INTRODUCTION

In December 2019, an outbreak of acute respiratory disease characterized by a series of clinical manifestations including fever, dry cough, short of breath, and pneumonia occurred in China.1 A new coronavirus belonging to β coronavirus was identified2 and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), meanwhile the disease was termed as coronavirus disease 19 (COVID-19). As of March 31, 2020, WHO announced 750,890 confirmed cases, including 36,405 deaths, in 203 countries/areas/territories.3 These figures are expected to increase further as they are updated daily. The pathogen of this unprecedented pandemic has several characteristics in common with SARS-CoV which caused about 8000 confirmed cases and more than 700 deaths in 29 countries during 2002-2003, with lethality reaching as high as 10%.4,5

1 | INTRODUCTION

In December 2019, an outbreak of acute respiratory disease characterized by a series of clinical manifestations including fever, dry cough, short of breath, and pneumonia occurred in China.1 A new coronavirus belonging to β coronavirus was identified2 and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), meanwhile the disease was termed as coronavirus disease 19 (COVID-19). As of March 31, 2020, WHO announced 750,890 confirmed cases, including 36,405 deaths, in 203 countries/areas/territories.3 These figures are expected to increase further as they are updated daily. The pathogen of this unprecedented pandemic has several characteristics in common with SARS-CoV which caused about 8000 confirmed cases and more than 700 deaths in 29 countries during 2002-2003, with lethality reaching as high as 10%.

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, ACE inhibitor; ACE2, angiotensin-converting enzyme 2; AEC II, alveolar epithelial type II cells; ARB, AT1R blocker; ARDS, acute respiratory distress syndrome; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; COVID-19, coronavirus disease 19; HIV, human immunodeficiency virus; RAS, renin-angiotensin system; RBD, receptor binding domain; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome coronavirus; TMPRSS2, transmembrane protease serine 2.
Genomic analysis showed that SARS-CoV-2 is 79.6% identical to the SARS-CoV,1,6 the etiological agent of SARS. Angiotensin-converting enzyme 2 (ACE2), as their common receptor, reemerges as a hotspot owing to its indispensable role in facilitating cellular entry of SARS-CoV-2 and SARS-CoV. Since its discovery in 2000, ACE2 is found protective in multiple pathophysiological processes, including alleviating pathological changes in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS),7-9 participating in inflammatory and fibrotic responses in diseases,10 assisting absorption of neutral amino acids in intestine as partner of amino acid transporters.11,12 In short, ACE2 is like a double-edged sword, which not only acts as receptor and opens door for coronavirus, but also protects body from severe pathological changes. In this review, we will look at the demerits and merits of ACE2, expecting comprehensive understanding of ACE2 providing informative clues for management of COVID-19 and related researches.

2 | ACE2: FUNCTIONS AND TISSUE DISTRIBUTION

2.1 | A peptidase in RAS and partner for amino acid transporter

The 40 kb ACE2 gene contains 18 exons and is mapped to the Xp22 chromosome. As a type I transmembrane glycoprotein of 805 amino acids, ACE2 weighs approximately 120 kDa and contains a single extracellular catalytic domain whose sequence is 41.8% identical with the domain of angiotensin-converting enzyme (ACE).7,13 Despite their homology and conservation of many key active residues, ACE2 and ACE show different preference for substrates. The former removes single amino acids as a carboxypeptidase, while ACE hydrolyzes dipeptides from the C-terminus of a peptide. ACE2 and ACE are two essential components of renin-angiotensin system (RAS), which maintains cardiovascular homeostasis, regulates blood pressure, fluid, and electrolyte balance, as well as the function of organs. After being produced in liver, angiotensinogen is cleaved by rennin to decapeptide angiotensin (Ang) I, which is then converted into octapeptide Ang II by ACE. Ang II is central to RAS activities by acting on angiotensin type 1 receptor (AT1R), thus induces contraction of bronchial smooth muscle, proliferation of pulmonary fibroblasts, apoptosis of alveolar epithelial cells, pulmonary vascular permeability, and ALI/ARDS.7 Meanwhile, ACE2 acts as a counter-regulator to the activities of ACE/Ang II/AT1R by hydrolyzing Ang II to Ang (1-7), which acts via the Mas receptor to promote vasodilation, hypotension and apoptosis. A similar protective role is also performed by Ang II binding with its angiotensin type 2 receptor (AT2R). Besides, ACE2 also cleaves Ang I into Ang (1-9), which can be converted to Ang (1-7) by ACE (Figure 1). Incidentally, ACE2 also participates in absorption of neutral amino acids in intestine as a partner for amino acid transporter B0AT1.7

2.2 | Tissue distribution

ACE2 is expressed in type I and type II alveolar epithelial cells, vascular endothelial cells, smooth muscle cells, enterocytes in small intestines, renal tubular epithelium, etc.14,15 Although coronavirus may invade human body in a variety of ways, causing severe pneumonia through invasion of respiratory tract is still the main pattern of its pathogenesis. Using single-cell sequencing technology, researchers demonstrated that 83% of ACE2-expressing cells
in normal lung tissues are alveolar epithelial type II cells (AEC II).\textsuperscript{3,16} Additionally, these AEC II cells with presence of ACE2 also process high levels of multiple genes closely related to viral assembly, viral life cycle, viral genome replication, and regulation for viral processes, suggesting that these cells not only act as viral reservoir for entry, but also facilitate coronaviral replication in the lung. Physiologically, the expression of ACE2 in the lung is both age, gender, and race-related. Asians and men express more ACE2 than other races and women, respectively, and their expression level are negatively correlated with age.\textsuperscript{16}

\section{ACE2 FACILITATES CELLULAR ENTRY OF SARS-COV AND SARS-COV-2 AS RECEPTOR}

\subsection{Identification of ACE2-led viral entry}

Phylogenetic analysis of the complete viral genome (29 903 nucleotides) of SARS-CoV-2 revealed that the virus shared 79.6\% sequence identity to SARS-CoV.\textsuperscript{1,17} Using the receptor binding domain (RBD) of SARS-CoV as a template, three-dimensional structure of SARS-CoV-2 RBD was modeled. Like SARS-CoV, the RBD of SARS-CoV-2 is composed of a core and an external subdomain.\textsuperscript{2} This similarity implicated that they may have common in mechanism for cellular entry. Several studies successively demonstrated in vitro that SARS-CoV-2 employs the SARS-CoV receptor ACE2 for host cell entry instead of aminopeptidase N and dipeptidyl peptidase 4 in different cell lines, while cells lacked ACE2 were resistant to the entry of SARS-CoV-2.\textsuperscript{5,17-19} Whether this finding applies in vivo needs further research in the future.

Similarly, ACE2 was identified as a functional receptor for SARS-CoV in vitro by co-immunoprecipitation in 2003.\textsuperscript{20} The virus showed efficient replication in cells present with ACE2, which had a high-affinity association with the S1 domain of SARS-CoV Spike protein. It is worth noting that cellular entry of SARS-CoV does not require nor affect the peptidase activity of ACE2.\textsuperscript{21} Cells expressing inactive ACE2 mutants without catalytic activity were still permissive for SARS-CoV, and substrates were accessible to the catalytic pocket of ACE2 and being hydrolyzed with SARS-CoV spike protein binding with ACE2. Consistent with these biological results, structure analysis of spike protein complexed with host cell receptor demonstrated that spike protein binded the tip of subdomain 1 of the ACE2 catalytic domain without contacting subdomain 2 nor occluding peptidase active site.\textsuperscript{21} In 2005, the first genetic proof was provided by Kuba\textsuperscript{4,13} proving that ACE2 functions as crucial receptor required for sufficient replication of infectious SARS-CoV in vivo. In ACE2 knockout mice, the quantity of infectious SARS-CoV and copy numbers of its spike RNA were greatly decreased compared to wild-type mice. Consistently, pathologic alterations in lungs were also remarkably reduced in ACE2 mutant mice.

It is understandable that ACE2 is a common receptor for SARS-CoV-2 and SARS-CoV given their homology and similar topological structure. However, NL63 coronavirus, a prevalent human respiratory virus who shares no structural homology in RBD cores or receptor-binding motifs with SARS-CoV, also utilizes ACE2 as entry receptor.\textsuperscript{22,23} Structure analysis of NL63-CoV-receptor interface showed that both NL63-CoV and SARS-CoV binded to the same regions, a virus-binding hotspot including three virus-binding motifs on the outer surface of ACE2.\textsuperscript{24} Considering the similarity between SARS-CoV and SARS-CoV-2, it is plausible that the latter also binds to the common hotspot of ACE2. Further structural studies of SARS-CoV-2-ACE2 interface are expected to elucidate the receptor-recognition mechanisms of this new coronavirus.

\subsection{Evolutionary conservation of ACE2 and interspecies transmission}

COVID-19 outbreak is the third documented epidemic resulted from coronavirus infection in only two decades.\textsuperscript{6} SARS-CoV-2-driven possible interspecies transmission is determined by the inherent characteristics of its receptor ACE2, which is widely expressed in animals with highly conserved primary structure.\textsuperscript{25} Comparison of human ACE2 with that of fish, frog, snake, bat, civet, and bird revealed amino acid sequence identity of 59\%, 60\%, 61\%, 81\%, 83\%, and 83\%, respectively,\textsuperscript{26} opening up the possibility of ACE2 being used for cross-species transmission. This is further supported by the recent findings that SARS-CoV-2 shared 96.2\% sequence identity at the whole-genome level with RaTG13,\textsuperscript{17} a bat coronavirus which was previously discovered in Rhinolophus affinis from Yunnan, China. The close phylogenetic relationship between these two viruses suggested that bats may be the natural reservoirs of SARS-CoV-2. However, RaTG13 cannot be considered as a direct progenitor of SARS-CoV-2, since they are just similar rather than exactly the same. The possible phylogenetic disparity and uncertainty of RaTG13 spike proteins to use human cellular receptor ACE2 need further elucidation. Additionally, SARS-CoV-2 was also able to utilize ACE2 proteins from Chinese horseshoe bats, civets, pigs, except mice, as an entry receptor to enter ACE2-expressing HeLa cells,\textsuperscript{18,27} implicating these animal species are also at risk of infection. However, whether these animals are part of transmission chains or intermediate hosts is ambiguous, whether people closely contacting them need protection awaits to be further evaluated.
As for SARS-CoV, it is quite clear that bat is its natural reservoir. In 2013, two novel bat coronaviruses (RsSHC014 and Rs3367), which were far more closely related to SARS-CoV than any other coronaviruses found before, were identified from Chinese horseshoe bats in Yunnan, China. A live SARS-like coronavirus (SL-CoV) processing typical coronavirus morphology and 99.9% sequence identity to Rs3367 was isolated from bat fecal samples. It was then proved to use ACE2 from humans, civets, and Chinese horseshoe bats for cell entry. These results revealed that intermediate hosts may not be essential to direct human infection by some SL-CoVs from bat. Anyway, expanding knowledge of natural host distribution and transmission routes of SARS-CoV-2 will facilitate its prevention and control as a strategy for pandemic preparedness.

### 3.3 Affinity of ACE2 with SARS-CoV and SARS-CoV-2

Surface plasmon resonance was employed to quantify the kinetics of SARS-CoV-2-ACE2 interaction. Importantly, they bound together with about 15 nM affinity, which was approximately 10- to 20-fold higher than SARS-CoV binding to ACE2. Consist with biophysical findings above, structural evidence was also provided by negative-stain EM. This high affinity of virus with human receptor may be a reasonable explanation for its notable contagiousness, given that COVID-19 has spread to 203 countries/areas/territories worldwide in just 4 months, leading to 750,890 confirmed cases. Further studies are required to investigate this hypothesis. Although ternary structure for RBD of SARS-CoV-2 and SARS-CoV are highly similar, SARS-CoV-2 owns a noted variation in a loop with flexible glycyl residues replacing rigid prolyl residues in SARS-CoV. A unique phenylalanine F486 in the flexible loop penetrating into a deep hydrophobic pocket in ACE2 might play a major role in enhanced affinity of SARS-CoV-2 with ACE2 by providing additional binding force. Additionally, several key residues in the SARS-CoV-2 RBD that are responsible for coronavirus-receptor binding were variable in SARS-CoV RBD (including Asn439, Asn501, Gln493, Gly485, and Phe486). Additional studies will be needed to clarify whether and how sequence variations and conformational deviations in key regions affect the affinity of SARS-CoV-2 and human ACE2.

### 3.4 Overlap of ACE2 distribution and clinical manifestations

There is a considerable overlap of ACE2 distribution with tissue tropisms of SARS-CoV-2 and symptomatic manifestations of COVID-19. We reasonably speculate that many important organs such as lung, kidney, and intestine are both reservoirs and targets of SARS-CoV-2 owing to their abundant expression of ACE2 receptor. As the most prominently targeted organ, lung showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. It also displayed desquamation of pneumocytes, pulmonary edema with hyaline membrane formation, indicating ARDS. These pathological changes were clinically featured by severe shortness of breath and hypoxemia with radiologically characterized by progressive pneumonia. Although the clinical manifestations of COVID-19 are dominated by respiratory symptoms, some patients showed other abnormalities indicating the rest organs being involved. For example, in a clinical study involving 41 confirmed COVID-19 patients, 12% of them developed acute fulminant myocarditis during treatment. Clinical manifestations included worsening cardiovascular contractility or cessation, hypotension, hemodynamic instability, progressive multiple organ failure, or even death. Some patients presented with cardiovascular system symptoms such as palpitation and chest distress, rather than fever, cough, and other respiratory symptoms, as their first complaints. So far, the pathophysiological mechanism underlying myocardial injury caused by COVID-19 remains elusive. Although researchers speculated that inflammatory storm caused by viral infection contributed to myocardial injury, the possibility of heart being directly attacked by SARS-CoV-2 due to its abundant expression of ACE2 cannot be excluded. Differing degrees of liver function abnormality were also found in 43 patients of 99 cases of COVID-19, characterized by increased aspartate aminotransferase or alanine aminotransferase. This damage was partly explained by the fact that chorangiocytes, instead of hepatocytes, expressed ACE2 which made chorangiocytes and even bile ducts direct target of SARS-CoV-2. A recent study found that 23 of 85 (27.06%) patients presented with acute renal failure, among which autopsies from six patients revealed severe acute tubular necrosis. Immunohistochemistry located the nucleocapsid protein antigen in renal tubules, this is consistent with the distribution of ACE2 in the proximal tubular brush border, indicating that SARS-CoV-2 directly infected human renal tubules and led to acute renal tubule damage. Although gastrointestinal discomforts were not as common as respiratory symptoms, they can also appear as initial symptoms. In view of the distribution of ACE2 in luminal surface of intestinal epithelial cells, SARS-CoV-2 may spread human to human through fecal-oral pathway.

The pathological features of SARS greatly resemble those seen in COVID-19. Patients with SARS often presented with acute diffuse alveolar damage in the early phase and combined acute fibrinous and organizing pneumonia in later phases. SARS-CoV virions, nucleocapsid inclusions, and localization of SARS-CoV RNA in pneumocytes together...
suggested that pneumocytes were directly attacked. Enteric involvement in SARS was also confirmed by diarrhea and presence of active viral replication within intestine, although minimal architectural disruption was observed. Moreover, systemic vasculitis and inflammation of various organs such as heart, kidney, and liver were also confirmed by autopsies. It is widely accepted that ACE2-expressed tissues being directly attacked by SARS-CoV and dysregulated inflammation accounted for the systemic pathological changes in patients with SARS. Given the phylogenetic and pathogenesis similarity shared by SARS-CoV and SARS-CoV-2, we infer similar pattern also presents in COVID-19, but this awaits to be studied.

One shall noticed in particular that even though ACE2 is expressed in these aforementioned organs, it remains to be seen whether SARS-CoV-2 can replicate abundantly after its cellular entry through ACE2, and then, release themselves out of host cells causing damage and further spread, just like it does in the lungs. Besides, relevant articles published earlier showed high and inconsistent incidences of complications, such as 17%33 or 29%31 of ARDS, or 15.6% of ARDS in severe and 1.1% in non-severe patients, 12% of explosive myocarditis, 31 27.06%35 or 3%33 of acute renal injury, or 2.9% of acute renal injury in severe and 0.1% in non-severe patients. The proportion of patients who eventually died due to deterioration in every study also varied. This is inconsistent with the epidemiological data we observed in other areas outside Wuhan, partly because the studies had small sample or mostly concentrated in Wuhan, which introduced bias in complication incidence. Therefore, a multicentered epidemiological investigation with large sample is needed to acquire accurate incidence of complications in patients with COVID-19.

3.5 | Expression level of ACE2 and possible susceptible population

In addition to the decisive role of ACE2 distribution in tissue tropism, its overall expression level in vivo also aroused concern owing to its tendency to pick susceptible population. For instance, adipose tissue was found to express higher level of ACE2 than lung. Although ACE2 expression in single adipocyte and adipose progenitor cell were similar between obese and nonobese individuals, the former was more susceptible to SARS-CoV-2 resulting from richer adipose and thus increased ACE2-expression cells. Specific kinds of tumor tissues also express higher ACE2 than adjacent tissues. Among them, the level of ACE2 in cervical cancer tissues was equivalent to lung tissues, while pancreatic cancer tissues expressed significantly more ACE2 than lung tissues. It follows that the possibility of SARS-CoV-2 infection in these cancer patients might be increased.

Physiologically, the expression of ACE2 is negatively correlated with age, and men show higher expression than women of comparable age. Severe SARS were concentrated in young and middle-aged people, however, severe COVID-19 were more often seen in elderly and male cases. Symptom severity was generally milder in women, and tended to be most serious in older men with underlying diseases, partly due to less expression of ACE2 in women. The above results suggest that personal protection should be strengthened for the highly vulnerable groups. As for the underlying pathogenesis, it is generally recognized that inflammation storm caused by SARS infection in young and middle-aged people with active immunity leads to worsening conditions, while we presume the different situation in COVID-19 results from not only inflammation responses to infection, but also receptor-positive cells being extensively attacked, which made the susceptible population unbearable to the widespread injury. Human body is an orchestrated and delicate system; ACE2 expression itself does not solely determine the course of COVID-19. Body immune response, viral load, possibly unidentified receptor, or protease mechanisms may jointly affect disease progression and prognosis.

4 | ACE2 PROTECTS BODY IN MULTIPLE PATHOLOGICAL SCENARIOS INCLUDING SARS

4.1 | Peptidase-dependent protection of ACE2 in the lung

ACE2 plays a beneficial role in numerous pathological conditions. Researchers found that SARS-CoV-infected mice in vivo or recombinant SARS-CoV spike protein-treated cell lines showed remarkably reduced ACE2 expression, significantly increased Ang II levels and serious lung pathologies. Block of AT1R, the crucial receptor mediating Ang II-induced severe ALI, with a specific inhibitor attenuated vascular permeability, pulmonary edema, and eventually acute severe lung injury. The absence of protective role of ACE2 leads to dysfunctional RAS and thus acute lung pathologies. Intriguingly, the key positive role of ACE2 in acute ALI is not only seen in SARS. In mice with severe ALI induced by acid aspiration or sepsis, loss of ACE2 resulted in massive lung edema, worsened oxygenation, increased hyaline membrane formations, and inflammatory cell infiltration. Recombinant human ACE2 (rhuACE2) protein with catalytic activity rescued the severe lung phenotype in ACE2 knockout mice, demonstrating that ACE2 can directly protect lungs from ALI. This protection was achieved by inactivating Ang II thus negatively regulating the RAS. ACE2 is also protective in ALI/ARDS caused by other predisposing factors, for
instance, infection of avian influenza H5N1 and H7N9. Plasma levels of Ang II were markedly elevated in both H7N9 and H5N1 infected patients and associated with disease progression, severity, and lethality. Both H7N9 and H5N1 infection led to unbalanced RAS characterized by descended ACE2 and subsequent elevated Ang II, which resulted in an off-balance seesaw of ACE/Ang II/AT1R axis and ACE2/Ang (1-7)/Mas axis. ACE2 deficiency in mouse further exacerbated H7N9 and H5N1-induced lung injury, indicating that ACE2 did protect mouse from severe lung injury. Targeting RAS disequilibrium as an option for intervention yielded promising results. Both AT1R blocker (ARB) and exogenous supplementation of rhuACE2 significantly ameliorated ALI, improved lung function and survival rate of mice. Last but not least, in an ALI model of rat, aged subjects showed significantly decreased ratio of ACE2/ACE in their bronchoalveolar lavage fluid, which aggravated their ALI, suggesting that age-dependent changes in the pulmonary RAS were associated with severity of lung injury. Therefore, maintaining the balance between ACE2 and ACE is very important.

Studies listed above show that ALI/ARDS caused by different pathogenic factors shares a common molecular mechanism, namely RAS dysregulation caused by ACE2 downregulation, suggesting that this pathogenesis mechanism may also explain ALI/ARDS caused by SARS-CoV-2. This underlying pattern also provides a molecular explanation why SARS or other disease causes acute and often lethal respiratory failure and implies a rational therapeutic target for SARS and possibly COVID-19. Since a large proportion of patients with COVID-19 developed ARDS and, among them, part of patients rapidly deteriorated and died of multiple organ failure, this molecular mechanism may have great value in clinical application (Figure 2).

4.2 Peptidase-dependent and -independent benefits of ACE2 in extrapulmonary organs

Accumulating evidence indicates that ACE2 also has positive significance in extrapulmonary organs. ACE2 knockout mice showed severe cardiac dysfunction characterized by significant decrease in cardiac contractility caused by slight ventricular dilatation and thinner left ventricle wall. These changes progressed with age and were more pronounced in male mice. Concomitant deletion of ACE gene against the ACE2 knockout background completely reversed increased Ang II levels and the cardiac phenotype, suggesting that ACE2 and its balance with ACE can modulate heart function. ACE2 also may increase as a compensatory response to the ischemic insult, followed by elevated production of Ang (1-7), to confer cardioprotective effects by counterbalancing Ang II. This theory was given increased credence by the
observation of Zisman et al and Burrell et al in failing heart or myocardial infarction.7,46,47

Although studies focusing the role of ACE2 in renal diseases suggested that ACE2 seems to be involved in the renal pathological process, its specific role is still unclear and needs further study. Among these opinions, the potential for ACE2 being reno-protective is suggested by the finding that ACE2 mutant mice and ACE2 inhibitor-treated wild-type mice developed glomerulosclerosis and albuminuria,48 which could be prevented by ARB, indicating Ang II dependency. Disturbed balance of ACE2 and ACE caused subsequent rise of Ang II, which functioned in regulating renal inflammation and fibrosis, accounting for, at least partly, progressive renal damage.49

The peptidase-independent benefits of ACE2 in the intestine as a partner of amino acid transporter is verified in gut microbiota and malnutrition.11,12 It is essential for the expression of B0AT1, a transporter, and absorption of amino acids such as tryptophan in epithelium of the small intestine. Tryptophan regulated the secretion of antimicrobial peptides that affected the composition of the intestinal microbiota. This is why ACE2 knockout mice are highly susceptible to experimentally induced colitis. Without efficient absorption of tryptophan, aberrant secretion of antimicrobial peptides caused an altered microbiota which conferred susceptibility to inflammation of the large intestine. Altogether, we reasonably propose that the potential protective effect of ACE2 in important organs other than lung in severe COVID-19 cases should not be underestimated. Considering the high transmissibility of SARS-CoV-2 and a huge group of suffer, it is of great significance to clarify whether and how ACE2 acts as a fighter and protects human body from severe pathological changes.

5 | LESSONS LEARNED FROM ACE2: POTENTIAL THERAPEUTIC TARGETS OF COVID-19

COVID-19 and SARS pose great challenges to all mankind. Their high incidence, lack of specific anti-viral treatment, high lethality especially exacerbated by the collapse of national health system following a widespread outbreak, enormous economic and social impact, possibility of renewed outbreaks make it paramount to understand their pathogenesis and study possible treatments. At present, clinical management of COVID-19 is mainly symptomatic treatment. Despite the comprehensive employment of modern intensive care treatment, death toll and mortality published by WHO are still disconcertingly high. Vaccine will not be available shortly since its development is time-consuming and labor-intensive. Moreover, SARS-CoV-2 constantly mutates during every replication cycle as a typical RNA virus, this may make vaccines based on viral-encoded peptides futile. In addition to reduce coronavirus-induced direct cytopathic effects by applying drugs disrupting viral dissemination and replication, host-directed therapies which restrain host responses and restore dysregulated RAS can also be alternative options (Figure 3).

Identification of ACE2 as viral entry receptor raises multiple possibilities, such as selectively blocking the interaction site of SARS-CoV-2 with ACE2 through ACE2 antibody or peptide. Soluble ACE2 is an promising candidate which competitively binds with SARS-CoV-2 and reduces viral cellular entry as well as protects the lung and possible extrapulmonary organs from severe pathological changes through its peptidase-dependent function. This is supported by studies showing exogenous rhuACE2 protects SARS-CoV, acid-induced,8,9,20 H5N1,41 H7N9-infected42 mice from developing severe ARDS. Inhibition of transmembrane protease serine 2 (TMPRSS2) can stop the priming of viral spike protein and thus entry and spread of SARS-CoV-219. A possibly dysfunctional RAS can also become potential direction of clinical management. ACE inhibitor (ACEI), ARB, and other possibilities including AT2R or Mas receptor agonists may be beneficial by restoring the corresponding dysfunctional parts of RAS. ARB has gained increased credence by the findings that it apparently alleviated ALI induced by various factors, including SARS,4 acid,8 H7N9,42 and H5N1.43 Blocking AT1R by ARB is supposed to be better than ACEI, since Ang II can be synthesized by different enzymes such as chymase, cathepsin, and trypsin while AT1R is the most important way for Ang II to function. It will be profound if shelved ACEI and ARB are effective with the prerequisite of maintaining acceptable blood pressure, since these products are widely applied and known as safe drugs that are rarely implicated in severe adverse drug events. As for the concern of ACEI and ARB leading to increased ACE2 expression and maybe thus elevated virulence of SARS-CoV-2, the evidence is not fully consistent and differs per ARB and per organ.50 The quickest way to clarify the paradox of ACEI and ARB is to compare clinical data objectively without bias. For example, collecting information about whether patients who were prescribed with ACEI or ARB prior to their diagnosis suffer from severe or non-severe symptoms can help understand how disease severity is affected; comparing disease progression and prognosis of patients who continue taking these drugs after infection with those who share similar demographic characteristics but no ACEI or ARB-related medication. Drug classes, doses, and different time courses of drug continuation are all necessary exposure parameters to consider. If statistical differences are found between these groups, this may verify or overthrow the notion that ACEI and ARB confer protection from severe symptoms among patients with COVID-19 and optimize current therapies.

Even ACEI or ARB can increase the expression of ACE2, its risk of aggravated ACE2-facilitated infection is still questioned.
Research on human immunodeficiency virus (HIV) infection seems to suggest otherwise. Higher expression of HIV binding sites CCR5 and CD4 protected patients from, instead of increased, HIV virulence. HIV avoids superinfection during the entry process by decreasing CCR5 through early gene Nef product. This decrease facilitated efficient replication of HIV and thus AIDS pathogenesis through enhancing the endocytosis rate of both CCR5 and CD4. It remains elusive whether a comparable mechanism for avoiding superinfection also exists in the scenario of coronavirus such as SARS-CoV-2 and SARS-CoV. Supposing this mechanism does exist, the move of applying ACEI or ARB will not seem contradictory. In addition, developing age-, gender-, and race-tailored treatments are necessary when possible since ACE2 expression is most likely affected by these variables.

So far, the end of the COVID-19 pandemic is not within the foreseeable future. ACE2 acts as a double-sided spy who is not only a traitor that leaves our front door open for SARS-CoV-2 and SARS-CoV, but also a fighter who protects our body from severe damage caused by multiple morbigenous factors including SARS-CoV. Lessons learned from the SARS outbreaks provide, despite its inherent tragedy, informative clues for the fight with COVID-19 pandemic, such as epidemic surveillance and clinical management. Enriched knowledge of ACE2 is also expected to play more far-reaching significance as common pathophysiological mechanism shared in other scenarios, for instance, ALI and ARDS caused by other diseases.

FIGURE 3  Potential therapeutic targets in ACE2-mediated SARS-CoV-2 infection. SARS-CoV-2 utilizes ACE2 as cellular receptor for entry after its spike protein is primed by transmembrane protease serine 2 (TMPRSS2). It replicates abundantly, and then, releases replications out of host cells, causing damage and further spread. Potential approaches include soluble form of ACE2 which competitively binds with SARS-CoV-2 and reduces viral cellular entry as well as protects the lung and possible extrapulmonary organs from severe pathological changes through its peptidase-dependent function; SARS-CoV-2 spike protein-based vaccine; anti-ACE2 antibody or peptide to block the receptor interaction surface of ACE2; TMPRSS2 inhibitor to stop the priming of viral spike protein; anti-viral drug such as Remdesivir which blocks the replication of SARS-CoV-2; ACE inhibitor (ACEI), AT1 receptor blocker (ARB), agonists for AT2 receptor and Mas receptor which aim to restore dysfunctional RAS. Regulating RAS can be promising in the clinical management of COVID-19 by increasing its protective function of ACE2/Ang (1-7)/Mas receptor axis and decreasing injury caused by ACE/Ang II/AT1 receptor axis.
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