



New perspectives on angiotensin-converting enzyme 2 and its related diseases

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Abstract

Since the worldwide outbreak of coronavirus disease 2019, angiotensin-converting enzyme 2 (ACE2) has received widespread attention as the cell receptor of the severe acute respiratory syndrome coronavirus 2 virus. At the same time, as a key enzyme in the renin-angiotensin-system, ACE2 is considered to be an endogenous negative regulator of vasoconstriction, proliferation, fibrosis, and proinflammation caused by the ACE-angiotensin II-angiotensin type 1 receptor axis. ACE2 is now implicated as being closely connected to diabetes, cardiovascular, kidney, and lung diseases, and so on. This review covers the available information on the host factors regulating ACE2 and discusses its role in a variety of pathophysiological conditions in animal models and humans.

Key Words: Angiotensin-converting enzyme 2; COVID-19; Salt; Renin-angiotensin-system inhibitors; Diabetes and cardiovascular disease; Renal and lung disease

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Core Tip: Angiotensin-converting enzyme 2 (ACE2) as the key cell receptor for the severe acute respiratory syndrome coronavirus 2 virus has received widespread attention. This paper will review the new perspectives on ACE2, covers available information on the host regulative factors of ACE2, and discusses its role in a variety of pathophysiological conditions. This review will help us with a better understanding of the biological function and role of ACE2 in coronavirus disease 2019 and its

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INTRODUCTION

Angiotensin-converting enzyme 2 (ACE2), as the key enzyme in the renin angiotensin system (RAS) and key cell receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has received considerable attention[1] since coronavirus disease 2019 (COVID-19) has spread worldwide. Patients with diabetes and renal and cardiovascular diseases are widely treated with ACE inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs), which are deemed to potentially increase ACE2 expression in the body; the consequent increased expression of ACE2 could facilitate infection with SARS-CoV-2. The paradox of the use of ACEI/ARB treatment to interfere with the RAS because ACE2 reduces inflammation (which has been suggested as a therapy for inflammatory lung diseases, diabetes, and hypertension) and the probable contribution of ACE2 to an increased risk of COVID-19 have puzzled clinicians and attracted much attention[2,3]. Therefore, it is necessary to further understand the characteristics of ACE2 and accurate details of the molecular mechanisms of ACE2 that underlie these phenomena. This review will focus on the biological function of ACE2 and its host regulatory factors. Moreover, we will discuss the role of ACE2 in a variety of pathophysiological conditions, including cardiovascular, kidney, and lung diseases and diabetes in animal models and humans. We aim to provide new perspectives on ACE2 and help us better understand the role of ACE2 in SARS-CoV-2 infection and its treatment nowadays (Figure 1).

BIOCHEMICAL CHARACTERISTICS AND DISTRIBUTION OF ACE2

ACE2 is a type I membrane protein that includes an N-terminal peptidase domain (PD) and a C-terminal collectrin-like domain. The PD of ACE2 provides a direct binding site for the S protein of coronavirus[4]. ACE2 was discovered in 2000 when Tipnis *et al*[5] and Donoghue *et al*[6] cloned ACE2 from a human heart failure (HF) cDNA library and a human lymphoma cDNA library and found to be a homolog of the ACE gene. The gene is located in the Xp22 region and has a total length of approximately 39.98 kb, including 18 exons and 17 introns. ACE2 can be hydrolyzed by depolymerase into soluble ACE2, and therefore, ACE2 has two forms, the membrane-linked type and the soluble type. Membrane-linked ACE2 is an extracellular enzyme that is distributed on the cell membrane surface and consists of four parts: The N-terminal signal peptide region, the zinc binding motif (amino acid residues 374 to 378), the transmembrane region (amino acids 740 to 768), and the C-terminal intracellular domain. Dissolved ACE2 is distributed mainly in the plasma and urine due to the lack of a transmembrane region and a C-terminal intracellular domain[5]. ACE2 is widely expressed in many organs, including the heart, kidney, testis, adipose tissue, brain tissue, vascular smooth muscle cells, gastrointestinal tract, and lung (type 2 alveolar epithelial cells) and is highly specific in tissues[7].

FUNCTIONS OF ACE2

ACE2 is a key enzyme in the RAS and is considered to be an endogenous negative regulator of vasoconstriction, proliferation, fibrosis, and proinflammation caused by the ACE-angiotensin II (Ang II)-angiotensin type 1 receptor (AT1R) axis[8]. In the RAS, ACE cuts Ang I to convert it into Ang II, and then Ang II binds to the G protein-coupled receptor AT1R, which causes vasoconstriction and increased blood pressure [9]. The function of ACE2 is opposite to that of ACE. ACE2 cuts Ang II and converts it

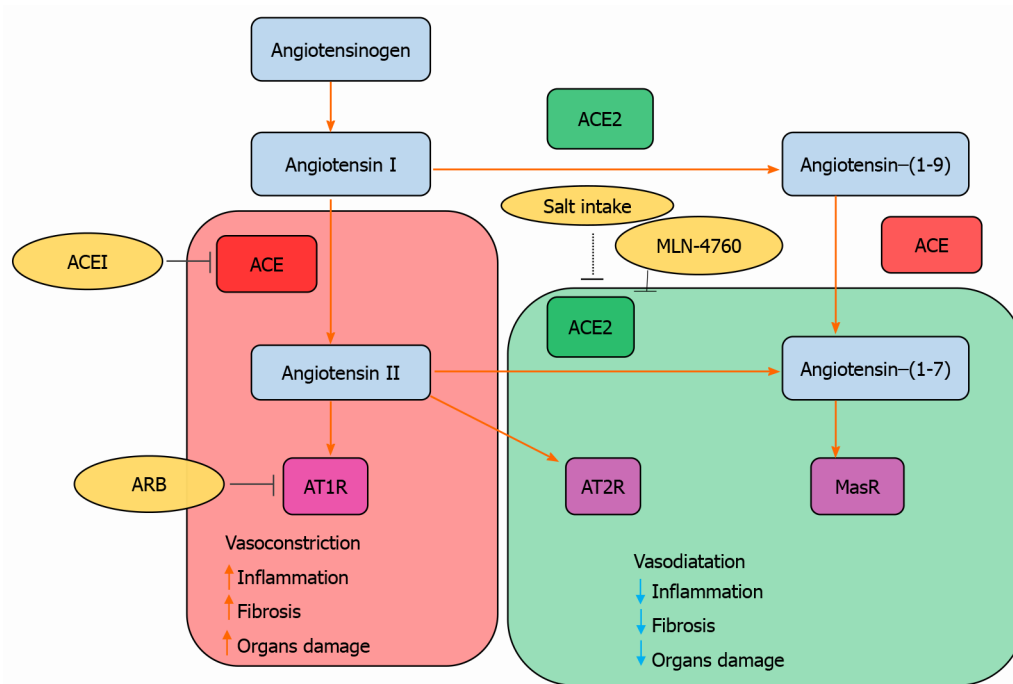


Figure 1 Composition and function of the renin-angiotensin system and its main regulators and inhibitors. RAS: Rennin angiotensin system; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; ACE: Angiotensin-converting enzyme; ACE2: Angiotensin-converting enzyme 2; AT1R: Angiotensin type 1 receptor; AT2R: Angiotensin type 2 receptor; MasR: Mas receptor; MLN-4760: A specific ACE2 inhibitor; Organ damage: Renal damage, lung damage, cardiovascular damage, etc.

into angiotensin 1-7 (Ang 1-7), which can lower blood pressure[10]. Increasing evidence demonstrates that ACE2 plays an important role in a variety of pathophysiological conditions. In the tumor microenvironment, ACE2 acts on Ang II to produce endogenous Ang 1-7. Ang 1-7 binds to the Mas receptor (MasR) and exerts antitumor effects such as antiproliferation, antiangiogenesis, anti-invasion, and antimetastasis effects through a series of signal transduction pathways. In diabetes, upregulation of ACE2 can improve hyperglycemia, and Ang 1-7 can improve metabolic syndrome through glucose intake and oxidative stress related to insulin resistance[11]. The expression of ACE2 is related to atherosclerosis[12]. The overexpression of ACE2 can improve endothelial-dependent vascular relaxation, increase the proliferative activity of endothelial cells, and facilitate the migration of endothelial cells. ACE2 exerts anti-infective properties through Ang 1-7[13]. The decrease in aortic ACE2 expression increases the expression of proinflammatory factors, such as tumor necrosis factor α , interleukin-6, monocyte chemotactic protein 1, vascular cell adhesion molecule 1, matrix metalloproteinase (MMP)-2 and MMP-9, which are conducive to the adhesion of leukocytes to endothelial cells and blood vessel walls. In addition, ACE2 can also regulate the adhesion of macrophages to endothelial cells[14]. The combination of Ang 1-7 and MasR can also inhibit the formation of thrombi[15] and liver fibrosis[16]. In ischemic stroke, Ang 1-7 can reduce the area of cerebral infarction and brain dysfunction by regulating the release of nitric oxide from different sources to protect the brain. In addition, Ang 1-7 in brain tissue can regulate learning and memory functions. In the reproductive system, Ang 1-7 can regulate endometrial function, spermatogenesis, follicular maturation, ovulation, and pregnancy-related processes[11]. ACE2 can also regulate the immunity of intestinal epithelial cells through amino acid homeostasis, expression of antimicrobial peptides, and regulation of the balance of intestinal microbes[17].

ACE2 AND SALT

It has been widely demonstrated that a high-sodium (HS) diet activates the RAS. Animal experiments have proven that salt intake is a powerful regulator of ACE2 expression in animal models[18]. Studies by Samuel *et al*[19] found that the relative expression patterns of ACE and AT1R increased, renin levels decreased, and ACE2, AT2R, and MasR remained unaltered in HS-fed lean Zucker rats. On the other hand,

HS intake caused an increase in the cortical expression of ACE and a decrease in ACE2, accompanied by increased blood pressure. Elevated blood pressure is associated with a significant increase in Ang II levels in the renal cortex in obese rats and a decrease in the expression of the ACE2-AT2R-MasR axis in obese Zucker rats. In a study of a left nephrectomy rat model[20], HS diet intake increased the glomerular ACE/ACE2 ratio, which was associated with decreased ACE2. In ACE2 KO mice, ACE2 deficiency significantly increased renal oxidative stress by reducing the production of Ang 1-7. In another study, the consumption of a HS diet in normotensive animals reduced ACE2 protein expression and raised renal oxidative stress[21]. Another study showed that the ACE/ACE2 protein ratio was increased in the kidneys of spontaneously hypertensive rats (SHRs) when fed diets with high levels of NaCl. At the same time, compared to the other SHR groups, there was an increase in kidney ACE2 protein and activity in the group fed a long-term low salt diet[18]. Similarly, Varagic *et al*[22] used an SHR model to prove that HS intake decreased cardiac ACE2 mRNA and protein expression. In Dahl salt-sensitive hypertensive rats, a HS diet reduced ACE2 mRNA expression and augmented the local RAS, which induced hypertension[23]. The HS diet also decreased ACE2 protein expression as assessed using immunohistochemistry compared to a normal-salt diet[24].

In summary, these findings show that a HS diet can reduce the expression of ACE2, thereby affecting the RAS. Further studies have reported that interventions that augment ACE2 expression or activity can be helpful to prevent cardiovascular damage [25]. Therefore, elucidating the precise mechanisms involved in the interaction of sodium intake and ACE2 will be conducive to predicting the physiological and pathological changes caused by a HS diet (Table 1).

ACE2 AND RAS INHIBITORS

Some studies in animal models have demonstrated that both ACEIs (lisinopril, enalapril, and ramipril) and ARBs (losartan, olmesartan, and telmisartan) can upregulate ACE2 expression. Ferrario *et al*[26] showed that ACE2 mRNA expression increased in the left ventricle of normotensive Lewis rats after 12 d of lisinopril or losartan treatment. Lisinopril increased ACE2 levels by 5-fold, while losartan increased ACE2 levels by 3-fold. A rat study from Ocaranza *et al*[27] showed that enalapril prevented the decrease in mRNA levels and activities of ACE2 in late ventricular dysfunction after myocardial infarction. The results of Ishiyama *et al*[28] indicated that the level of ACE2 mRNA increased after ARB treatment in rats with coronary artery ligation. A mouse study by Soler *et al*[29] showed that ACE2 is preferentially localized in the tunica media of kidney arterioles, and its expression is amplified after administration of telmisartan. On the other hand, some association studies have shown no increase in ACE2 mRNA after ACEI or ARB treatment. An animal study by Burrell *et al*[30] found that ramipril attenuated cardiac hypertrophy and inhibited cardiac ACE but had no effect on cardiac ACE2 mRNA in rats after coronary artery ligation. Subsequent studies by Burchill *et al*[31] provided evidence that there was no increase in ACE2 mRNA or protein expression in rats after coronary artery ligation and treatment with valsartan, ramipril, or both when compared to the control group. In general, these studies on experimental animals did not provide consistent evidence to prove the effect of ARB/ACEI administration on ACE2 protein expression. In the case of simulating human drug delivery, further experimental studies are needed.

With the pandemic of COVID-19 spreading since January 2020, it has been inferred that increased ACE2 expression in the lungs correlated with a higher risk of SARS-CoV-2 infection in patients with cardiac and renal diseases, hypertension, and diabetes treated with ACEIs or ARBs. However, a review from Sriram and Insel[32] showed that there was no clear evidence that elevated ACE2 expression when using ACEIs/ARBs could increase the risk of SARS-CoV-2 infection. In a study of 362 hospitalized hypertensive COVID-19 patients, there was no significant difference between severe and noncritical patients or between non-survivors and survivors according to the use of ACEIs and/or ARBs[33]. Conversely, in a recent meta-analysis from Chu *et al*[34], it was suggested that ACEI treatment reduced the risk of infection with SARS-CoV-2 and that blocking the RAS might decrease all-cause mortality in COVID-19 patients. This study also reported that ACEIs reduced the risk of non-COVID pneumonia and all-cause mortality caused by non-COVID pneumonia. The effect of ACEIs/ARBs on the expression of ACE2 and the effect on human infection with SARS-CoV-2 remain unknown and complex. Some research has supported the hypothesis

Table 1 List of animal studies on the high-sodium diet and angiotensin-converting enzyme 2

Animal	Study details	Main findings	Ref.
Zucker rats	Lean and obese Zucker rats were fed a normal-sodium diet (0.4%) or a high-sodium diet (8%) for 2 wk	ACE2 mRNA and protein expression was significantly reduced in HS-fed obese Zucker rats	Samuel <i>et al</i> [19]
Wistar rats	Rats were fed three salt concentrations (0.2%, 1.2%, 8.2%) for 4 wk after uninephrectomy of the left kidney	HS diet increased the glomerular ACE/ACE2 ratio	Bernardi <i>et al</i> [20]
Wistar rats	After 4 wk of induction of hypertension (2-kidney 1-clip model), rats were fed a normal-sodium diet (0.4%) or a high-sodium diet (8%) for 2 wk	HS diet decreased urinary angiotensinogen, ACE, and ACE2 expression in the clipped and unclipped kidneys	Shimoura <i>et al</i> [21]
SHR	Rats were fed three NaCl content diets (0.03%, 0.3%, 3%) for 6 mo	HS diet decreased ACE2 protein expression in kidney tissues	Berger <i>et al</i> [18]
SHR	Rats were fed an 8% salt diet for 5 wk	HS diet decreased cardiac ACE2 mRNA and protein levels	Varagic <i>et al</i> [22]
DS and DR rats	DS and DR rats were fed low-sodium chow (0.45%) or high-sodium chow (7%) for 8 wk and treated with or without eplerenone (100 mg/kg/d), candesartan (10 mg/kg/d), or both drugs for 8 wk	HS diet increased angiotensinogen mRNA and decreased ACE2 mRNA in the hearts of DS rats; candesartan increased ACE2 mRNA levels in the heart	Takeda <i>et al</i> [23]
SD rats	Rats were fed an 8% NaCl high-salt or 0.4% NaCl (normal-salt) diet for 3 wk, with or without antioxidant supplementation with tempol	HS diet decreased ACE2 expression; tempol reversed the imbalance of renal RAS components (decrease in Ang II and AT1R and increase in AT2, ACE2, Ang 1-7, and MasR staining intensity)	Cao <i>et al</i> [24]

SHR: Spontaneously hypertensive rats; DS rats: Dahl salt-sensitive hypertensive rats; DR rats: Dahl salt-resistant rats; SD rats: Sprague-Dawley rats; HS: High-sodium; ACE2: Angiotensin-converting enzyme 2; MasR: Mas receptor; AT1R: Angiotensin type 1 receptor; AT2: Angiotensin type 2; Ang 1-7: Angiotensin 1-7; RAS: Renin angiotensin system.

that ACE inhibition by ACEIs might stimulate negative feedback, upregulating ACE2 expression but decreasing overall inflammation in the absence of angiotensin II[35]. Thus, the effects of ACEIs/ARBs vary depending on the clinical stage: Negative in the initial infection phase but positive in the tissue inflammation stage[36,37]. Most researchers believe that the use of ARB or ACEI drugs should not be stopped for the purpose of reducing SARS-CoV-2 infection. Stopping maintenance treatment may cause blood pressure imbalance or HF. The guidelines should be revised quickly based on various clinical data, and personalized treatment should be carried out in accordance with clinical manifestations[38] (Table 2).

ACE2 AND DISEASES

The functional components of the RAS are in balance with each other to maintain the health of the body. Under certain pathological conditions, Ang II, AT1R, or ACE levels can increase or become unbalanced, which is detrimental. It has been two decades since the discovery of ACE2. During this period, efforts towards the characterization of this enzyme have provided greater insights into the RAS. The ongoing studies provoked more questions, particularly regarding the role of ACE2 in the development and progression of hypertension and renal injury, as well as other pathologies, including diabetes, HF, liver fibrosis, and lung injury (Tables 3 and 4).

ACE2 and its role in the kidney and diabetes

The kidney possesses a fully functional local RAS capable of producing Ang II, a major contributor to the progression of chronic kidney disease. ACE2 is highly expressed in the kidney and predominantly localized to proximal tubules and glomerular podocytes[39,40]. Several lines of evidence indicate that ACE2 serves as a key protective enzyme to prevent progressive renal damage by reducing oxidative stress, inflammation, and fibrosis[41-43].

The study of ACE2 in the context of diabetes has focused primarily on the kidney. ACE2 may be an important target for the treatment and prevention of diabetic nephropathy (DN). ACE2 expression in the kidney has been studied in both type 1 diabetes (T1D) and type 2 diabetes (T2D) models. The majority of animal studies indicate that ACE2 expression is downregulated in the glomeruli in diabetes, whereas tubular ACE2 expression is upregulated[41,44-46]. Tikellis *et al*[47] first reported that ACE2 expression was reduced in the kidneys of rats with longstanding diabetes

Table 2 List of animal studies on renin angiotensin system inhibitors and angiotensin-converting enzyme 2

Animal	Model	Study details	Main findings	Ref.
Lewis rats	Normotensive	Rats were assigned to drink water containing losartan or lisinopril at 10 mg/kg/d for 12 d	Lisinopril or losartan increased cardiac ACE2 mRNA, but the combination did not produce this effect	Ferrario <i>et al</i> [26]
SD rats	MI	Enalapril was given to rats after sham operation or LCA ligation	Enalapril prevented the decrease of ventricular ACE2 mRNA levels and activities post-MI	Ocaranza <i>et al</i> [27]
Lewis rats	MI	Losartan and olmesartan was administered for 28 d after coronary artery ligation	The level of ACE2 mRNA increased after treatment with losartan and olmesartan	Ishiyama <i>et al</i> [28]
C57BLKS/J mice	Normotensive	Mice were treated with telmisartan at 2 mg/kg/d for 2 wk	Telmisartan increased ACE2 expression in the tunica media of renal arterioles	Soler <i>et al</i> [29]
SD rats	MI	SD rats received ramipril at 1 mg/kg/d for 28 d after MI operation	Ramipril inhibited cardiac ACE but had no effect on cardiac ACE2 mRNA after MI	Burrell <i>et al</i> [30]
SD rats	MI	Ramipril (1 mg/kg/d) and valsartan (10 mg/kg/d) were given for 28 d after MI operation	Cardiac ACE2 expression was not augmented after either treatment alone or in combination	Burchill <i>et al</i> [31]

MI: Myocardial infarction; LCA: Left ventricular artery; SD rats: Sprague-Dawley rats; ACE2: Angiotensin-converting enzyme 2.

mellitus. In 8-wk-old db/db mice, a model of early T2D, ACE2 expression is elevated, while ACE expression is decreased in both glomeruli and the cortex[48] prior to the development of DN. In another study of db/db mice, Chodavarapu *et al* [45] demonstrated that the protein expression of ACE2 was reduced in glomeruli, while tubular ACE2 and a disintegrin and metalloprotease 17 were increased. In two models of T1D [streptozotocin (STZ)-induced and Akita mouse (Ins2WT/C96Y) models], ACE2 gene deletion accelerated the development of DN[49,50], which could be ameliorated by perindopril or irbesartan. Moreover, treatment with recombinant human ACE2 (rhACE2) in male Akita mice led to reductions in albuminuria, hypertension, plasma Ang II levels, activation of NADPH oxidase, glomerular hypertrophy, and mesangial matrix expansion, thereby preventing the progression of DN[51]. In another rat study, the injection of adenoviral (Ad)-ACE2 in STZ-induced diabetic rats for 4 wk improved many signs of DN[52]. Furthermore, Ad-ACE2 and ACEI had similar effects, whereas the combined use of Ad-ACE2 and ACEI offered no additional benefits[52].

In humans, the expression of ACE2 was significantly reduced in both the glomeruli and proximal tubules in biopsy samples collected from patients with T2D-induced kidney disease[53]. Conversely, in a real-time polymerase chain reaction study, ACE2 mRNA expression was not significantly changed in eight diabetic patients with overt proteinuria compared with 66 nondiabetic patients with renal disease[54]. The differences in the results obtained in human studies of T2D nephropathy might be due to the different stages of diabetes. To date, no human studies of early-stage diabetes have been conducted. Moreover, genetic variation in and around the gene encoding ACE2 is most often detected using single nucleotide polymorphisms (SNPs). In a recent study, 14 ACE2 polymorphisms were genotyped by matrix-assisted laser desorption ionization time-of-flight mass spectrometry in the Uygur population of the Xinjiang region of China. Among them, the ACE2 SNPs rs2074192, rs4240157, rs4646188, and 879922 were associated with increased microalbuminuria in T2D patients[55].

Taken together, the above studies suggest that ACE2 might play a protective role against the development of DN.

ACE2 and hypertension

The role of ACE2 has been intensively studied in models of hypertension. Crackower *et al* [56] first reported that ACE2 transgenic mice exhibited lower blood pressure than wild-type mice. Subsequent studies reported that ACE2 probably has a small effect on blood pressure in mice under normal conditions[57-59]. However, it plays a much more prominent role in the regulation of hypertension, especially when Ang II levels are elevated. Existing studies have shown that ACE2 was reduced in kidneys from rat models of hypertension, such as salt-sensitive Sabra hypertensive rats, SHR, and stroke-prone SHR (SHRSP)[56,60]. Moreover, in a sheep model of fetal programmed hypertension, the administration of betamethasone on the 80th day of gestation markedly reduced ACE2 activity in the proximal tubules and urine in adolescent sheep[61]. Rentzsch *et al* [62] assessed the role of ACE2 in the pathogenesis of

Table 3 List of animal studies on the role of angiotensin-converting enzyme 2 in diabetes, hypertension, cardiovascular disease, and acute lung injury

Disease	Animal	Study details	Main findings	Ref.
Diabetes	db/db mice	Mice were randomly assigned to four treatment groups: (1) Control group fed normal chow; (2) Control group fed rosiglitazone diet; (3) db/db group fed normal chow; and (4) db/db group fed rosiglitazone diet	Protein expression of glomerular ACE2 was decreased in the kidneys of db/db mice, while tubular ACE2 and ADAM17 were increased. Rosiglitazone treatment of db/db mice normalized hyperglycemia, attenuated renal injury, and decreased urinary ACE2 and renal ADAM17 protein expression	Chodavarapu <i>et al</i> [45]
	db/db mice	Mice were treated for 16 wk with a specific ACE2 inhibitor (MLN-4760) alone or combined with telmisartan.	ACE and ACE2 colocalized on the apical surface of the proximal tubules, whereas in glomeruli, ACE2 is present in podocytes and, to a lesser extent, in glomerular mesangial cells, whereas ACE is present only in endothelial cells. Telmisartan prevented the increase in UAE associated with the ACE2 inhibitor	Ye <i>et al</i> [46]
	db/db mice	ACE and ACE 2 expression was measured in the kidney and heart	ACE2 protein in renal cortical tubules was increased, whereas ACE protein was decreased. In heart tissue, there were no significant differences between db/db and db/m mice in either ACE or ACE2 expression	Ye <i>et al</i> [48]
	STZ-induced diabetic SD rats	ACE2 and ACE gene and protein expression was measured in the kidney	ACE2 and ACE mRNA levels were decreased in diabetic renal tubules by approximately 50% and were not influenced by ramipril	Tikellis <i>et al</i> [47]
	STZ-induced diabetic Wistar rats	Diabetic Wistar rats were treated with DIZE	Treatment with DIZE restored ACE2 expression in glomeruli and increased the expression of AT2 receptors in whole kidney and isolated glomeruli	Goru <i>et al</i> [44]
	Akita and Ace2 ^{-/-} mice	Ace2 ^{-/-} mice were crossed with Akita mice (Ins ^{2WT/C96Y}), and four groups of mice were studied: Ace2 ^{+/y} Ins ^{2WT/WT} , Ace2 ^{-/-} Ins ^{2WT/WT} , Ace2 ^{+/y} Ins ^{2WT/C96Y} , and Ace2 ^{-/-} Ins ^{2WT/C96Y} . The Ace2 ^{+/y} Ins ^{2WT/C96Y} and Ace2 ^{-/-} Ins ^{2WT/C96Y} mice were treated with the ARB (irbesartan)	Deletion of the ACE2 gene was associated with accelerated kidney injury and reduced ACE2 expression in diabetic mice. Irbesartan reduced urinary albumin excretion rate in Ace2 ^{-/-} Ins ^{2WT/C96Y} mice	Wong <i>et al</i> [49]
	STZ-induced diabetic C57BL/6J mice and ACE2 knockout (KO) mice	Control and diabetic C57BL/6J and ACE2 KO mice, after 5 wk without treatment, were randomized to receive the ACE inhibitor perindopril. Wild-type mice were further randomized to receive the selective ACE2 inhibitor MLN-4760	Induction of diabetes in wild-type mice was associated with a reduction in renal ACE2 expression and decreased Ang 1-7. In diabetic mice receiving MLN-4760 and in ACE2 KO mice, diabetes-associated albuminuria was enhanced	Tikellis <i>et al</i> [50]
	Akita mice	Male diabetic Akita mice (Ins ^{2(WT/C96Y)}) and control C57BL/6J mice (Ins ^{2(WT/WT)}) were injected daily with placebo or with rhACE2 (2 mg/kg) for 4 wk	Treatment with rhACE2 increased plasma ACE2 activity, normalized blood pressure, and reduced the urinary albumin excretion	Oudit <i>et al</i> [51]
	STZ-induced diabetic Wistar rats	Diabetic Wistar rats were divided into 5 groups: No-treatment group, adenoviral (Ad)-ACE2 group, Ad-green fluorescent protein (GFP) group, ACEI group receiving benazepril and Ad-ACE2 + ACEI group	Rats in Ad-ACE2 group exhibited reduced SBP, urinary albumin excretion, creatinine clearance, glomeruli sclerosis index, and renal malondialdehyde level; downregulated transforming growth factor (TGF)-β1, vascular endothelial growth factor (VEGF), and collagen IV protein expression; and increased renal superoxide dismutase activity. Ad-ACE2 and ACEI had similar effects, whereas combined use of Ad-ACE2 and ACEI offered no additional benefits	Liu <i>et al</i> [52]
Hypertension	Salt-sensitive Sabra hypertensive rats, SHR, and SHRSP	ACE2 expression levels were determined in the kidneys	ACE2 levels were reduced in all of these hypertensive rat strains	Crackower <i>et al</i> [56]
	ACE2-deficient mice	Ang II peptide was administered by i.v. infusion in wild-type and ACE2-deficient mice	Blood pressure measurements were substantially higher in the ACE2-deficient mice	Gurley <i>et al</i> [57]
	SHR and Wistar Kyoto (WKY) rats	Expression of ACE2 was examined in the kidney from SHR and normotensive WKY rats	The tubular expression of ACE2 fell while glomerular expression of ACE2 was paradoxically increased in the SHR	Tikellis <i>et al</i> [60]
	Sheep	Sheep were administered with betamethasone or vehicle at the 80th day of gestation and delivered at term	Antenatal steroid treatment resulted in the chronic alteration of ACE and ACE2 in the circulatory and tubular compartments of adolescent sheep, which may contribute to the higher blood pressure in this model of fetal programming-induced hypertension	Shaltout <i>et al</i> [61]

	Transgenic rats	Transgenic rats were generated in an SHRSP genetic background expressing human ACE2 in vascular smooth muscle cells by the use of the SM22 promoter (SHRSP-ACE2 model)	Mean arterial blood pressure was reduced in SHRSP-ACE2, and the vasoconstrictive response to intraarterial administration of angiotensin II was attenuated	Rentzsch <i>et al</i> [62]
	SHR	Male WKY rats were randomized to receive either placebo or rhACE2 and were subsequently infused with Ang II	Treatment with rhACE2 partly corrected the hypertension, NADPH oxidase activation, and increased superoxide generation in the heart, kidney, and blood vessels	Lo <i>et al</i> [63]
	Mice	ACE2 activity was measured in kidney cortex from mice that had received injection of MLN-4760 or DX600	A marked increase in serum ACE2 activity. Mouse ACE2 abolished the hypertension induced by Ang II infusion. These effects were blocked by MLN-4760 but not by DX600	Ye <i>et al</i> [64]
Cardiovascular disease	ACE2-deficient mice	ACE2 mutant mice were generated, and heart parameters were measured	Genetic inactivation of ACE2 using homologous recombination resulted in increased AngII peptide levels, upregulation of hypoxia genes in the heart, and severe cardiac dysfunction	Crackower <i>et al</i> [56]
	ACE2-deficient mice	Ang II peptide was administered by i.v. infusion in WT and ACE2-deficient mice	No evidence for a role of ACE2 in the regulation of cardiac structure or function was found	Gurley <i>et al</i> [57]
	SD rats	Lentiviral vector encoding mouse ACE2 (lenti-mACE2) or GFP was injected intracardially in Sprague-Dawley rats	ACE2 overexpression resulted in protective effects on AngII-induced cardiac hypertrophy and fibrosis	Huentelman <i>et al</i> [71]
	SHR	Lentiviral vector encoding mouse ACE2 (lenti-mACE2) or GFP was injected intracardially in SHR and normotensive WKY rats	ACE2 overexpression exerted protective effects on high BP and cardiac pathophysiology induced by hypertension in the SHR	Diez-Freire <i>et al</i> [72]
	Rabbits	66 male New Zealand white rabbits were fed an atherogenic chow and were randomly divided into three groups: Treatment with a suspension of Ad-ACE2, treatment with a suspension of Ad-EGFP, and no treatment	ACE2 inhibited the development of early atherosclerotic lesions by suppressing the growth of VSMCs and improving endothelial function	Zhang <i>et al</i> [73]
Acute lung injury	ACE2 mutant mice	Acid aspiration-induced, sepsis-induced, and endotoxin-induced acute lung injury animal models were generated. Mice received intraperitoneal injections of rhACE2 protein	ACE2 and AT2 protected mice from severe acute lung injury. rhACE2 can protect mice from severe acute lung injury	Imai <i>et al</i> [82]
	ACE2 knockout mice	Mice were intranasally inoculated with SARS-CoV virus	SARS-CoV receptor ACE2 had a protective role in acute lung failure	Kuba <i>et al</i> [84]
	BALB/c mice	LPS-induced acute lung injury mice were treated with ACE2 activator resorcinolnaphthalein (RES) or ACE2 inhibitor MLN-4760	ACE2 activation can reduce the severity of LPS-induced acute lung injury <i>via</i> the AMPK/mTOR pathway	Zhang <i>et al</i> [87]
	c57BL/6j mice	Transgenic mice expressing the human ACE2 receptor driven by the cytokeratin-18 (K18) gene promoter (K18-hACE2)	Intranasal inoculation of SARS-CoV-2 in K18-hACE2 mice resulted in high levels of viral infection in lungs	Winkler <i>et al</i> [91]
	c57BL/6j mice	Mice expressing hACE2 in the lung were transduced by oropharyngeal delivery of the recombinant human adenovirus type 5 that expresses hACE2 (Ad5-hACE2)	Mice were infected with SARS-CoV-2 and developed interstitial pneumonia associated with perivascular inflammation, accompanied by a higher viral load in the lungs	Han <i>et al</i> [92]

UAE: Urinary albumin excretion; STZ: Streptozotocin; SD rats: Sprague-Dawley rats; SHR: Spontaneously hypertensive rats; SHRSP: Stroke-prone spontaneously hypertensive rats; SM22: Smooth muscle 22 α ; LPS: Lipopolysaccharide; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2.

hypertension. These authors generated transgenic rats in a SHRSP genetic background, called SHRSP-ACE2, which expressed human ACE2 in vascular smooth muscle cells under the control of the smooth muscle 22 α promoter. They found that endothelial function was significantly improved in SHRSP-ACE2 rats compared with SHRSP rats. These data indicate that vascular ACE2 overexpression in SHRSP reduces hypertension, probably through local Ang II degradation and by improving endothelial function. Existing animal studies have shown that the administration of recombinant ACE2 (rACE2) degrades Ang II, lowers blood pressure, and attenuates Ang II-induced

Table 4 List of epidemiological studies on the role of angiotensin-converting enzyme 2 in diabetes, hypertension, cardiovascular disease, and acute lung injury

Disease	Source country	Patients	Main findings	Ref.
Diabetes	Canada	Renal biopsies from 13 diabetic and 8 control patients	ACE2 mRNA and protein expression were significantly reduced in both the glomeruli and proximal tubules of the diabetic patients	Reich <i>et al</i> [53]
	Japan	66 nondiabetic and 8 diabetic patients with biopsy-proven renal diseases	ACE2 mRNA expression was not significantly changed in the diabetic patients	Konoshita <i>et al</i> [54]
	China	275 Uyghur T2D patients and 272 nondiabetic Uyghur individuals	ACE2 SNPs rs1978124, rs2048683, rs2074192, rs233575, rs4240157, rs4646156, rs4646188, and rs879922 were associated with T2D	Liu <i>et al</i> [55]
Hypertension	Australia	503 Caucasian subjects with type 2 diabetes	Genetic variation in ACE2 was associated with hypertension and reduced systolic function in men, and hypertension and increased LV mass in women	Patel <i>et al</i> [65]
	China	275 Uyghur T2D patients and 272 nondiabetic Uyghur individuals	ACE2 SNPs rs2048683, rs233575, rs4240157, rs4646156, rs4646188, and rs879922 were associated with increased SBP, while rs2074192, rs4646188, and rs879922 were associated elevated DBP	Liu <i>et al</i> [55]
	China	402 hypertensive patients and 233 normotensive individuals	ACE2 variant rs2074192 was associated with EH, while rs4240157, rs4646155, and rs4830542 were associated with EH- and hypertension-related atrial fibrillation and left atrial remodeling	Luo <i>et al</i> [66]
	China	3408 untreated hypertensive patients	The T allele of ACE2 rs2106809 was found to confer a 1.6-fold risk for hypertension in women	Fan <i>et al</i> [67]
	China	96 patients with EH and 96 healthy controls	Aberrant methylation of the ACE2 promoter may be associated with EH risk	Fan <i>et al</i> [68]
Cardiovascular disease	United States	11 individuals with dilated cardiomyopathy, 15 individuals with hypertrophic cardiomyopathy, and 16 controls with nonfailing hearts from the Penn Human Heart Tissue Biobank	ACE2 expression was downregulated in fibroblasts, pericytes, and vascular smooth muscle but upregulated in cardiomyocytes in dilated cardiomyopathy and hypertrophic cardiomyopathy	Fan <i>et al</i> [67]
	Hungary	45 healthy individuals, 239 hypertensive individuals, 141 patients with heart failure (HF) and reduced ejection fraction (HFrEF), and 47 patients with HF and preserved ejection fraction (HFpEF)	ACE2 activity was further increased in HFrEF patients. Serum ACE2 activity was negatively correlated with left ventricular systolic function in HFrEF	Úri <i>et al</i> [74]
	United States	113 patients with chronic systolic heart failure	Elevated plasma soluble ACE2 (sACE2) activity was associated with greater severity of myocardial dysfunction and was an independent predictor of adverse clinical events	Epelman <i>et al</i> [75]
	14 countries across five continents	10753 Prospective Urban Rural Epidemiology participants	Increased concentration of plasma ACE2 was associated with a higher risk of incident heart failure, myocardial infarction, stroke, and diabetes	Narula <i>et al</i> [76]
	Italy	Healthy subjects (C) and EH and Bartter's/Gitelman's (BS/GS) patients	ACE2 was significantly elevated in BS/GS compared with either C or EH	Calò <i>et al</i> [77]
	China	275 Uyghur T2D patients and 272 nondiabetic Uyghur individuals	ACE2 SNPs rs2074192 and rs879922 were associated with carotid arteriosclerosis stenosis and ACE2 SNPs rs2048683, rs4240157, rs4646156, rs4646188, and rs879922 were linked to heavier left heart remodeling	Liu <i>et al</i> [55]
	United States	44 patients with acute respiratory distress syndrome (ARDS)	GSK2586881, a rhACE2, was well-tolerated in patients with ARDS, and has been found to reduce Ang II levels and increase Ang 1-7 levels	Khan <i>et al</i> [94]

T2D: type 2 diabetes; EH: Essential hypertension; ACE2: Angiotensin-converting enzyme 2; ARDS: Acute respiratory distress syndrome; SNP: Single nucleotide polymorphism; HF: Heart failure; HFrEF: Heart failure and reduced ejection fraction; HFpEF: Heart failure and preserved ejection fraction; Ang 1-7: Angiotensin 1-7.

organ injury. One study showed that in the SHR model, rhACE2 partly corrected hypertension and NADPH oxidase activation and increased superoxide generation in

the heart, kidney, and blood vessels over a 14-d period[63]. Moreover, the prevention of Ang II-induced hypertension by mouse rACE2 was completely abolished by the specific ACE2 inhibitor MLN-4760, a nonpeptide inhibitor no longer available from Millennium Pharmaceuticals[64].

In human studies, Patel *et al*[65] found that in Caucasians with T2D, genetic variation in *ACE2* is associated with hypertension and reduced systolic function in men and hypertension and increased left ventricular mass in women. Liu *et al*[55] found that the *ACE2* SNPs rs2048683, rs233575, rs4240157, rs4646156, rs4646188, and rs879922 were associated with increased systolic blood pressure (SBP), while rs2074192, rs4646188, and rs879922 were associated with elevated diastolic blood pressure in Uyghur T2D patients. Luo *et al*[66] revealed that the *ACE2* variant rs2074192 was associated with essential hypertension (EH), while three *ACE2* variants (rs4240157, rs4646155, and rs4830542) were associated with EH- and hypertension-related atrial fibrillation and left atrial remodeling in south Xinjiang, China. In another study, the *ACE2* rs2106809 T allele was found to confer a 1.6-fold risk for hypertension in women[67]. Additionally, one study showed that aberrant methylation of the *ACE2* promoter may be associated with EH risk[68].

These findings indicate that ACE2 is a key regulator that maintains the balance of blood pressure. In animal studies, it has been demonstrated that the administration of recombinant ACE2 has a beneficial effect on the treatment of hypertension. Currently, large clinical trials to explore this and related alternative interventions are underway.

ACE2 and cardiac function, ventricular remodeling, and HF

SARS-CoV-2 enters the upper respiratory epithelium and lungs predominantly through ACE2. Nevertheless, in a single-center report of 416 patients hospitalized with COVID-19, 19.7% showed evidence of cardiac injury, suggesting a possible pathologic role for myocardial ACE2 expression[69]. ACE2 is present on endothelial cells and can undergo so-called shedding into the circulation. In patients with cardiovascular disease, increased ACE2 activity in the circulation predicts adverse cardiovascular outcomes in patients with HF, coronary artery disease, and aortic stenosis[70].

Crackower *et al*[56] demonstrated the first evidence that ACE2 may have a role in cardiac function. They found that ACE2 deletion in mice resulted in a severe heart contractility defect, increased levels of Ang II in the kidney, heart, and plasma, and upregulation of hypoxia-induced genes in the heart. Conversely, Gurley *et al*[57] reported that ACE2 deletion enhanced susceptibility to Ang II-induced hypertension but had no effect on cardiac structure or function. Huentelman *et al*[71] showed that ACE2 overexpression protects the heart from Ang II-induced hypertrophy and fibrosis. Another study on SHR hypertensive rats also showed that ACE2 overexpression exerted protective effects against high blood pressure and cardiac pathophysiology induced by hypertension[72]. Similarly, in a rabbit atherosclerosis model, local overexpression of ACE2 significantly inhibited the development of early atherosclerotic lesions[73].

In humans, increased circulating ACE2 activity is associated with coronary heart disease and HF, and a large proportion of the variation in plasma ACE2 levels is attributed to hereditary factors. One study showed that ACE2 activity was significantly increased in HF patients with reduced ejection fraction (HFrEF). Serum ACE2 activity was negatively correlated with left ventricular systolic function in HFrEF[74]. In addition, one study measured soluble ACE2 (sACE2) activity in 113 patients with chronic systolic HF and showed that elevated plasma sACE2 activity was associated with greater severity of myocardial dysfunction, which indicated that plasma sACE2 activity might be an independent predictor of adverse clinical events[75]. A recent study published in *Lancet* presented one of the largest epidemiological datasets on plasma ACE2 concentration in the general population[76]. They performed a case-cohort study involving 10753 participants from the multinational Prospective Urban Rural Epidemiology study, including 5084 patients randomly selected as the sub-cohort and 5669 with an incident event of interest. They reported that ACE2 concentration was the highest-ranked independent predictor of death compared with standard cardiovascular risk markers (smoking, diabetes, SBP, non-high density lipoprotein cholesterol, and body mass index). An increased concentration of plasma ACE2 was associated with an increased risk of all-cause mortality [hazard ratio (HR): 1.35 per 1 standard deviation (SD) increase; 95% confidence interval (CI): 1.29-1.43], incident HF (HR: 1.27 per 1 SD increase; 95%CI: 1.10-1.46), stroke (HR: 1.21 per 1 SD increase; 95%CI: 1.10-1.32), myocardial infarction (HR: 1.23 per 1 SD increase; 95%CI: 1.13-1.33), and incident diabetes (HR: 1.44 per 1 SD increase; 95%CI: 1.36-1.52). Other studies have investigated whether the *ACE2* gene is associated with left ventricular hypertrophy and coronary artery disease. The *ACE2* SNPs most frequently used in

association studies are rs2285666 and rs1978124[77]. Recently, Liu *et al*[55] found that the ACE2 SNPs rs2074192 and rs879922 were associated with carotid arteriosclerosis stenosis and that the ACE2 SNPs rs2048683, rs4240157, rs4646156, rs4646188, and rs879922 were linked to more substantial left heart remodeling. Furthermore, one study assessed ACE2 expression by performing bulk and single nucleus RNA-Seq on the left ventricles of 11 individuals with dilated cardiomyopathy, 15 individuals with hypertrophic cardiomyopathy, and 16 controls with nonfailing hearts from the Penn Human Heart Tissue Biobank. They found that cardiac ACE2 expression was down-regulated in fibroblasts, pericytes, and vascular smooth muscle but upregulated in cardiomyocytes[69].

Investigations of ACE2 as well as its role in cardiac function and HF will undoubtedly provide greater insight into the roles of this enzyme. However, carefully conducted large-scale clinical studies are urgently needed to clarify the potential role of ACE2 in cardiovascular diseases more precisely.

ACE2 and acute lung injury

Like many other organ lung cells also have a local RAS[78], which influences the pathogenesis of lung injury *via* cellular effects, including changes in vascular permeability, vascular tone, fibroblast activity, or alveolar epithelial cell apoptosis[79, 80]. ACE2 plays a pivotal role in Ang II degradation in the RAS cascade and thus limits inflammation and fibrosis in the lung[81]. Imai *et al*[82] investigated the role of ACE2 in acute respiratory distress syndrome (ARDS) by using ACE2 knockout mice. In three different ARDS models (acid-aspiration-induced, endotoxin-induced, and peritoneal sepsis-induced ARDS), it was shown that a loss of ACE2 expression in mutant mice resulted in enhanced vascular permeability, increased lung edema, engendered neutrophil accumulation, and worsened lung function. Importantly, treatment with catalytically active recombinant ACE2 protein improved the symptoms of acute lung injury in both wild-type mice and ACE2 knockout mice. Thus, ACE2 plays a protective role in acute lung injury. Mechanically, the finding that reduced ACE2 on lung cell surfaces is correlated with lung damage due to an uncontrolled RAS cascade is supported by data about the effects of long-lasting hyperoxia on pulmonary tissue[82-86]. In addition, a study revealed that ACE2 activation can reduce the severity of lipopolysaccharide-induced acute lung injury *via* the activated serine/threonine protein kinase/mammalian target of rapamycin pathway[87].

In the current pandemic of COVID-19, both bioinformatics modeling and *in vitro* experiments indicate that SARS-CoV-2 likely utilizes ACE2 as a receptor to gain entry into human cells[88-90]. A recent study evaluated lung function in a mouse model of SARS-CoV-2 infection. They used transgenic mice expressing the human ACE2 (hACE2) receptor driven by the cytokeratin-18 (K18) gene promoter (K18-hACE2) and found that intranasal inoculation of SARS-CoV-2 in K18-hACE2 mice resulted in high levels of viral infection in the lungs, with spread to other organs[91]. Similarly, one study also used a model of mice expressing hACE2 in the lung. In this study, the mice were transduced by oropharyngeal delivery of recombinant human adenovirus type 5 expressing hACE2[92]. They found that mice were infected with SARS-CoV-2 at day 4 post-transduction and developed interstitial pneumonia related to perivascular inflammation. On the other hand, as described above, a similar decrease in ACE2 has also been seen in cases of COVID-19 with severe lung injury, which might be attributable to the negative consequences that arise from insufficient Ang II degradation[93]. In human trials, GSK2586881, a rhACE2, was well tolerated in 44 patients with ARDS and has been found to reduce Ang II levels and increase Ang 1-7 levels, although it failed to improve the physiological and clinical indicators of ARDS in patients[94]. This study likely represents the first clinical application of rhACE2 in the field of ARDS, so we speculate that rhACE2 may become one of the most promising approaches for protecting against lung injury in patients with COVID-19.

Based on the above description, ACE2 plays a complex role in COVID-19-induced acute lung injury. On the one hand, high levels of ACE2 receptors on the cell surface may accelerate the invasion of SARS-CoV-2 during the very early phase of infection. On the other hand, low levels of ACE2 can ultimately worsen the disease course due to insufficient Ang II conversion in cases of severe COVID-19 with pulmonary complications.

CONCLUSION

As a vital component of the RAS, ACE2 is closely related to the occurrence and

development of RAS-associated diseases. A better understanding of the biological functions of ACE2 will be beneficial to the treatment. Previous studies show that a high-salt diet can decrease the expression of ACE2 and cause RAS disorders. Recent reports have not yet indicated that ARBs or ACEIs will increase the level of ACE2, thereby aggravating SARS-CoV-2 infection. Therefore, the mechanisms involved need to be further improved. As ACE2 is an important receptor through which SARS-CoV-2 can invade cells, further studies on ACE2 should focus on the development of drugs that inhibit the virus from entering cells and impede the binding of the S protein to ACE2 for COVID-19 treatment. More research on ACE2 should be conducted in the future to carry out targeted and effective treatment at a higher level.

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