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REVIEW

Association Between ACE2 and Lung Diseases

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Abstract: Angiotensin-converting enzyme 2 (ACE2) is an important regulator of the Renin-Angiotensin System (RAS). Additionally, it has been identified as a functional receptor for the Coronavirus. Research indicates that ACE2 plays a role in the regulation of cardiovascular systems by modulating blood pressure and electrolyte balance. Its role in pulmonary diseases has also garnered significant attention due to the widespread prevalence of Coronavirus. There is solid evidence linking ACE2 to other pulmonary diseases, including chronic obstructive pulmonary disease, acute respiratory distress syndrome, allergic asthma, among others. However, the exact pathological and physiological mechanisms of ACE2 in these diseases remain elusive. Our research aims to review and explore the latest advancements in ACE2-related studies in pulmonary diseases. These findings have the potential to open new avenues for utilizing ACE2 as a potential biomarker for early diagnosis and monitoring of pulmonary diseases.

Keywords: ACE2, lung diseases, ARDS, Lung Cancer, COPD

Introduction

Angiotensin-converting enzyme 2 (ACE2) was discovered 20 years ago.[1] It is the main regulator of Renin-Angiotensin System (RAS), plays a crucial regulatory role by converting inactive angiotensin I (AngI) into the vasoconstrictor angiotensin II (AngII),[2] which is the central effector molecule of the RAS system. AngII mediates numerous biological responses through angiotensin receptors (AT1 and AT2). ACE2, a homologue of ACE, can cleave AngII into the peptide Ang1-7 (Figure 1). It has protective effects on the heart, vasodilation, anti-growth, and anti-proliferation properties, and it can also enhance the activity of bradykinin.[3] In addition, ACE2 has multiple functions, including the transportation of amino acids and serving as a functional receptor for the severe acute respiratory syndrome (SARS) and other coronavirus diseases.[4,5] These functions have gained significant attention in recent years.

First reported to express in the heart, kidney, and testis, the ACE2 gene has since been found to be more extensively expressed in the upper respiratory tract, lung, intestinal tract, and liver (Figure 2).[6] The tissue distribution study of the ACE2 gene indicates that it is primarily concentrated in type II alveolar cells and macrophages in the respiratory system, but it is also present in lung fibroblasts, bronchial and tracheal epithelial cells, and macrophages.[6,7] The main entrance point for Coronavirus is ACE-2.[8] Heart failure (HF), pulmonary hypertension (PH), myocardial infarction (MI), and cardiovascular consequences of diabetes are all demonstrated in laboratory models of human disease to involve ACE2.[9]

Due to the high expression of the ACE2 gene in various tissues and organs, as well as its ability to regulate the self-functional properties of the RAS system, ACE2 can modulate multiple pathological processes in the body, such as fibrosis, inflammation, oxidative stress, and vasoconstriction. Studying the changes in ACE2 gene expression may provide valuable insights into the susceptibility and complications of pulmonary diseases, as well as the pathogenic mechanisms associated with risk factors for pulmonary diseases. For example, environmental factors such as smoking can increase the expression of ACE2,[10,11] and smoking is a well-established risk factor for many pulmonary diseases. In certain pulmonary diseases such as chronic obstructive pulmonary disease (COPD), ACE2 is overexpressed in the

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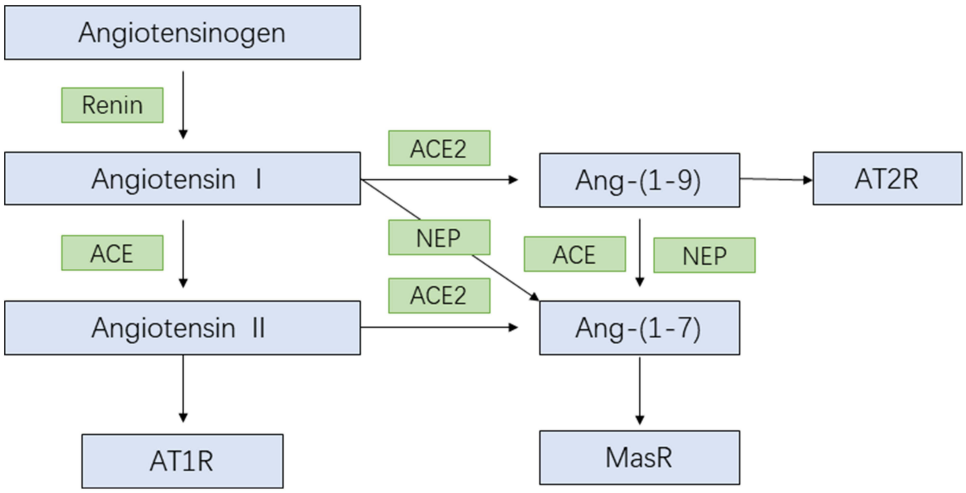

Figure 1 Schematic representation of classical RAS and the counter-regulating RAS axis.

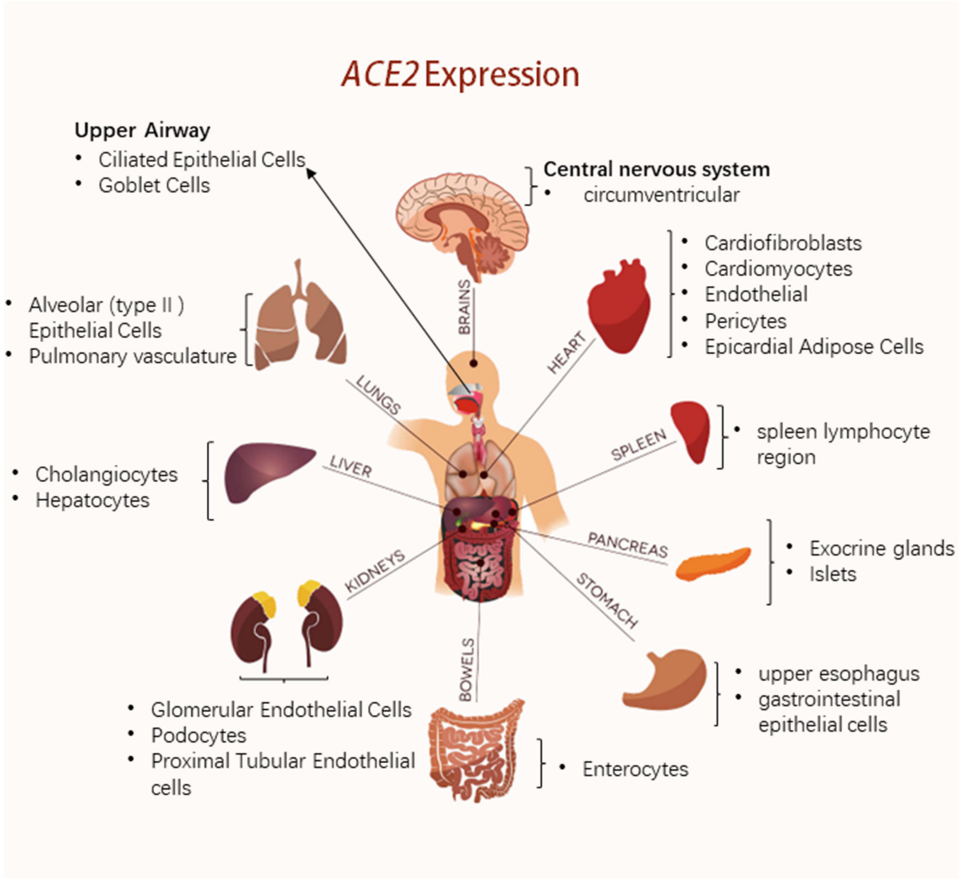

Figure 2 Distribution of ACE2 expression.

alveolar and bronchial epithelium.[12] It can be speculated that smoking increases the risk of developing pulmonary diseases by affecting ACE2 expression.

The expression of ACE2 can be regulated through various mechanisms, including transcriptional, post-transcriptional, and translational processes. For instance, the use of BRD2 inhibitors can inhibit Coronavirus infection by reducing the transcription of ACE2, which is the receptor present on host cells.[13] In the case of upper respiratory tract Coronavirus

infection, the transcription of ACE2 in the nasopharynx plays a contrasting role. However, the transcription of the soluble form of ACE2 showed a negative correlation with the viral RNA load, even after considering factors such as age, biological sex, and TMPRSS2 transcription.[14] During the aging process, the telomere DNA damage response promotes the transcription of ACE2, making older individuals more susceptible to Coronavirus infection;[15] Additionally, exposure to certain chemicals can increase the transcription levels of ACE2.[16] Therefore, regulating the expression of ACE2 may have implications in delaying or treating diseases associated with ACE2 and the RAS system.

Due to its involvement in the occurrence and progression of various diseases, ACE2 has recently gained significant attention as the receptor for Coronavirus, the virus responsible for the occurrence of some Coronavirus diseases. This article aims to explore the relationship between ACE2 and major lung diseases while considering its newfound significance in the context of Coronavirus.

Coronavirus and ACE2

At the beginning of 2020, Coronavirus spread rapidly worldwide within a few months. As of February 2023, there have been over 753 million confirmed cases and 6.8 million deaths reported globally.[17] The World Health Organization declared Coronavirus infecion a pandemic.[18] The mild clinical manifestations of Coronavirus primarily present as upper respiratory tract infection, while patients with moderate disease exhibit pneumonia, and in the most severe cases, it may progress to acute respiratory failure requiring mechanical ventilation.[19]

Coronavirus is responsible for causing some Coronavirus diseases. This virus belongs to the coronavirus family, which includes other viruses such as SARS-CoV (Severe Acute Respiratory Syndrome or SARS) and MERS-CoV (Middle East Respiratory Syndrome or MERS). Due to their similar genomic sequences, namely SARS and MERS, Coronavirus also utilizes the ACE2 receptor as a binding site to enter cells. The RBD of the Coronavirus virus binds to the N-terminus of the receptor using its external structural domain, forming a hydrophilic contact network that dominates the RBD/ACE2 interaction. Following binding to ACE2, the fusion between the Coronavirus envelope and the host cell membrane is mediated by the S2 subunit. It is worth mentioning two proteases, namely ADAM17 metalloproteinase and serine transmembrane protease TMPRSS2, which have been reported to play a role in the entry of coronaviruses into host cells and their binding to ACE2.[20]

The basic reproduction number (R0) of Coronavirus is typically estimated to be between 2 and 3. However, on average, R0 of the some Coronavirus was measured at 9.5.[21] This indicates that each infected individual may transmit the virus to 9.5 other people. Some study about ACE2 helping to explain its more widespread transmission. They found that the Coronavirus spike (S) protein exhibits a binding affinity to ACE2 that is approximately 10–20 times greater than the Coronavirus spike (S) protein.[20] This makes Coronavirus more prone to invade the human body, resulting in a higher level of infectivity.

Moreover, apart from binding affinity, there appears to be a nuanced connection between the level of ACE2 expression and the susceptibility as well as the severity of Coronavirus. Research indicates a heightened expression of ACE2 in the elderly and in males.[22] Remarkably, the epidemiological characteristics of Coronavirus underscore a pronounced concentration among the elderly population. This observation aligns with studies highlighting the correlation between elevated ACE2 levels and increased vulnerability to and intensity of infection with the virus, shedding light on the complex interplay between ACE2 expression and Coronavirus outcomes. Certainly, the transmissibility of Coronavirus manifests intricacies within populations, influenced by factors such as public health policies, the immunological barrier provided by vaccines, human behavior, and more. The exact association between ACE2 gene expression and susceptibility to Coronavirus requires further substantiation with additional evidence.

In addition, olfactory loss is one of the sequelae caused by Coronavirus,[23] and the localization studies of ACE2 may help us identify how Coronavirus affects the sense of smell in the human body. Both ACE2 and TMPRSS2 are expressed in the olfactory mucosa of mice, nonhuman primates, and humans. However, single-cell sequencing has revealed that ACE2 is exclusively expressed in Sertoli cells, stem cells, and perivascular cells, but not in neurons. ACE2 protein is universally expressed in maintenance cells and pericytes of the olfactory bulb in the dorsal olfactory epithelium of mice. These findings suggest that anosmia and associated odor perception disorders in Coronavirus patients result from Coronavirusinfection of non-neuronal cell types.[24]

This section summarizes the role of ACE2 as the binding site for Coronavirus infection in the human body, seemingly playing a crucial role in the transmissibility of Coronavirus, susceptibility to infection, and olfactory loss. Simultaneously, the section also outlines the mode of interaction between Coronavirus and ACE2, with its significantly higher affinity compared to other members of the coronavirus family. However, there is a need for more evidence to establish a clear correlation.

ARDS and ACE2

Acute respiratory distress syndrome (ARDS) is a syndrome characterized by low levels of oxygen in the blood and chest imaging reveals bilateral fluid accumulation without signs of heart failure. Risk factors for ARDS include various types of pneumonia, aspiration of stomach contents, and sepsis.[25] Treatment primarily focuses on protective mechanical ventilation and supportive care to prevent excessive fluid overload.[26] However, despite these measures, the mortality rate of ARDS remains as high as 30%.[27]

ACE2 and RAS play important roles in the development of acute respiratory distress syndrome. A mouse model of ARDS caused by smoking has been constructed. Studies have shown that inflammatory pulmonary edema and histological changes caused by lung injury caused by smoke inhalation may be attributed to abnormal expression of ACE and ACE2-related pathways.[28] In a study in the early 2000s, researchers constructed a severe model of lung disease in mice, revealing that ACE2 had a pulmonary protective effect on ARDS in the acute phase,[29] while mice lacking ACE also showed significant improvement in the disease.[29] Researchers have found that wild-type mice infected with Coronavirus or treated with recombinant Coronavirus spike protein exhibit a significant reduction in ACE2 expression in the lungs. These mice show an increased severity of pathological conditions in acute lung injury. Treatment of ACE2 knockout (KO) mice with the SARS spike protein does not exacerbate ARDS symptoms. Therefore, the downregulation of ACE2 expression during Coronavirus infection may play a causal role in the pathogenesis of Coronavirus diseases, providing a reasonable explanation for the progression to ARDS in patients.[30]

Research on acute respiratory distress syndrome caused by Coronavirus has indicated that individuals with ARDS tend to be older (61 years vs 49 years), have a higher likelihood of having comorbidities (20.8%vs1.8%), and experience significantly elevated mortality rates (49.1% vs 8.9%) compared to those without ARDS. Furthermore, the clinical characteristics of patients vary depending on the severity of the acute respiratory distress syndrome, with patients suffering from moderate to severe ARDS exhibiting higher mortality rates than those with mild ARDS.[31] It has been observed that antiviral, glucocorticoid, or immunoglobulin therapy does not substantially enhance the survival rate of patients with Coronavirus-induced acute respiratory distress syndrome.[31] Patients with ARDS and SARS exhibit typical ARDS lesions in the lungs.[5] We hypothesize that Coronavirus may share similar pathogenic mechanisms and pathological manifestations. Therefore, the use of ACE2 inhibitors in the treatment of Coronavirus-induced ARDS could be beneficial. This hypothesis was supported by a cohort study, wherein they observed ACE2 inhibitors play a crucial role in modulating the inflammatory processes in ARDS patients with Coronavirus infection. ACE2 inhibitors can mitigate immune dysregulation, inflammation, and alveolar dysfunction, thereby reducing the progression of ARDS, particularly in patients with concurrent Coronavirus infection.[32]

ARDS is currently a clinically high-mortality disease, which, as previously mentioned, may be due to RAS overactivation caused by Coronavirus infection. ACE2 has protective effect on acute respiratory distress syndrome caused by Coronavirus. Therefore, the development of drugs that enhance ACE2 activity or the use of RAS blockers, such as angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, may be one of the most promising methods to treat severe Coronavirus diseases.[33]

COPD and ACE2

Chronic obstructive pulmonary disease (COPD) is a major global health concern, leading to significant morbidity and mortality.[34] COPD is a broad term encompassing emphysema, which involves irreversible damage to the alveolar sacs, and chronic bronchitis, characterized by a productive cough and abnormal inflammatory responses in the airways and lungs.[35] Symptoms of COPD include chronic cough and progressive difficulty in breathing. Smoking is the primary risk factor, although genetic predisposition and occupational exposure also play a role in its development.[36] In China, the

prevalence of COPD is 13.6% in adults 40 years of age.[37] The study was primarily conducted in hospitalized patients, whereas only 1.1% of the studies that included both hospitalized and outpatients had a diagnosis of COPD. [38]

Chronic inflammation, characterized by inflammatory cell infiltration and the chronic release of pro-inflammatory cytokines, plays a pivotal role in the pathogenesis of COPD.[39] The chronic inflammation observed in COPD patients is often attributed to the excessive activation of the Renin-Angiotensin System (RAS). Studies indicate that RAS activation is achieved through the pro-inflammatory actions of Angiotensin II (Ang II), which concurrently mediates the generation of reactive oxygen species (ROS), mitochondrial dysfunction, and disruptions in redox signaling.[40] And significant increases in the AT 1R/AT 2R ratio were observed in the lung tissue of COPD patients with reduced lung function.[41] ACE2, in contrast, typically acts as a regulator in this chronic inflammatory context. Elevated expression of ACE2 has been associated with significant improvements in lung function among COPD patients. Furthermore, increased ACE2 levels correlate with reduced concentrations of pro-inflammatory cytokines such as TNF-α, IL-8, IL-2, and IL-1β within the patient's system.[42] The significant reduction in ACE2 mRNA expression in the lungs of COPD rats compared to wild-type rats suggests a potential association between ACE2 regulatory inhibition and ACE/ACE2 imbalance with the onset and progression of COPD.[42]

Therefore, the RAS system in which ACE2 is located participates in the pathogenesis of COPD mainly through the Ang II/AT1R axis mediated proinflammatory and profibrotic effects. With the Coronavirus diseases occurance, COPD patients are also at increased risk of severe Coronavirus patients.[43] One reason is the increased expression of the entry receptor ACE2 for Coronavirus,[44] Results from a cohort study indicate a significant elevation in ACE-2 expression in COPD patients compared to controls with no prior history of illness.[12] Another reason may be that Coronavirus patients with a history of COPD produce relatively fewer effective antibodies compared to those without underlying diseases.[45] The diminished antibody production could compromise the efficacy of humoral immunity, thereby manifesting more severe clinical symptoms.[46]

This section, through a review of research progress, highlights the pivotal role of chronic inflammation in the pathogenesis of COPD, typically stemming from the excessive activation of the RAS. ACE2, functioning as a regulatory factor in this chronic inflammatory environment, exhibits elevated expression associated with significant improvements in lung function among COPD patients, along with a concurrent reduction in concentrations of pro-inflammatory cytokines. However, the increased expression of ACE2 in COPD patients also renders them more susceptible to Coronavirus infection, potentially leading to a more severe course of Coronavirus infection, possibly due to the relatively lower production of effective antibodies in these individuals.

Asthma and ACE2

Asthma is a diverse respiratory disorder characterized by persistent inflammation of the airways. Global estimates suggest that over 339 million individuals are affected by asthma.[47] The development of asthma is influenced by various factors, involving a complex interplay between genetic and environmental elements. Common symptoms of asthma comprise coughing, wheezing, difficulty breathing, and chest tightness. The pathophysiology of most asthma patients is dominated by type II inflammatory processes.[48]

A study examining gene expression data from nasal and airway epithelial cells of children and adults with asthma and allergic rhinitis revealed a significant reduction in ACE2 expression in nasal and airway epithelial cells associated with type 2 asthma and allergic rhinitis. This decrease in ACE2 expression is attributed to the cytokine IL-13, generated during type II inflammatory processes.[49] Additionally, a retrospective cohort study similarly confirmed that individuals with asthma exhibited a reduction in ACE2 protein expression in the lower airways.[50] Type 2 inflammation is thought to be responsible for the decreased ACE2 gene expression in the airways of allergic asthma.[51,52]

As mentioned earlier, ACE2 plays a role in the renin-angiotensin system (RAS) by deactivating Ang II and activating Ang1-7. Researchers confirmed, through a type 2 asthma mouse model, that Ang1-7 can reduce perivascular and peribronchial inflammation, fibrosis, and goblet cell hyper/metaplasia in allergic asthma. These findings substantiate the significant protective role of Ang1-7 in allergic asthma and underscore the anti-inflammatory function of ACE2.[53]

Patients with chronic respiratory conditions, such as asthma and COPD, often experience an increased susceptibility to complications arising from acute respiratory viral infections.[54] However, the question of whether asthma serves as

a risk factor for unfavorable outcomes in patients with Coronavirus remains a matter of debate.[55] A study reporting 140 cases of Coronavirus in China, found no self-reported cases of asthma, allergic rhinitis, atopic dermatitis, or food allergy among infected patients,[56] making it inconclusive regarding the susceptibility of asthma patients to Coronavirus. Large systematic reviews and meta-analyses examining the comorbidity of asthma and Coronavirus have also failed to establish a clear association between adult asthma and severe outcomes of Coronavirus diseases.[57,58] While the relationship between asthma and adverse outcomes in Coronavirus diseases remains elusive, as mentioned earlier, ACE2 is involved in the regulation of type 2 inflammatory responses, primarily exerting a protective role against inflammation. Consequently, numerous studies have observed a reduced expression of ACE2 in asthma patients, leading to a decreased risk of adverse outcomes in Coronavirus diseases.[59] This highlights the potential correlation between the downregulation of ACE2 in asthma and a lowered occurrence of unfavorable outcomes associated with Coronavirus diseases. A recent systematic review has summarized the association between asthma and Coronavirus, revealing that several studies consistently reported a higher prevalence of asthma maintenance medication usage (measured by inhaler dose or frequency of use) and more frequent asthma exacerbations in adult asthmatics, which corresponded to an increased risk of adverse Coronavirus diseasesoutcomes.[60] Therefore, poorly controlled asthma in patients represents a risk factor for severe Coronavirus diseases.

Our systematic review has summarized the progress in research on the association between asthma and ACE2. Studies have shown a notable decrease in ACE2 expression in nasal and airway cells linked to type 2 asthma and allergic rhinitis, potentially influenced by the cytokine IL-13. This underscores a plausible connection between the pathophysiology of asthma and the susceptibility to Coronavirus infection. Despite the increased vulnerability to viral infections in chronic respiratory conditions such as asthma, ongoing debates persist regarding whether asthma unequivocally represents a risk factor for adverse outcomes in Coronavirus diseases. Systematic reviews and studies examining the role of ACE2 in allergic airway diseases present conflicting findings, adding complexity to the understanding of this relationship.

Lung Cancer and ACE2

Lung cancer stands as one of the most severe malignant tumors jeopardizing human health and life. Originating from abnormal cells in pulmonary tissues, the most prevalent types are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The correlation between lung cancer and factors such as prolonged smoking, exposure to environmental hazards (such as asbestos, radioactive substances, and air pollutants), and genetic predisposition is well-established.

In recent years, enhanced expression of ACE2 has been frequently observed in lung cancer patients, with research indicating a pivotal role for ACE2 in the initiation and progression of lung cancer.[61] Within lung cancer tissues, the heightened expression of ACE2 appears to be associated with the regulation of epigenetic factors, including HAT-1, HDAC-2, and KDM5B,[62] which are known to augment ACE2 transcription. While the signaling pathways underlying the upregulation of ACE2 expression remain unclear, literature suggests that the induction of ACE2 expression may facilitate the catalysis of growth-inhibitory Ang1-7 peptide synthesis, thereby slowing tumor growth through mas receptor activation and subsequent MAP kinase inhibition.[63,64]

Clinical studies have validated the correlation between elevated ACE2 expression and a more favorable prognosis in non-small cell lung cancer,[65] consistent with the foundational research discussed earlier. A Mendelian randomization study confirmed an increased risk of lung cancer in individuals prescribed formulations of angiotensin-converting enzyme inhibitors,[66] aligning with the conclusions of a meta-analysis that contradicted the protective role of ACE2 against lung cancer.[67]

Conclusion

Through a comprehensive review of recent literature on the association between ACE2 and pulmonary diseases, we have observed significant advancements in research. The synthesis of current findings reveals that ACE2, as elucidated in the latest literature, plays a crucial role in the pathogenesis of lung disorders. This scrutiny underscores the importance of

exploring the intricate interplay between ACE2 and pulmonary conditions. This overview serves to contribute valuable insights into the evolving landscape of ACE2-related research, particularly in the context of respiratory diseases.

We highlights the critical role of ACE2 as the binding site for Coronavirus, influencing the virus's transmissibility, susceptibility, and impact on olfactory function. The higher affinity of Coronavirus for ACE2, compared to other coronaviruses, is discussed, emphasizing the need for additional evidence to establish a definitive correlation. ARDS, associated with high mortality, may result from RAS overactivation due to Coronavirus infection. ACE2's protective effect against Coronavirus-induced ARDS suggests potential treatments involving ACE2 enhancement or the use of RAS blockers, such as angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. The association between ACE2 and various respiratory conditions, including COPD, asthma, and lung cancer, reveals diverse outcomes. While COPD patients exhibit elevated ACE2 expression, debates persist about asthma's role as a unequivocal risk factor for adverse outcomes in Coronavirus, adding complexity to understanding the relationship between ACE2 and allergic airway diseases. The correlation between elevated ACE2 expression and a more favorable prognosis in non-small cell lung cancer is validated clinically, but conflicting findings from Mendelian randomization studies and meta-analyses add nuance to the protective role of ACE2 against lung cancer.

In addition to COPD, ARDS, asthma, Coronavirus diseases and lung cancer, ACE2 is also associated with pulmonary hypertension, smoking-induced lung damage and other lung diseases. In the context of pulmonary hypertension, ACE2 functions as a protective factor. Experimental models have demonstrated that exogenous ACE2 and Ang 1–7 inhibit the activity of Ang II, thereby slowing the progression of pulmonary hypertension.[68,69] This deceleration in progression is likely attributed to the excessive expression of ACE2, which inhibits fibrosis in the pulmonary artery wall.[70] Further investigations confirm that smoking increases the expression of ACE2, with current smokers exhibiting higher ACE2 expression levels compared to ex-smokers and never-smokers. This observation has been validated in diverse cohorts of lung tissues and airway epithelial samples from different research groups,[12,71] and additional evidence supports an association between ACE2 expression and nicotine exposure.[72]

Regarding the correlation between ACE2 and these diseases, as well as other pulmonary conditions, more comprehensive research progress and evidence are required in the future. We are committed to summarizing these research advancements in a more thorough, clear, and academically formal manner, aligning with the requirements of medical academic literature.

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Disclosure

The authors report no conflicts of interest in this work.

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