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Review Article

ACE2: the node connecting the lung cancer and COVID-19

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Abstract: Angiotensin-converting Enzyme 2 (ACE2) collaborates with Angiotensin (Ang) 1-7 and Mas receptors to establish the ACE2-Ang (1-7)-Mas receptor axis. ACE2 impacts lung function and can cause lung injury due to its inflammatory effects. Additionally, ACE2 contributes to pulmonary vasculature dysfunction, resulting in pulmonary hypertension. In addition, ACE2 is a receptor for coronavirus entry into host cells, leading to coronavirus infection. Lung cancer, one of the most common respiratory diseases worldwide, has a high rate of infection. Elevated levels of ACE2 in lung cancer patients, which increase the risk of SARS-CoV-2 infection and severe disease, have been demonstrated in clinical studies and by molecular mechanisms. The association between lung cancer and SARS-CoV-2 is closely linked to ACE2. This review examines the basic pathophysiological role of ACE2 in the lung, the long-term effects of SARS-CoV-2 infection on lung function, the development of pulmonary fibrosis, chronic inflammation in long-term COVID patients, and the clinical research and mechanisms underlying the increased susceptibility of lung cancer patients to the virus. Possible mechanisms of lung cancer in SARS-CoV-2-infected individuals and the potential role of ACE2 in this process are also explored in this review. The role of ACE2 as a therapeutic target in the novel coronavirus infection process is also summarized. This will help to inform prevention and treatment of long-term pulmonary complications in patients.

Keywords: ACE2, COVID-19, lung cancer, pulmonary fibrosis, chronic inflammation, SARS-CoV-2

Introduction

The Coronavirus Disease 2019 (COVID-19) was initially identified in Wuhan in 2019 and rapidly spread worldwide, resulting in numerous fatalities [1]. The infection mechanism of SARS-CoV-2 was investigated and compared to SARS-CoV. Angiotensin-Converting Enzyme 2 (ACE2) was discovered to play a crucial role in SARS-CoV-2 infecting host cells. ACE2 is a key regulator of the pathophysiology of several systems, including the cardiovascular, respiratory, renal and gastrointestinal systems. The widespread expression of ACE2 in multiple organs and tissues explains why patients may develop complications involving multiple organs after being infected with SARS-CoV-2 [2].

Of particular concern is the occurrence and progression of lung diseases, as they are part of the respiratory system that SARS-CoV-2 primarily affects. Complications or pre-existing underlying diseases interact with pneumonia caused by the SARS-CoV-2 virus. Lung cancer, the second most common cancer worldwide after breast cancer, has a high mortality rate [3]. The routine screening, diagnosis, and treatment of lung cancer have been significantly impacted by the COVID-19 pandemic [4]. Nevertheless, researchers have been still actively investigating the mutual pathophysiology of SARS-CoV-2 infection and various lung diseases, including lung cancer.

ACE2 is a key component of the renin-angiotensin system (RAS) and has a wide distribution throughout the body. Its functions in the lungs are very important due to its pro-inflammatory and vasodilation effects [5]. Any disturbance in the quality or quantity of ACE2 can lead to various diseases such as acute lung injury and pulmonary arterial hypertension [6, 7]. ACE2 is highly expressed in lung cancer tissues, which increases the susceptibility to SARS-CoV-2

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infection [8]. Infection with SARS-CoV-2 results in a decrease in ACE2 levels in host cells and an increase in serum levels of Ang II, leading to severe complications such as ARDS [9]. Studies are underway to determine whether SARS-CoV-2 infection causes other long-term pulmonary complications via ACE2.

This narrative review outlines the current knowledge surrounding the physiological function of ACE2, its role as the receptor for SARS-CoV-2, and the importance of ACE2 in host cells infected with COVID-19. Additionally, we discuss the evidence demonstrating that high levels of ACE2 in lung cancer patients increase susceptibility to SARS-CoV-2 infection. We investigated whether SARS-CoV-2 infection has negative effects on pulmonary function, including lung cancer. Finally, the role of ACE2 targeting in the treatment of novel coronaviruses of recent years is discussed.

Pathophysiological function of ACE2 in the lung

Angiotensin-converting Enzyme 2 (ACE2), identified in the early 2000s in a library of genetic material from humans with heart failure [10], cleaves Ang I into Ang (1-9) and also converts Ang II into Ang (1-7) [11]. ACE2 is a type of integral membrane glycoprotein, which is divided into membrane-bound form and soluble form [12]. In recent times, there has been a proposal for the ACE2-Ang-(1-7) and Mas receptor axis to neutralize the impacts of the conventional Renin-Angiotensin System. This novel axis works by expanding the blood vessels, inhibiting cell growth, decreasing inflammation, and more [5]. As a crucial component of the RAS, ACE2 has been observed in various types of tissues, such as the lung, heart, kidney, and intestine, with its primary role being to regulate the volume of extracellular fluid and blood pressure [13]. ACE2 is most prominently expressed in the gastrointestinal tract, followed by the kidney, testis and heart [14]. It has been reported that apelin signaling can increase the activity of ACE2 promoters, leading to increased levels of ACE2 mRNA and protein. However, ACE2 has been shown to cleave and deactivate apelin peptides through a negative feedback mechanism. This feedback mechanism serves a protective role in cardiovascular disease [15]. ACE2 also functions as a chaperone protein for the transporter B^0AT1 (SLC6A19) in the absorption of neutral amino acids in the intestine and kidney [16]. The balanced expression of ACE2 and RAS has certain benefits in heart disease, vascular disease, diabetic vascular comorbidity, and lung disease [17]. Detailed relationships between the traditional RAS and the ACE2-Ang-(1-7)-MAS axis show in **Figure 1**.

Although the expression of ACE2 in the lung is relatively low compared to other organs and tissues, it plays a crucial role in acute lung injury and protects the lung from severe acute lung failure [18]. Within the lung, ACE2 has been identified in type II pneumocytes, ciliated epithelial cells, as well as the motile cilia of epithelial cells, but not in secretory goblet cells [19]. The expression of ACE2 is particularly low in the lung tissues of normal individuals, which is beneficial in limiting the spread of pathogenic microorganisms in the lung [20]. No difference in the expression of ACE2 has been found between healthy and diseased lungs. The expression levels of ACE2 vary in different populations. In the lung, the ACE2 levels are lower in the elderly than in children, especially in the lower lung [21]. Several studies have confirmed the high expression of ACE2 in smokers, suggesting that long-term smoking may be a risk factor for COVID-19 [22, 23]. Exposure to enriched particles in the environment, use of ibuprofen, and atherosclerosis may increase the levels of ACE2 in the lungs [24-26].

ACE2 levels are regulated or modified by transcriptional, post-transcriptional and post-translational effects. At the transcriptional level, it can be upregulated by transcription factors such as Ikaros, HNFs, GATA6, STAT3 or SIRT1, and downregulated by BRG1-FOXM1 complex or ERR α. At the post-transcriptional level, it can be regulated by histone modification or miRNA-induced instability. At the level of post-translational regulation, ACE2 can be phosphorylated, ubiquitinated and methylated to regulate its activity [27]. Phosphorylated Stat3 is one of the major transcription factors. The expression of lung ACE2 is positively correlated with Stat3, which can increase the expression of ACE2 stimulated by Il-6 in 16HBE cells. Additionally, 6-0 angeloylplenolin (6-OAP) is a relatively effective ACE2 inhibitor [28].

Evidence suggests that ACE2 plays a pivotal role in acute lung injury by influencing inflam-

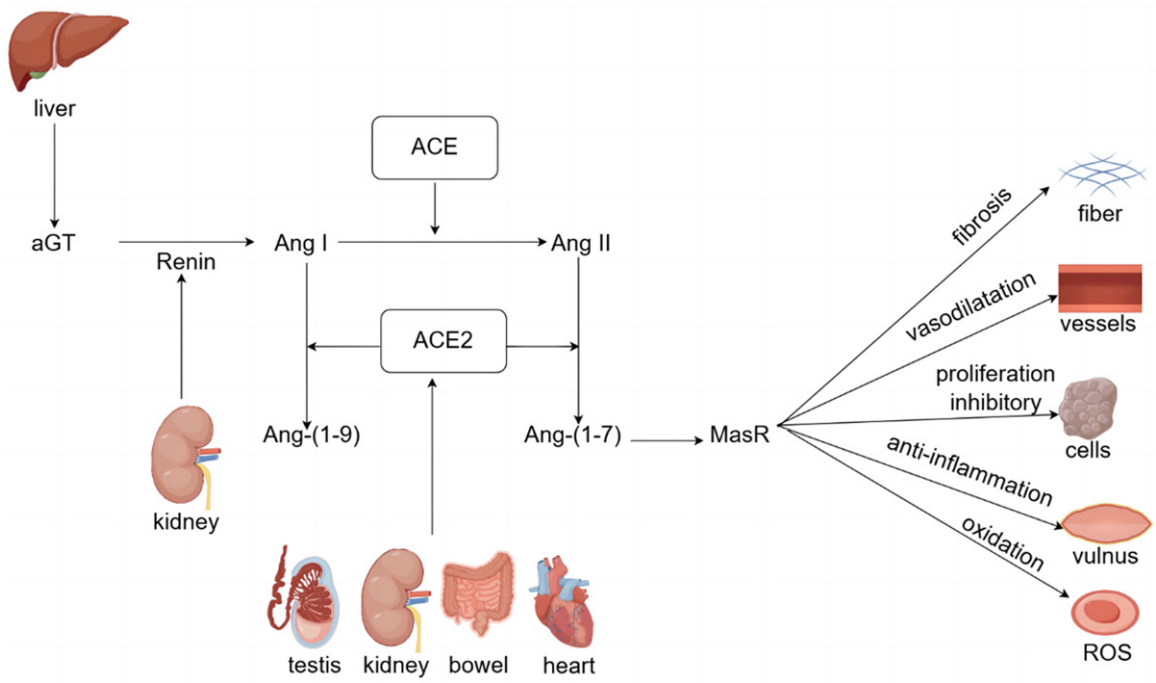

Figure 1. Angiotensinogen is produced in the liver and converted to ANG I by renin from the kidneys. ANG I is then converted to Ang II by ACE. This process promotes inflammation, fibrosis, oxidative stress, and the production of NO. ACE2 can convert Ang II to Ang-(1-7), which has an effect against the Ang II-AT1 axis. ACE indicates angiotensin-converting enzyme; Ang I, angiotensin I; MasR, Mas receptor; ROS, reactive oxygen species [32] (By FigDraw).

mation and autophagy. Supplementation with rhACE2 may improve pulmonary hemodynamics and reduce levels of oxidative stress and markers of inflammation [29]. By activating the AMPK/mTOR pathway, ACE2 is able to inhibit inflammation and autophagy, resulting in amelioration of acute lung injury [30]. Further research has indicated that the signaling pathways p-ERK1/2 and p-STAT3 mediate PM2.5 particle-induced acute lung injury. ACE2 knockout can increase pulmonary p-ERK1/2 and p-STAT3 levels in PM2.5 particle-induced acute lung injury. An increased abundance of secretory cells expressing ACE2 may upregulate the response of ACE2 to inflammatory signals [31]. It is worth mentioning that ACE2 is also closely associated with pulmonary hypertension. Even though the expression of ACE2 decreases in patients with COVID-19, they still experience increased vasodilation. ACE2 has the potential to be involved in the treatment of pulmonary hypertension given its ability to dilate blood vessels [26]. In particular, ACE2 can be targeted by a biomimetic nanoparticle delivery system that delivers ACE2 to the pulmonary vascular endothelium to inhibit pulmonary artery smooth muscle cell proliferation and reduce pulmonary vascular remodeling [32].

ACE2 in pulmonary host cells infected with COVID-19

In the winter of 2019, COVID-19 pandemic emerged and rapidly spread worldwide, resulting in numerous fatalities. Widespread transmission of the SARS-CoV-2 virus was responsible for causing this epidemic [33]. As of August 18, 2023, the World Health Organization (WHO) has reported a total of 769,774,646 confirmed cases and 6,955,141 confirmed deaths globally. Many cases with mild or no symptoms may have gone undetected. Since the SARS pandemic in 2003, the ACE2 protein has been identified as a key factor in severe lung diseases and has been extensively studied in animal models to understand its protective effects on lung tissue. ACE2 interacts with the downstream product Ang1-7 through the Mas receptor, further confirming its role in lung protection [34, 35]. With the outbreak of COVID-19, ACE2 regained prominence as it was ascertained to be the most potential biomarker and cell entry receptor [36]. On the outer shell of the SARS-

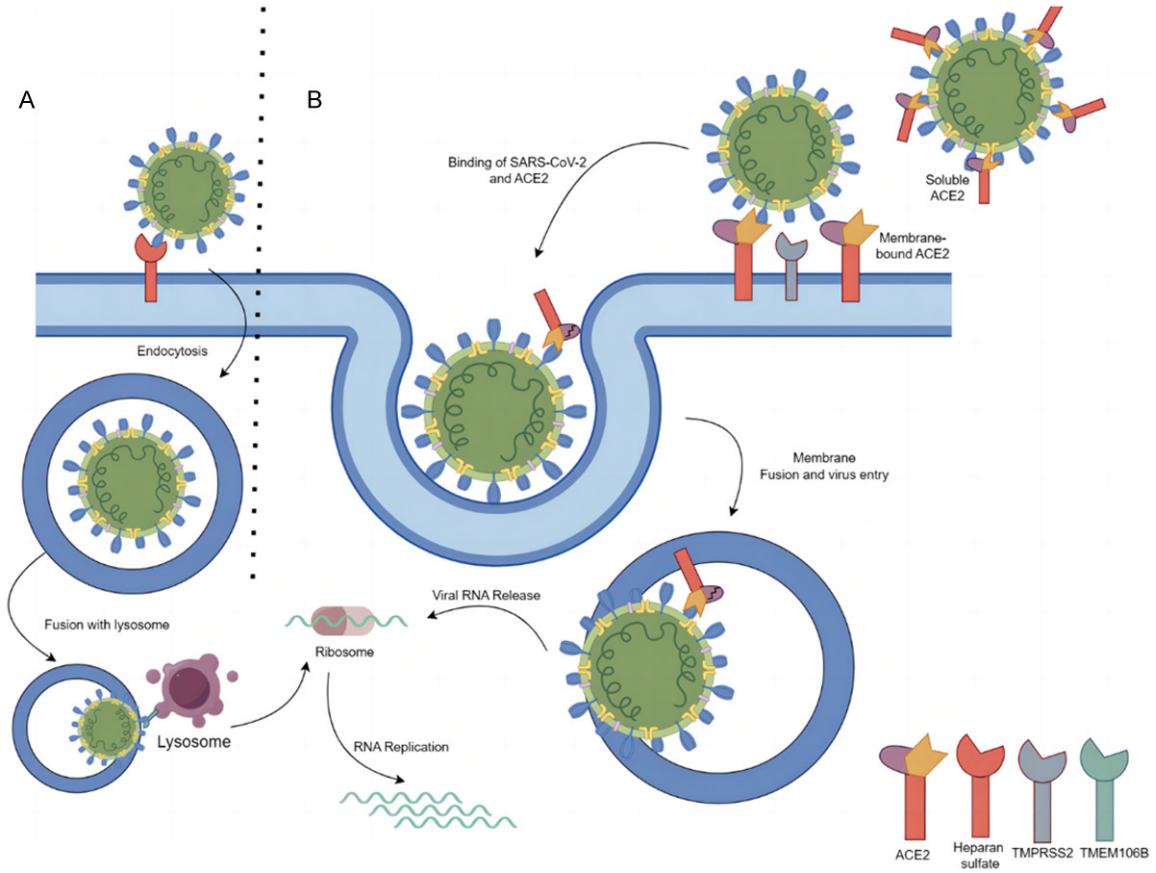

Figure 2. Cell entry of SARS-CoV-2 (By FigDraw). A: TMEM106B has recently identifies a pro-viral host factor for cell entry of SARS-CoV-2 in cells with low expression of ACE2. Located at the membrane of the lysosome, TMEM106B functions independently of ACE2 [41]. B: ACE2 is a classic receptor for SARS-CoV-2 to infect host cells. After the S1 subunit of the S protein binds with ACE2, TMPRSS2 facilitates the cleavage of the S protein, which is an important process of cell entry of SARS-CoV-2.

CoV-2 virus, there are glycoproteins called spike (S) proteins that play a critical role in identifying and specifically binding to the ACE2 receptor on host cells. This binding occurs through a conformational change in the S protein [37]. The S protein consists of two subunits, S1 and S2. The S1 subunit is responsible for binding and interacting with the ACE2 receptor, while the S2 subunit facilitates fusion of the virus and cell membranes by separating the two units [38]. Through bioinformatics analysis, researchers have discovered that the signal transducer and activator of transcription 3 (Stat3) promotes the expression of ACE2 and can regulate its function by stimulating interleukin 6 [28]. The membrane proteins TMPRSS2 and heparan sulphate, and the lysosomal membrane protein TMEM106B are extra-specific receptors of SARS-CoV-2 [39, 40] (**Figure 2**).

It has been observed that after ACE2 binds to the virus, it induces the up-regulation of Orai1, which is a key component of cellular calcium channels. This process also involves the formation of clusters of piezoelectric 1 and TRPC1, which promote the activation of piezoelectric 1 and SOCC channels and the increase in [$Ca2^{+}$]i. These changes ultimately lead to increased apoptosis and persistent damage to the pulmonary vascular endothelium. However, Kobophenol A can inhibit these effects by blocking the binding of ACE2 and S proteins [41]. It is also worth noting that ACE2 expression decreases with the progression of acute lung inflammation and rises in the lung epithelium of mice with interstitial pneumonia. In a model of pulmonary fibrosis, hypoxia is mediated by HIF 1α and fibrosis-related cytokines reduce ACE2 expression [42]. The mechanism of ACE2 reduction after lung infection involves the forma-

tion of a complex between ACE2 and spike protein, which is then degraded by clathrin-mediated endocytosis and PAK1-mediated cytoskeletal rearrangement. This results in restoration of ACE2 cell surface expression by the PAK inhibitor FRAX-486 after viral infection [43]. ACE2 contains 6 potential glycosylation sites (Asn53, Asn90, Asn103, Asn322, Asn432, Asn546), and mutations in these sites can regulate its binding to coronaviruses. N90A deletions increase the affinity of ACE2 and S proteins, N322A deletions slightly increase affinity, and the N53A deletions minimize affinity. N90A/N322A/N322A triple-gene deletions have the highest affinity [44, 45].

Patients with lung cancer are prone to infect SARS-CoV-2 and have severe events

Current clinical research

Since the outbreak of the pandemic, many studies have been conducted to validate that patients diagnosed with lung cancer have a higher risk of being infected with SARS-CoV-2 and may be more prone to confront severe events. Especially at the acute stage of the SARS-CoV-2 infection, patients with lung cancer have higher mortality and they were found easily to get into intensive care unit and need mechanical ventilation [46, 47]. In a clinical study conducted in 2020, researchers discovered that out of the 105 patients with cancer, 22 of them had lung cancer. These patients had a higher risk of mortality from COVID infection (OR 2.34, 95% CI [1.15, 4.77]; P=0.03). Additionally, these cancer patients had a higher rate of occupancy in the intensive care unit (OR 2.84, 95% CI [1.59, 5.08]; P < 0.05) [48]. In a retrospective study conducted in 2021, a total of 1200 individuals who were diagnosed with cancer were found to have a significantly higher likelihood of developing novel coronary pneumonia. Specifically, the study included 100 patients with lung cancer (aOR, 7.66 [95% CI, 7.07-8.29]; P < 0.001). The adjusted odds ratio (aOR) used in the study takes into account only the specific risk factors being examined and excludes other potential contributing factors [49]. Later, 69 patients with lung cancer were included to investigate the impact of PD-1 blocking therapy on SARS-CoV-2 infection. The results showed that PD-1 therapy did not have any significant influence on the severity of COVID-19 in lung cancer patients. Out of the participants in the study, 62% of the lung cancer patients required hospitalization due to SARS-CoV-2 infection, and 24% of them passed away as a result of the virus [50]. In another study, with a higher infection rate of in-hospital patients than that reported in the overall Chinese population, patients with cancer (including lung cancer) were deemed easier to be infected with COVID-19, the figure for cancer patients and the overall population was 2.5% and 0.29%, respectively. The same defection is that the sample of this research is too small and the documentation on the patient's data is not complete [46]. Similarly, a study also found that SARS-CoV-2 infection was very severe among patients with lung cancer, with a mortality of 25% and hospitalized rate of 62%. What is interesting is that COVID-19 made up a small part of overall lung cancer deaths during the pandemic, only 11% [51].

In a more recent study, lung cancer was considered the crucial predictor with the other 4 predictors, and SARS-CoV-2 Omicron variants delayed to be cleared in patients with cancer and is asymptomatic COVID-19, with a *P* value of 0.018 [52]. ACE2 expression has also been investigated in various types of lung cancer. There was no variation in the expression of the ACE2 gene at each pathological stage of LUAD and LUSC. Similarly, data from the Human Protein Atlas (HPA) demonstrated that LUAD and LUSC exhibited higher levels of ACE2 protein compared to normal lung tissue, indicating no discrepancy in lung cancer sensitivity to the novel coronavirus at different pathology stages [53]. Ilikci Sagcan et al [54] conducted gene sequence analysis of 1097 lung cancer patients, including ACE2, TMPRSS2, CD147/BSG, and FURIN/PCSK3, from the cBioPortal portal, which validated the aforementioned findings. Furthermore, they observed that 8.1% of the subjects had at least one mutation in one gene, with ACE2 being the most frequently mutated gene, including 8 missense mutations and 1 splice site. They also identified missense mutations at the H34 amino acid site of the virus-bound S protein ACE2 in genomic analysis of LUAD patients as p.H34N. In a study of non-small cell lung cancer, it was found that mACE2 and sACE2 were more frequently expressed in patients with EGFR mutations and not in patients with KRAS mutations [55]. The expres-

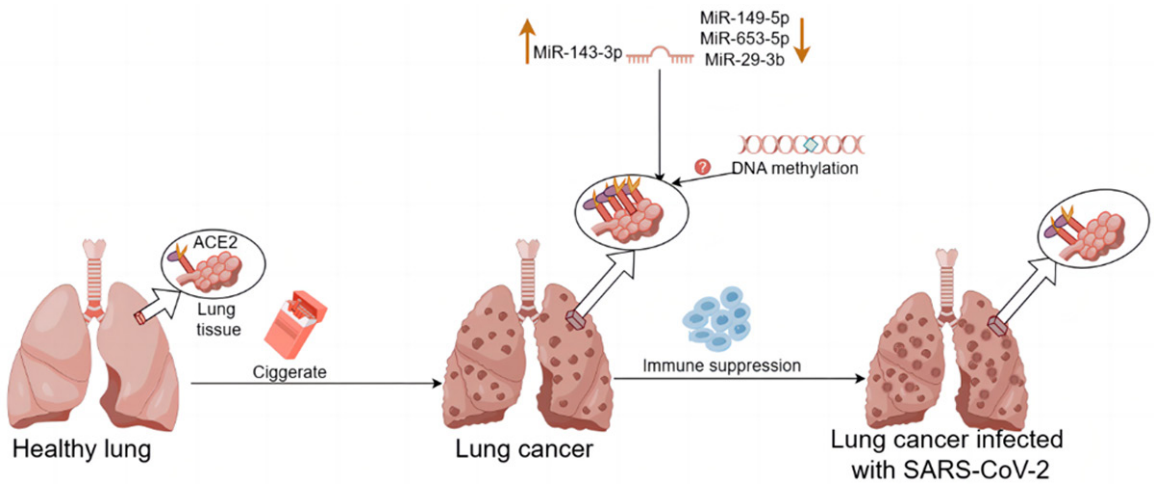

Figure 3. Up-regulation of ACE2 in lung cancer leads to higher susceptibility to SARS-CoV-2 (By FigDraw).

sion of ACE2 transcripts in the normal lung tissue of patients with non-small cell lung cancer is higher in patients with advanced disease, leading to increased inducible T cell costimulatory factors in immune and cytokine reactivity, potentially resulting in more severe lung injury from COVID-19 [56].

Potential molecular mechanism involved in ACE2

Besides the clinical studies performed to confirm the susceptibility of SARS-CoV-2 to infect individuals diagnosed with lung cancer, there have also been published scientific papers that aim to explain the mechanism involving ACE2 in this process. First of all, via molecular biology experiments and bioinformatics analysis, it was clear that ACE2 expressed a higher level in lung cancer compared with normal lung tissue and the level of ACE2 may represent the sensibility of lung cancer patients to be infected with SARS-CoV-2 [57]. Recent literature reported that through single-cell transcriptomic analysis, ACE2 was found to be highly expressed in the NSCLC cells and alveolar cells while low level in other types of cells, which is one of the reasons why lung cancer patients are more susceptible to SARS-CoV-2 than normal person. There was no disparity in the expression between cancer cells of lung squamous cell cancers (LUSC) and lung adenocarcinoma (LUAD) [58]. Based on the single-cell RNA sequencing analysis of bronchial tube samples from smokers with lung cancer, it was observed that goblet cells had a significant increase in the expression of ACE2. This finding suggests that smoking can result in a greater viral load [59]. Additionally, the upregulation of ACE2 has been discovered to be associated with immune suppression, particularly in the inhibition of immune cell activation: $CD8^+$ T cells, $CD4^+$ regulatory T cells, NK cells, and T cells. Various immune markers, including CD8A, KLRC1, GZMA, GZMB, NKG7, CCL4, and IFNG, decrease as the expression level of ACE2 increases. These mechanisms could potentially make patients with lung cancer more susceptible to SARS-CoV-2 [60]. To explore the reason for the upgrade of the ACE2, certain literature reported that DNA methylation may be the underlying mechanism [61]. Moreover, dysregulation of microRNAs may be one of the potential mechanisms for patients with lung cancer who are more vulnerable to SARS-CoV-2 infection. In detail, the downregulation of MiR-143-3p, upregulation of MiR-149-5p, MiR-653-5p and MiR-29-3b increases the level of expression level of ACE2 [62] (**Figure 3**).

SARS-CoV-2 leads to further pulmonary changes

Current clinical research

One review concluded that COVID-19 infection may worsen the pathogenetic condition of patients with chronic respiratory disease, particularly interstitial lung disease [63]. Pulmonary fibrosis and chronic lung inflammation have the potential to progress to lung cancer. Abnormal lung function, pulmonary fibrosis, chronic inflammation and lung cancer are discussed

below as potential sequelae of SARS-CoV-2 infection.

Decreased lung function: Much of the literature has focused on changes in lung function following SARS-CoV-2 infection. A study was conducted on 110 individuals who tested positive for SARS-CoV-2 to investigate the extent to which their pulmonary function deteriorated after being discharged from the hospital. The results showed that the severity of pneumonia was directly related to the decline in pulmonary function. Specifically, the diffusion capacity was significantly impaired, while the measurements of ventilatory function remained relatively stable [64]. In another separate study, González et al conducted a 3-month prospective cohort involving 62 critically ill patients. They utilized chest CT scanning, pulmonary function tests, and exercise tests. The results revealed that a significant majority of the patients, specifically over 82%, experienced a decrease of more than 20% in their pulmonary diffusion [65]. Later, an observational study that lasted for more than 12 months discovered that patients with extremely severe conditions who required ECMO treatment still experienced pulmonary impairment in their lung function [66].

Pulmonary fibrosis: Quantities of epidemiological evidence highlight the potential link between idiopathic pulmonary fibrosis (IPF) and lung cancer. The relative risk of lung cancer in patients with IPF is about seven times higher than that of the general population, and it can increase the likelihood of being diagnosed with lung cancer by 7% to 20% [67, 68]. Recent studies have found that IPF is an increased independent risk factor for lung cancer, even when smoking is considered [69, 70]. The causes of lung cancer caused by pulmonary fibrosis may include lymphatic obstruction, carcinogen aggregation, and impaired monitoring mechanisms [67]. Additionally, studies have investigated the microscopic mechanisms of IPF and lung cancer, which may be attributed to the unbalanced expression of oncogenes and tumor suppressor genes, the dysregulation of non-coding RNAs, and genetic and epigenetic alterations leading to aberrant activation of common transduction pathways, such as Wnt/b-catenin and phosphoinositide 3-kinase/protein kinase [71]. Furthermore, guanine nitrification may be a major risk factor for the development of IPF lung cancer [72].

Scientists have always been interested in the possibility of pulmonary fibrosis emerging as a long-term consequence of SARS-CoV-2, similar to what was observed with SARS and MERS [73]. Post-COVID-19 pulmonary fibrosis (PCPF) is a highly significant long-term complication that has been identified. It is characterized by a significant decrease in pulmonary function, which can be measured using various indicators such as a reduced diffusing capacity for carbon monoxide (DLCO) [74]. A total of 114 patients with SARS-CoV-2 infection were included in a 6-month prospective cohort study. These patients underwent CT scanning to assess their pulmonary function. The results revealed that approximately one-third of the patients had fibrosis-like changes in their CT images. Additionally, 26% of the patients showed a decrease in DLCO, with a higher prevalence observed in those who exhibited abnormal changes in their CT images [75]. Lack of newest long-term clinical evidence that SARS-CoV-2 infection induces chronic pulmonary fibrosis, however, in a prospective cohort study done on 71 patients and lasting for 15 years, it was reported that pulmonary function of SARS-CoV infection patients with interstitial changes improved less than that without this lesions, which may provide suggestions for the long-term pulmonary pathological change after SARS-CoV-2 infection [76].

Chronic inflammation: Inflammation has been found to have a causal relationship with the development of cancer, with processes involving genotoxicity, abnormal tissue repair, proliferative responses, invasion, and metastasis [77]. Infections of the lung, such as Mycobacterium tuberculosis and Chlamydia pneumoniae, can alter cytokine levels, promote angiogenesis and cell proliferation, and thus contribute to the occurrence and progression of lung cancer [78]. Additionally, inflammation can infiltrate the microenvironment of tumor cells. In non-small cell lung cancer patients, the immunity of the tumor microenvironment is related to different types of immune cell infiltration [79]. Moreover, increased vitamin B6 catabolism associated with inflammation and immune activation is linked to a high risk of lung cancer [80]. Evidence demonstrates that

chronic inflammation leads to lung cancer: Chronic inflammation is one of the risk factors for lung cancer and can participate in the whole process of tumorigenesis and development, and studies have shown that macrophages can create the necessary microenvironment for tumor growth [81, 82].

Chronic inflammation is also involved in the long-term complications of SARS-CoV-2. Inflammation storm is severe in patients infected with SARS-CoV-2, especially in patients with cancer: Blood hypersensitivity C-reactive protein, erythrocyte sedimentation rate, IL-2 receptor, and IL-6 were elevated in cancer patients with SARS-CoV-2 infection [83]. IFN-β and IFN-λ 1 were found to be continuously increased in patients with long COVID-19 and continued to remain at high levels for 8 months [84]. In comprehensive research which compared features of patients with long COVID with uninfected individuals and patients under convalescence, patients with long COVID have an increase in nonclassical monocytes, activated B cells, double-negative B cells, depleted T cells, and $CD4^+$ T cells-secreting IL-4/IL-6 cells, as well as regular DC1 and central memory $CD4^+$ T cells [85].

Lung cancer: As for lung cancer, although long-term clinical evidence is lacking for the reason that less than five years have passed since the pandemic began, researchers have always been concerned about the changes in the condition of patients with cancer and other chronic diseases. For example, in a research carried out in UK, researchers used multivariate Poisson regressions to compare 2019 and 2020 counts and calculate incidence rate ratios of NSCLC and the figure was 0.91 (95% CI: 0.90-0.92, $P < 0.001$) for the potential reason that delayed access to lung cancer screening [86], while emergency presentation diagnosis of NSCLC was found to increase by 9.5% (Q2-2020) and 16.3% (Q3-2020)-later stage diagnosis [87]. Later, the Canada Academy Center found that in the second year of the pandemic, the diagnosis rate saw an obvious increase from the figure during the first year of the pandemic, by 75% [88]. A South Korean scientific study also showed that the proportion of patients with advanced-stage NSCLC added during the pandemic [89].

Potential molecular mechanism of ACE2 in lung cancer induced by SARS-CoV-2 infection

When infected with SARS-CoV-2, lung cancer tissues were validated to be at an immune-tolerant state because of the high level of $CD8^+$ cytotoxic T cells and NK cells in high-ACE2 expression, which indicates that potential comorbidity risk between SARS-CoV-2 infection and NSCLC [56]. After the outbreak of the pandemic, acute respiratory distress syndrome (ARDS), as one of the most crucial complications of SARS-CoV-2, has been studied by many researchers on its mechanism. When the SARS-CoV-2 binds to ACE2 to infect the host cells, expression of ACE2 of host cells is downregulated, which increases Ang II level in the blood and induces lung injury [90]. In addition, a higher level of Ang II activates inflammatory mediators and leads to RAS dysfunction, which may be one of the mechanisms that SARS-CoV-2 functions in severe cases [91]. In previous research, through making analogies with other types of coronavirus, like SARS-CoV, and MERS-CoV, researchers had proposed assumptions that many risk factors and pathophysiological processes of COVID-19 can induce the occurrence, invasion and metastasis of lung cancer, they believe chronic airway inflammation, pulmonary fibrosis, immune suppression or certain molecular mechanism like the up-expression of HIF-1 [92].

As for the role that ACE2 plays in the happening or prognosis of lung cancer, the interaction between HIF-1α and ACE2 and Ang-(1-7) and ACE2 may explain the relationship between SARS-CoV-2 and lung cancer. The presence of low oxygen levels, known as hypoxia, triggers the activation of a protein called HIF-1α. HIF-1α is known to have a suppressive impact on ACE2. In a model of hypoxic pulmonary hypertension, it has been demonstrated that HIF-1α directly hampers the activity of a specific microRNA called let-7b, which is encoded by ACE2 [93]. Both hypoxia and the HIF prolyl hydroxylase inhibitor Roxadustat can decrease the level of ACE2 in lung epithelial cells. This, in turn, hinders the entry and reproduction of new coronaviruses by utilizing the HIF-1α-dependent pathway [94]. In human pulmonary artery smooth muscle cells, an accumulation of HIF-1 in the later stages leads to a decrease in ACE2 levels to near baseline levels [95]. Up-expre-

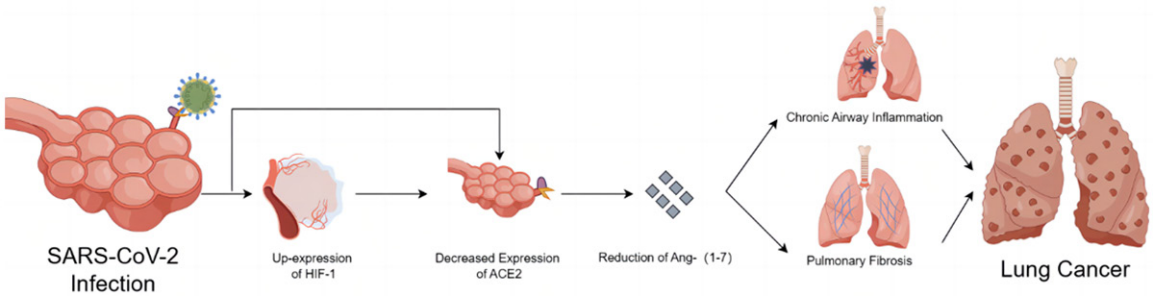

Figure 4. Potential mechanisms of lung cancer induced by ACE2 as a key node after SARS-CoV-2 infection (By FigDraw).

ssion of HIF-1 leads to a low level of ACE2 and a subsequent reduction of Ang-(1-7). Early in 2004, under the vitro condition, human adenocarcinoma cells were treated with serum containing Ang-(1-7) and serum lacking Ang-(1-7), and tumour cells in the former group were inhibited from growing which indicated that Ang-(1-7) may provide new ideas for the treatment of lung cancer. In this experiment, researchers also found Ang-(1-7) blocks the growth of lung cancer cells through inhibition of the (ERK)1 signal transduction pathway and was mediated by MAS receptor [96]. Later, the same laboratory further researched Ang-(1-7) functioning as an inhibitor in the growth of lung cancer cells. Animal experiment was conducted to build human lung tumor xenograft models which were treated by Ang-(1-7) and saline respectively. They found that using Ang-(1-7) to treat lung tumor reduce the size of the tumor by 30% [97].

In further research, Ang-(1-7) was found to produce the antagonism of vessel formation and endothelial formation in the chick and it can reduce vascular endothelial growth factor-A protein and mRNA in lung tumors in mouse models, which reminders that Ang-(1-7) can work during the process of inhibiting tumor's development [98]. At the genetic level, research has demonstrated that the LncRNA MIR-99AHG can compete with miR-136-5p for the degradation of USP4. As a result, the expression of ACE2 remains unaltered. This has the effect of reducing fibrosis in alveolar epithelial cells, preventing epithelial-mesenchymal transition, and inhibiting the advancement of pulmonary fibrosis to LUAD [99] (**Figure 4**).

Treatment targeted ACE2

Given the importance of ACE2 in lung cancer and novel coronaviruses, drugs and therapies targeting ACE2 have been developed. Since enhancement of ACE activity and reduction of ACE2 activity lead to lung injury, and the use of Ang II blockers has potential side effects including hypotension, ACE2 is seen as a more suitable target [100]. Potential treatments related to ACE2 are currently focused on immunotherapies targeting the binding of ACE2 and S proteins, and on altering ACE2 expression levels.

Chloroquine and hydroxychloroquine are able to interfere with the glycosylation of the ACE-2 receptor, thereby preventing novel coronavirus receptor binding and subsequent infection [101]. Antibody B38 and antibody H4 were able to block the binding between the viral S-protein RBD and the cellular receptor ACE2, whereas they became potential virus-targeting monoclonal antibodies and it was demonstrated in a mouse model that these antibodies reduced the viral gradient in infected lungs [102]. NACE2i, a peptide inhibitor of ACE2, was able to inhibit viral replication two days after viral infection prevent inflammatory infiltration and limit macrophage invasion [103].

rhACE2, a recombinant human ACE2, was able to reduce Ang II levels while Ang-(1-7) and Ang-(1-5) levels were elevated, alleviating lung injury. Khan et al [104] examined the safety and efficacy of GSK2586881, a recombinant human ACE2 (rhACE2), which was well tolerated by metronomic increments in patients without significant haemodynamic changes. ACE2-1-618-dDC-ABD, a soluble ACE2 protein, was able to attenuate severe lung injury and renal tubular injury seen in a mouse model of neocoronavirus infection [105]. In addition, the ACE2-like enzyme, B38-CAP, was protective against novel coronavirus-induced lung injury: in animal experiments, B38-CAP significantly ameliorated pulmonary oedema and lung inju-

ry; however, it was unable to neutralise the cellular entry of SARS-CoV-2 [106].

Conclusion

This review provides a brief overview of the basic research on ACE2 and its involvement in the association between lung cancer and SARS-CoV-2 infection. It suggests that individuals with lung cancer may be more susceptible to COVID-19 and are more likely to develop severe disease. Additionally, individuals who have infected with the novel coronavirus may be at increased risk of developing ARDS, lung fibrosis, chronic pneumonia and possibly lung cancer. However, more research and longer follow-up periods are needed to improve our understanding in this area. Lung cancer is the second most commonly occurring cancer globally, after breast cancer. It is the most common cause of death in male cancer patients and the second most common cause of death in female cancer patients [107]. According to the World Health Organization (WHO), approximately 2.21 million individuals succumbed to lung cancer in 2020. The COVID-19 pandemic has led to difficulties in the diagnosis and the treatment of lung cancer. Additionally, treatment of lung cancer patients has been delayed due to the immunosuppressive effects of radiotherapy and chemotherapy, which may make patients more vulnerable to infection with the new coronavirus [108]. The exact number of lung cancer patients who have died specifically from COVID-19 remains uncertain. It is known that lung cancer patients are more susceptible to contracting SARS-CoV-2 due to the upregulation of ACE2 receptors. However, little clinical research has been done on the different stages of lung cancer. Additionally, the exact impact of COVID-19 on lung cancer is still unknown due to the lack of reliable clinical evidence. As mentioned above, SARS-CoV-2 can significantly impair lung function and lead to the development of pulmonary fibrosis. This condition has been identified as a long-term consequence of the virus and has been recognized as a risk factor for lung cancer in recent research. It is exciting to note that the establishment of the International COVID-19 Collaboration on Thoracic Cancer (TERAVOLT) took place at the beginning of the epidemic in March 2020. Its main objective is to study in detail the prognosis of people who have successfully recovered from the new coronavirus infection. In addition, TERAVOLT aims to analyse the epidemiological and clinical features associated with this particular virus [109]. In any case, further basic and clinical studies are urgently needed to determine the interaction between COVID and lung cancer and the role of ACE2 in this.

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Disclosure of conflict of interest

None.

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