72].

Acute Respiratory Distress Syndrome (ARDS)

In intensive care units (ICUs), the occurrence of severe respiratory problems such as ARDS and ALI in patients with infection is common. The major causes of these difficulties in hospitalized patients are linked to the fundamental functions of pulmonary alveolar AECs, which are the critical cells of the respiratory system responsible for the production and secretion of surfactants liquid. Many researchers have recently focused on detecting inflammatory chemicals such MCP-1, IL-6, and other inflammatory cytokines/chemokines that are significant causes of respiratory failure in ARDS/ALI patients. Based on these findings, Zhou

et al. reported that inhibiting long noncoding RNA nuclear paraspeckle assembly transcript 1 (NEAT1) in AECs in vivo (C57BL/6 mice) and in vitro (cell line A549) models can be a promising strategy for reducing acute inflammation of AECs in ARDS and ALI by controlling the production of inflammatory agents such as IL-6 and TNF- and also blocking the activation of the RAGE/HMGB1/NF-κB signaling pathway [12, 73].

Previous research has found that ARDS frequency has increased dramatically in individuals with sepsis who had also had pneumonia. The crucial causes of the lung damages of ARDS-suffered patients are the accumulation of lung fluid (AFC) in the alveolar space, which is secreted from AECs. Based on these findings, Wang H et al. evaluated the mechanism by which amounts of AFC fluid is increased in the alveolar space of lungs in the ARDS /ALI in vivo model (RAGE$^{+/+}$ and RAGE$^{-/-}$ mice). They discovered that in the presence of RAGE (RAGE $^{+/+}$ mice), downregulation of some membrane channel proteins in the lungs, such as Na/K-ATPase, ENaC, and ZO-1 increased AFC fluids in the mice lungs [74].

Consequently, modulating the RAGE pathway in ARDS patients might be a promising new treatment option for reducing AFC buildup. In a study accomplished by Audard et al. they explored the anti-RAGE antagonist peptide in an ARDS-induced animal model, which is called RAP; this monoclonal antibody (mAb) reduced the pro-inflammatory activities of these ligands by inhibiting the binding of HMGB1 and S100 proteins to RAGE. The investigation results suggested that suppressing RAGE reduced AFC fluid accumulation and alveolar cell injury in piglet model with ARDS [75].

Acute Lung Injury (ALI)

ALI is a progressive disorder that affects ICU patients who have damaged lungs due to infection, exogenous shock, or trauma. Anti-inflammatory drugs reduce the accumulation of fluid in the airspaces of the lungs, edema, and levels of pro-inflammatory chemicals (such as HMGB1, IL-1, and IL-6) in the body [76]. Numerous research has recently been conducted to investigate novel treatment strategies such as cell and gene therapy in patients with ALI to reduce mortality. Gene therapy has received much attention for treating ALI among the new therapeutic techniques that have been tried so far. As an example, Piao C et al. used polyamidoamine (PAM; a polymeric nanocarrier) that conjugated with Dexamethasone drug (a potent glucocorticoid) (PAM-D)/RAGE-antagonist peptide (RAP) for delivery of adiponectin plasmid (pAPN) to Raw264.7 cells (Mouse Leukemic monocyte macrophage) and the animal model. The results demonstrated that the presence of RAP along with pAPN/PAM-D complex increased the

anti-inflammatory effects of Dexamethasone drug and pAPN; they reasoned that RAP's intrinsic anti-inflammatory properties bolstered the complex's anti-inflammatory effects. The previous experiment reported that RAP could block the binding of pro-inflammatory ligands including HMGB-1, S100 family, β-amyloid, and LPS to RAGE receptor; thus, using these peptides in gene therapy helps to decrease inflammation [77, 78]. Dexmedetomidine (DEX) was identified as a potential drug for administration in clinical studies in ALI patients by Hu et al. in 2017. DEX decreased the expression of RAGE gene in rats and downregulated HMGB1, NF-κB, and MAPK [76].

Furthermore, lidocaine (Lido) protects against a variety of lung injuries, including ALI, sepsis-induced lung injury, and ARDS, by inhibiting pro-inflammatory cytokines including IL-1, IL-6, and TNF-α [79–82]. According to Zhang et al. treatment of ALI-rats with 'Lido' suppresses acute inflammatory responses in rat lung tissues by lowering RAGE and HMGB1 expression. Altogether, lowering RAGE expression and pro-inflammatory ligands in ALI patients is a potential prospective technique for decreasing mortality due to their multifunctional involvement in pathways including MAPK and NF-κB [83].

LPS is one of the most harmful pro-inflammatory ligand (pathogenic factor) that activates inflammatory pathways in alveolar epithelial cells in individuals with ALI by interacting with the RAGE receptor [84]. Yang et al. employed 'Ketamine' to reduce the pathogenic effects of LPS, based on the mediatory functions of RAGE/ligands in ALI. In their investigation, Ketamine administration dramatically reduced RAGE, HMGB1, and TLR9 expression in ALI-Rats [85].

COVID-19 and RAGE/Ligands Axis

Inflammatory Pathways which are Involved in the Severity of COVID-19 Disease

The corona virial family, such as SARS-CoV-2, has four proteins in its structure; among these proteins, spike (S) is a glycoprotein that targets ACE2 on the surfaces of epithelial cells in the respiratory system. The high mortality rate of patients with COVID-19 is related to the increased levels of cytokines (cytokines storm), including IL-10, IL-7, IL-6, MIP-1A, IP-10, and TNF-α in the respiratory system, and as a result, the incidence of acute respiratory symptoms especially ARDS. The activation of cytokines, ROS, and other pro-inflammatory chemicals by LPS attachment to the TLR4 receptor on the surfaces of AECs are one of the significant molecular drivers in ARDS in COVID-19 patients. Petruk et al. investigated the likely mechanism by which LPS affects the COVID-19 based on the association between blood levels of LPS and complications of numerous conditions such as metabolic syndrome, inflammatory bowel syndrome (IBD), Kawasaki disease, COPD, Periodontitis, and obesity. They discovered that the binding of LPS to spikes glycoprotein increased the pro-inflammatory effects in vivo and in vitro models by boosting cytokine levels in peripheral blood mononuclear cells (PBMC) and triggering the NF-κB pathway (see Fig. 2a and b for this section).

Consequently, they suggested that measuring LPS levels in patients with severe COVID-19 might be helpful in managing the respiratory system's serious ramifications [86–88]. According to these findings, Teixeira PC et al. demonstrated that in hospitalized COVID-19 patients, increased levels of LPS and pro-inflammatory systemic cytokines and chemokines are associated with the occurrence of severe symptoms in patients with COVID-19 [89]. In 2022, Jose et al. evaluated the anti-inflammatory properties of Kaba Sura kudineer (KSK), a poly-herbal formulation, in LPS-activated RAW 264.7 cells. Its anti-diabetic, anti-viral, and anti-bacterial properties have been discovered in previous studies. Furthermore, this research revealed that KSK, together with Vitamin C and Zinc, lowered the viral load of COVID-19 patients. According to their findings, KSK (25 g/mL) has an anti-inflammatory impact via downregulating TLR4, thereby suppressing the pro-inflammatory effects of LPS [90]. Bindings of multiple ligands, including LPS, bacteria, viruses, and damage-associated molecular patterns (DAMPs) to TLR4, stimulate the production of pro-inflammatory compounds in the cells. Several studies conducted during the COVID-19 pandemic found that targeting TLR4 and RAGE receptors, as well as their ligands, could be beneficial in controlling the severity of COVID-19 patients with ARDS. Considering the importance of genetic heterogeneity of TLR4 and severity of COVID-19, a study was undertaken to investigate the probable associations of TLR4 SNPs in Thr399Ile/Asp299Gly with the severity of COVID-19 patients in the Egyptian population. It is recognized that minor alleles (G and T) of 299Gly and 399Ile of the TLR4 gene are related to the severity symptoms in COVID-19 patients [91]. In addition, Sohn KM et al. found that severe COVID-19 patients have high levels of S100A9 in PBMCs, rather than mild COVID-19 patients, because S100A9 binding to TLR4 promoted the release of different cytokines/chemokines (cytokine storm) during severe COVID-19 conditions [92].

Calprotectin (S100A8/A9 heterodimer) is mainly produced by macrophages, platelets, and neutrophils during inflammation in the immune system. Calprotectin expression is frequently elevated in a variety of diseases, including sepsis, lupus, trauma, and COVID-19. Calprotectin levels in the blood, stool and other body fluids have been described in previous research as a useful biologic marker for diagnosing inflammation. The binding of calprotectin to TLR4 and
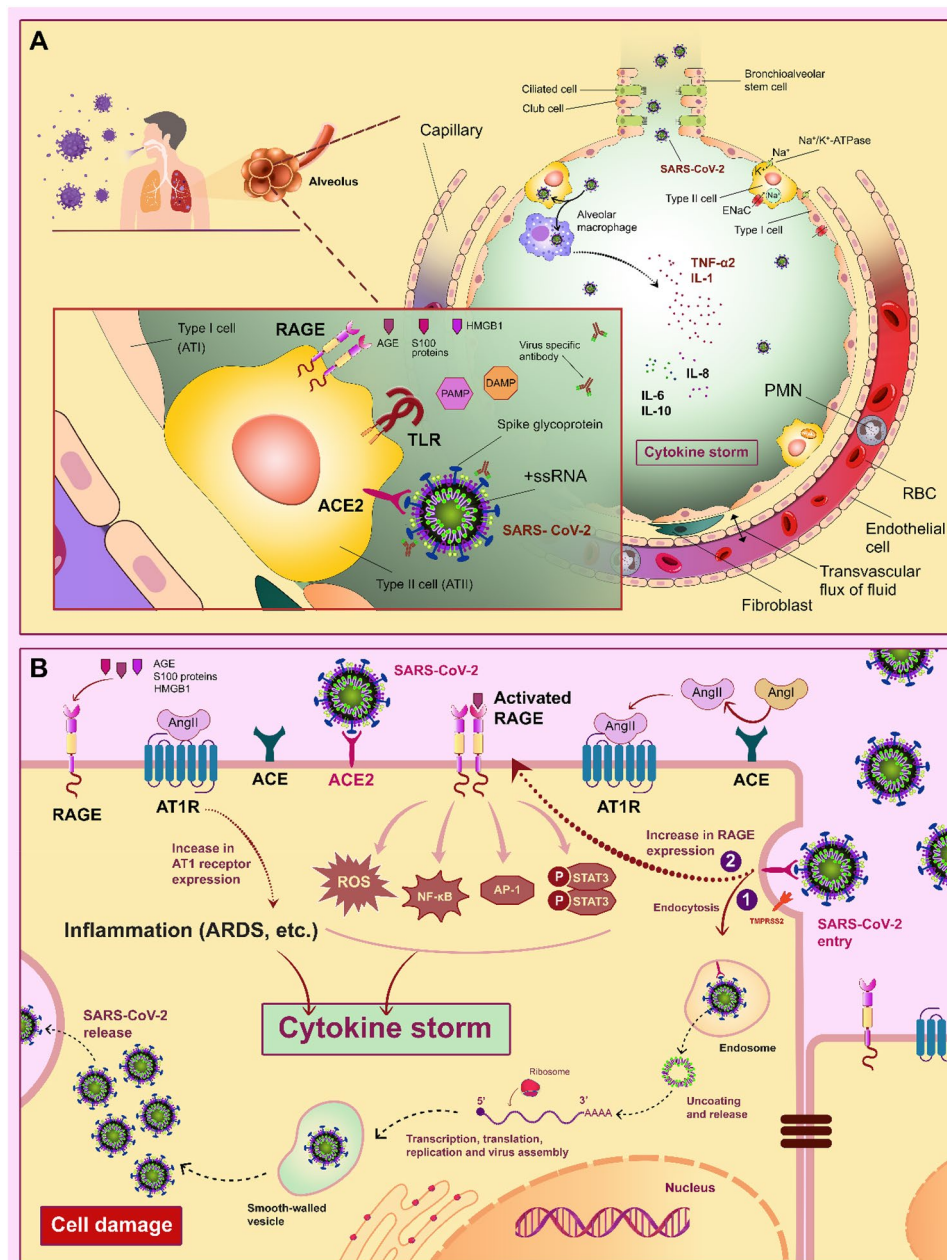
Fig. 2 Contribution of RAGE, AT1R (type 1 angiotensin receptor), ACE2 (angiotensin-converting enzyme 2), and TLR (Toll-like receptor) in alveolar epithelial cells related to COVID-19 pathogenies in a cytokine storm. **A** SARS-CoV-2-specific receptor (ACE2), RAGE, and TLR in the surface of type 2 alveolar epithelial cells, and related inflammatory ligands including DAMPs (damage-associated molecular patterns), PAMP (pathogen-associated molecular pattern), S100 proteins, and AGE trigger cytokine storm in the respiratory system. In the infected alveolar macrophages with SARS-CoV-2, production and releasing the pro-inflammatory cytokine such as IL-1, IL-6, IL-8, IL-10, and tumor necrosis factor alpha (TNF-α) are stimulated. B-1) Entry of the SARS-CoV-2 is mediated by ACE2/endocytosis in type 2 alveolar epithelial cells. B-2) Binding of S100 proteins, AGE, and HMGB1 to V-domain of RAGE in the surface of type 2 alveolar epithelial cells by regulating the pro-inflammatory transcription factors (Activator protein 1 (AP-1), STAT3, and NF-κB) have key roles in the production of ROS and cytokine storm. Expression of the RAGE gene in alveolar epithelial cells is increased after binding SARS-CoV-2 to ACE2. The binding of angiotensin (Ang) II to AT1R is mediated cell apoptosis, chronic inflammation, pulmonary edema, and cytokine storm in alveolar epithelial cells. Source The Authors

RAGE receptors induced the production of ROS, nitric oxide, and cytokines in the cells. According to a systematic review conducted by Udeh R et al., when compared to other biomarkers such as D-dimer, C-reactive protein, and creatine kinase for diagnosing and predicting the severity of COVID-19 patients, measurements of calprotectin

concentration significantly increased in the serum of these patients relatively mild type of COVID-19 patients [93]. In particular, Lee and Shi found that calprotectin concentration was considerably higher in severe COVID-19 patients. Ultimately, their findings showed that elevated levels of calprotectin in the blood of COVID-19 patients with severe conditions function as a pro-inflammatory factor in their respiratory failure [94, 95].

HMGB1 is one of the essential types of DAMP molecules. The concentration of HMGB1 in the plasma of patients with severe inflammation, such as ARDS and pneumonia, was discovered to be higher. Previous research suggested that binding HMGB1 to TLR4 caused the synthesis and release of cytokines into the bloodstream (cytokines storm). HMGB1 also facilitated SARS-CoV-2 entry into the lung cells by increasing the amount of ACE2 receptors on the surface of AECs (Fig. 2a and b). According to the substantial pro-inflammatory effects of HMGB1 in the severity of patients with COVID-19, targeting HMGB1 is a possible point for preventing the highly loaded SARS-CoV-2 in the cells and releasing pro-inflammatory molecules like IL-6 and TNF in AECs [96, 97]. Headache, loss of appetite, diarrhea, anosmia, nausea, weight loss, and pulmonary injury are observed in patients suffering from severe COVID-19. Bolay H et al. demonstrated that elevated levels of various pro-inflammatory molecules such as D- dimer, IL-6, IL-10, ACE2, and HMGB1 in the serum of hospitalized patients with severe COVID-19 likely lead to headache; the results of their study showed that levels of HMGB1 in the serum of hospitalized patients with severe COVID-19 with Pulmonary involvement as a robust biomarker significantly increased [98].

Levels of sRAGE and esRAGE in the Blood of COVID-19 Patients

Despite numerous studies on the pathophysiology of severe COVID-19 patients with respiratory and hypoxemia abnormalities, little attention has been paid to investigating appropriate biomarkers for early detection of respiratory injury, particularly in COVID-19–associated ARDS (CARDS) and death prevention in patients with severe conditions. Among the biomarkers associated with respiratory injury in severe COVID-19, measuring the concentration of sRAGE in the blood is a valuable indicator in these patients. According to the evidence so far, the central cells in the production of sRAGE are alveolar cells in the lungs (type I); thereby, changing the level of them in the plasma is a beneficial marker for detecting the onset of respiratory complications in CARDS patients with severe thromboembolic, capillary leakage in organs, and angiopathy for mechanical ventilation and mortality prevention [99]. Lim et al. evaluated the possible correlation between high serum sRAGE concentration and respiratory failure in COVID-19 patients in the ICU in 2021; they stated that monitoring sRAGE in these patients is worthwhile for coping with mortality and severe pulmonary complications that necessitate mechanical ventilation and high-flow nasal oxygen therapy [6]. Microangiopathy, capillary congestion, and widespread alveolar destruction are the major causes of severe pulmonary injury in CARDS patients. In classical ARDS, evaluation of specific endothelial injury biomarkers such as soluble intercellular adhesion molecules, selectin family (P and E types), soluble vascular cell adhesion molecule, Ang-2, and soluble forms of RAGE in alveolar epithelial injury is considered a predicting marker for reducing respiratory symptoms and death rate. Although the recruitability of CARDS patients is lower than that of classical ARDS patients, a histopathological study revealed that their pathophysiology is identical. The assessments of certain alveolar and endothelia biomarkers in hospitalized severe patients with CARDS and classical ARDS in the University Hospital of Ferrara were utilized to clarify the distinctions between respiratory symptoms of CARDS patients and classical ARDS patients. The levels of soluble intercellular adhesion molecules or ICAM-1 and Ang-2 in the lungs of CARDS patients were higher than in classical ARDS patients due to significant vascular damage in the lungs. However, the levels of RAGE were lower. Furthermore, in CARDS individuals, P-selectin was lower than E-selectin [100].

It is well recognized that measurements of angiotensin II and ACE2 levels are poor biomarkers in severe respiratory dysfunctions such as ALI/ARDS; however, blocking the ACEI and AT1R are robust procedures for alleviating the inflammatory response and mortality in severe COVID-19 patients. As previously stated, NF-κB-related cell signals are activated by Ang II binding to AT1R independent of the presence of RAGE ligands. Altogether, inhibiting the RAGE/NF-B pathway reduced cytokine storms in COVID-19 patients with severe disease and lessened the damaging effects of the AT1R/Ang II in human cells, particularly in respiratory cells [21].

Levels of sRAGE and esRAGE in the Blood of COVID-19 Patients with Diabetes Mellitus

Thrombosis and micro/macrovasecular inflammation are two main complications in DM patients. Through the RAGE signaling pathway, infection with SARS-CoV-2, as well as the creation of AGEs molecules in diabetic patients' blood, exacerbate thrombosis and vasculopathy [101]. The most critical mediator in the morbidities of DM is the hyperactivity of the RAGE receptor. Studies have indicated that the entrance of SARS-CoV-2 to respiratory cells is mediated by ACE2 and AT1R receptors which trigger RAGE

receptors in the cells' surface regardless of the presence of RAGE-related ligands. Recently, Krishnamachary et al. have reported that RAGE-containing vesicles (extracellular vesicles) which are released from damaged cells in patients with COVID-19, can be used as a suitable biomarker in patients with severe COVID-19 with DM [82]. Based on the pro-inflammatory functions of RAGEs in the pathobiology of DM and respiratory involvements, Dozio et al. investigated the probable link between levels of soluble isoforms of RAGE and DM in patients with COVID-19. Overall, they suggested that measurements of cRAGE/esRAGE ratio along with other biomarkers could be as most applicable biomarker of RAGE group in all Covid-19 participants with or without DM, but to confirm these results, more extensive studies are needed [13].

Conclusions

RAGE is a multi-ligands receptor that predominantly is expressed in alveolar epithelial cells of the respiratory system. Measurements of soluble forms of RAGE in our blood, particularly sRAGE and esRAGE, as well as the RAGE gene's expression rate, are as applicable biomarker in chronic inflammatory diseases such as diabetes, cardiovascular disease, neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease), pulmonary disease, classic ARDS, and also for reducing their mortality. Moreover, several studies have shown that targeting the RAGE receptor and its particular ligands, including HMGB1, LPS, AGEs, and the calprotectin family are novel techniques for inhibiting pro-inflammatory pathways in human cells.

Acute respiratory symptoms are the leading cause of mortality with the COVID-19 condition. The AT1R/Ang-2 and RAGE/TLR4/NF-B signaling pathways are activated when pro-inflammatory chemicals such as Ang-2, DAMPs, systemic cytokines, AGEs, and other compounds accumulate in the blood and alveolar spaces of the respiratory system. As a result, the current investigation focused on the involvement of the RAGE/ligands axis and associated pro-inflammatory levels of sRAGE and esRAGE in the severity of COVID-19 patients with ARDS who were hospitalized. Measurements of sRAGE, esRAGE, and sRAGE/esRAGE in patients with CARDS are as powerful biomarkers for alleviating respiratory symptoms and early diagnosis of pulmonary involvements for managing cytokines storms in lung cells, according to clinical research. Due to the multitude roles of RAGE and ligands in the related complications with the severity of COVID-19 such as DM, we suggest that targeting the RAGE/NF-κB signaling pathways along with AT1R/Ang-2 could alleviate pulmonary involvements in the ARDS COVID-19 patients.

Author Contributions All the authors conceived this study and contributed equally to this work. HP, MS and SA participated in drafting the document and created the figures. HP was mentor and contributed to the supervision of the entire work. All the authors read and approved the final manuscript.

Declarations

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