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The Role of ACE2 in Blood Pressure and Hypertension: Insights from ACE2-Null Mice

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ABSTRACT

Angiotensin-converting enzyme 2 (ACE2) is a transmembrane protein that plays a crucial role in fluid balance, the regulation of blood pressure, and lung function. Alteration in ACE2 enzyme by various factors, including genetic factors, hormones, cytokines, and environmental stimuli that lead to the onset of cardiovascular diseases, including heart failure, diabetic nephropathy, and atherosclerosis. It has a counter-regulatory function in developing comorbidities. Despite the extensive research conducted on ACE2, there is still a need for more specific research to address gaps in understanding. This review aims to explore the genetic factors and molecular mechanisms that regulate ACE2 and its role in the pathogenesis of hypertension and cardiovascular disorders. All the previous strategies that were used for preparing ACE2 null mice for research purposes are discussed in details. The inheritance pattern of hypertension associated with ACE2 is still unknown. In addition, the effect of overexpression of ACE2 effect brain-gut-lung communication in ACE2 null mice is not reported. Therefore, studies need to be done to fill these gaps and then to go for possible treatment. This review aims to address the existing research gaps and highlight the potential for future studies to enhance our understanding of ACE2. Ultimately, this knowledge could help to gain insight into the research gaps and to inform the development of new treatments for cardiovascular diseases, diabetic comorbidities, and related conditions.

Keywords: Blood pressure; Hypertension; Cardiovascular disorders; Renin-angiotensin system (RAS); Angiotensin; ACE2-null mice

INTRODUCTION

Angiotensin-converting enzyme 2 (ACE2) is a significant transmembrane protein that plays a crucial role in fluid balance, the regulation of blood pressure, and lung function [1]. It is divided into a large extracellular domain and a small intracellular domain. The extracellular domain of ACE2 contains the active site that cleaves angiotensin II (Ang II) into angiotensin 1-7 (Ang 1-7), a potent vasodilator [2]. The intracellular domain of ACE2 also plays a role in the regulation of its activity and cellular localization. The activity and expression of ACE2 are regulated by various factors, including genetic factors, hormones, cytokines, and environmental stimuli [3]. For instance, estrogen upregulates ACE2 expression in human atrial tissue, while oxidative stress downregulates it [4].

ACE2 is primarily known for its role in the renin-angiotensin system (RAS) (**Figure 1**), which regulates blood pressure and fluid balance. ACE2 acts as a physiological counterbalance to ACE, which cleaves angiotensin I to form Ang II, a potent vasoconstrictor [5]. By cleaving Ang II into Ang 1-7, ACE2 reduces the levels of Ang II and affects blood pressure and fluid

balance [6] . In addition, ACE2 has been shown to have anti-inflammatory and antifibrotic properties, making it an attractive target for the treatment of various diseases, including heart failure, hypertension, and diabetes [7]. Previous genetic mutations have shown to be affecting the working mechanism of controlling hypertension (**Table 1**). This review article aims to summarize the current knowledge on ACE2, focusing on the structure, function, and regulation of ACE2, its role in hypertension and COVID-19, and its therapeutic potential and approach against ACE2.

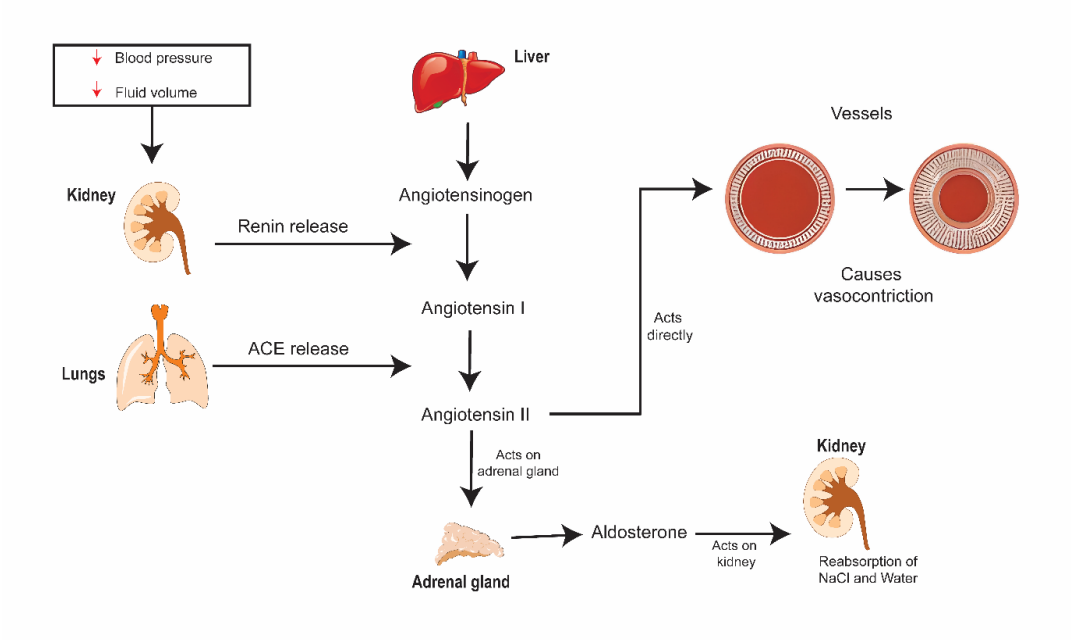

Figure 1. *Mechanism of RAAS*

Table 1. *Previously reported mutations of ACE2 gene [8]*

Mutation type	Total number of reported mutations	Pathogenicity
	dbSNP	
Frameshift	5	Uncertain
Missense	312	191 pathogenic/ deleterious 121 non-pathogenic/ tolerated
Synonymous	127	Uncertain
Start loss	1	Least pathogenic
Stop gain	5	Uncertain
In frame deletion	2	Uncertain
Missense variant ~ splice region variant	20	11 pathogenic/ deleterious 9 non-pathogenic/ tolerated
Splice region variant ~ synonymous variant	3	Uncertain
Splice region variant ~ synonymous variant	2	Uncertain
	COSMIC	
Splice region variant ~ coding sequence variant	19	Uncertain
Coding sequence variant	271	Uncertain

ACE2 role in hypertension and cardiovascular disorders

Hypertension, or high blood pressure, is a leading cause of premature death that leads to cardiovascular disorders, stroke, renal dysregulation, blindness, and brain damage [9]. The RAS pathway plays a critical role in blood pressure regulation and can be affected by mutations in ACE2. ACE2 mutations can cause an imbalance in blood concentration, leading to hypertension [10]. For instance, [11] demonstrated that in hypertensive patients, *ACE2* gene is highly express in the endothelium of arteries, arterioles, and venules of the heart and kidney, which decreases Ang II and increases Ang-(1-7) levels.

Volume 6, Issue 2, 2025 | https://doi.org/10.53576/bashir.006.02.0260

These changes in the RAS contribute to the development and progression of hypertension. Increasing ACE2 expression reduces the risk of hypertension, whereas ACE2 deficiency increases it [12].

ACE2 also plays a significant role in the pathogenesis of cardiovascular diseases (CVDs), including heart failure (HF), diabetic nephropathy, and atherosclerosis [2]. ACE2 may play a critical role in the development of these diseases due to its altered expression and activity [13]. Genetic ACE2 deletion worsens the cardiac dysfunction brought on by myocardial infarction (MI), the extent of the infarct, the activation of MMP (matrix metalloproteinase)2/MMP9, and the rupture of the extracellular matrix [14]. Moreover, explanted human hearts from individuals with dilated cardiomyopathy had heterozygote deletion of ACE2 was enough to enhance vulnerability to heart disease [15].

ADAM17 (A Disintegrin and Metalloprotease 17) regulates the release of ACE2 from the cell membrane-bound domain, which reduces the brain's ability to compensate for ACE2 depletion and results in neurogenic hypertension [16]. The ACE2/Ang 1-7/MasR axis of the RAS has a counter-regulatory function in developing diabetic comorbidities, including cardiovascular and renal disease. The ACE2/Ang 1-7 axis can stop diabetes mellitus by exposing CD34+ cells to Ang 1-7, restoring bioavailable nitric oxide (NO), and lowering reactive oxygen species [7, 17].

In epicardial adipose tissue, the removal of ACE2 causes an increase in proinflammatory M1-phenotype macrophage polarization and reduces the anti-inflammatory M2-phenotype macrophage polarization site. Ang 1-7 possesses significant anti-inflammatory actions and protects against diabetic cardiomyopathy and nephropathy in the adipose tissue of obese type 2 diabetes mice models [18].

ACE2-null mice

ACE2 (angiotensin-converting enzyme 2) null mice are genetically engineered mice that lack the ACE2 gene. ACE2 null mice were developed to study the pathological and physiological roles of ACE2 in various organs and pathways. The first ACE2 null mice were created in 2002 by researchers at the University of North Carolina at Chapel Hill, led by Dr. Monteith S. T. Hodge.

The importance of ACE2 null mice in research and clinical studies lies in their potential to shed light on the mechanisms underlying various diseases, including hypertension, heart failure, and respiratory diseases such as COVID-19 [13]. In addition, ACE2 null mice have been used to study the effects of angiotensin receptor blockers (ARBs) and ACE inhibitors on blood pressure regulation and cardiovascular function. These drugs are commonly used to treat hypertension and heart failure, and they work by targeting the renin-angiotensin system [19]. By studying ACE2 null mice, researchers can gain a better understanding of how these drugs affect the system and potentially develop more effective treatments.

In studying the molecular mechanisms of diseases such as hypertension, ACE2 null mice have been shown to have higher blood pressure and impaired heart function compared to wild-type mice. By studying ACE2 null mice, insights can be gained into the underlying mechanisms of hypertension and potentially develop new therapies for the condition [2].

Method for ACE2 null mice preparation

Method for the preparation of ACE2 null was first prosed by Josef Penninger [20, 21]. A detailed description provided in the present protocol is the combination of different studies [22-25]. The protocol described here is significant as it details the creation and confirmation of knockout mice for the ACE2 gene. The schematic method of this protocol is shown in Figure 2.

Vector construction involved identifying BAC145d21 by Southern hybridization using a human ACE2 cDNA probe, cloning the target fragment into the YCpLac22 vector, and generating a recombinant plasmid through restriction digestion, ligation, and bacterial amplification. A NEO/URA3 cassette was PCR-amplified and introduced into yeast to achieve homologous recombination, followed by selection of G418-resistant clones. The finalized targeting construct was linearized and electroporated into embryonic stem cells, and resistant colonies were screened by Southern blotting. Correctly targeted ES cells were injected into C57BL/6H blastocysts and implanted into surrogate mothers to produce chimeric mice. Heterozygous offspring were identified, bred, and genotyped, and ACE2 gene deletion was confirmed by Southern and Northern blot analyses. Interbreeding of heterozygous mice yielded ACE2 knockout mice, which were subjected to phenotypic analysis across different genetic backgrounds.

Volume 6, Issue 2, 2025 | https://doi.org/10.53576/bashir.006.02.0260

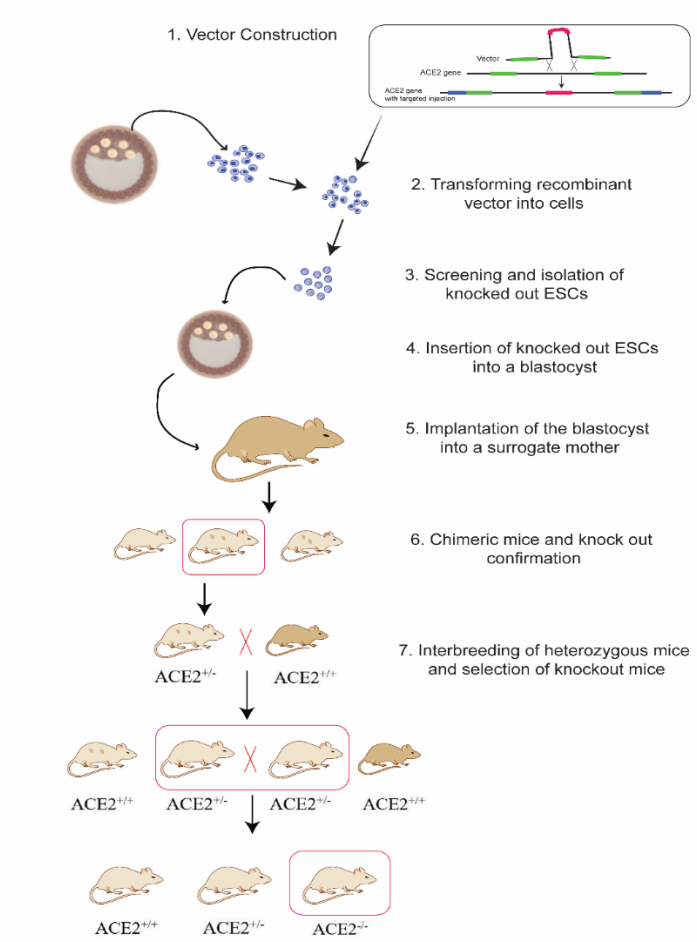

Figure 2. *Previously used methodology for preparation of ACE2 null mice*

Role of ACE2 in Regulating Blood Pressure and Vascular Functioning: Insights from ACE2-null mice

Several factors, including hormones, cytokines, and environmental factors, regulates the expression and activity of ACE2. For example, estrogen has been shown to upregulate ACE2 expression in human atrial tissues, while oxidative stress downregulates it [4]. In addition, ACE2 activity is also regulated by its localization within the cell, with the protein being expressed on the cell surface or within the intracellular compartment, where it can act as a decoy receptor.

A vital part of the RAS, ACE2 is important for controlling blood pressure and preventing the development of hypertension. The complex system of enzymes, hormones, and receptors known as the RAS controls the body's fluid balance and blood pressure. Angiotensin (1-7) (Ang-(1-7)), which possesses vasodilatory and anti-inflammatory properties, is produced when ACE2 breaks down the powerful vasoconstrictor angiotensin II (Ang II) [1]. Studies have shown that ACE2-/- mice model demonstrated an increased levels of inflammatory cytokines and chemokines, IL-1a, IL-1b, CCL2, CXCL8, and TNF-α [26]. Another study has also shown that ACE2-deficient mice have reduced levels of endothelial nitric oxide synthase (eNOS) and nitric oxide (•NO), significance of ACE2 in modulating vascular functioning through regulation of oxidative and nitric oxide [27].

According to several studies, ACE2 regulates heart function in vivo, and other peptide systems may also be important regulators of renal and cardiovascular function [28]. Age-dependent cardiomyopathy is associated with increased Ang II-mediated neutrophil infiltration and oxidative stress through AT1 receptors in ACE2-deficient mice [28]. The absence of ACE2 has been shown to activate the myocardial NADPH oxidase system and increase superoxide generation, MMP activation, and pathological signaling, resulting in significant unfavorable cardiac remodeling and dysfunction [29]. Similarly, [30] reported that pressure overload-induced cardiac dysfunction in ACE2-/y mice resulted in an increase in heart angiotensin II levels and mitogen-activated protein (MAP) kinase activity. Therefore, ACE2 markedly regulates normal cardiac functioning. Additionally, increased oxidative stress in Ang ACE2 KO's myocardial and aorta has been reported, and in the aorta of ACE2 KO, macrophage inflammatory protein 1a (MIP 1a) levels were elevated thrice [25]. Studies in the ACE2 KO model have also

Volume 6, Issue 2, 2025 | https://doi.org/10.53576/bashir.006.02.0260

shown that ACE2 is involved in the unfavorable responses of the heart and aorta to Ang II stimulation [25], resulting in increased remodeling employing physiological, structural, and biochemical indicators.

Moreover, the role of ACE2 in the prevention of heart failure caused by Ang II has been demonstrated through genetic and pharmaceutical methods. Studies have shown that AT1R blockade and Ang 1-7 significantly improved systolic dysfunction by reducing NADPH oxidase activity, downregulating the expression of Nox2 and p47phox subunits, and restoring abnormal signaling pathways in pressure-overloaded ACE2-null animals [24]. The latter authors also found that ACE2 has a significant role in heart disease associated with obesity. ACE2 loss also disrupts RAS balance in a diabetic state, causing impaired vascular function. Angiotensin II causes the breakdown of ACE2 and is associated with TNF-α converting enzyme (TACE), regulating the positive feedback mechanism in the RAS [7]. Hence, ACE2 is a critical component of various biological processes, including the regulation of blood pressure, amino acid absorption and digestion, and heart function (**Table 2**). Understanding the regulation of ACE2 expression and activity can potentially lead to the development of targeted therapies for cardiovascular diseases and other related disorders.

Table 2. *Previous studies done on ACE2 null mice*

Study	Disease	Animal model	Pathological changes	Molecular mechanism	Findings
[14]	Heart disease	Female ACE2 (+/-) (heterozygote) mice	Worsening systolic and diastolic dysfunction and increased LV dilation. Myocardial fibrosis, pathogenic and hypertrophy gene expression were all increased. Increased vascular fibrosis and stiffness	Phosphorylation of the STAT-3, JNK1/2, and ERK1/2 pathways has increased. Increased Vascular superoxide and nitrotyrosine levels	Increased vulnerability to heart and vascular disorders brought on by Ang II.
[31]	Vascular inflammation and atherosclerosis	C57Bl6, ACE2 knockout (KO), apolipoprotein E (ApoE) KO and ApoE/Ace2 double KO mice	Increased plaque accumulation	Elevated expression of inflammatory cytokines and adhesion molecules, baseline activation, and increased inflammation in response to TNF-α.	Genetic Ace2 loss increases response to proinflammatory stimuli and upregulates potential atherogenesis pathways.
[27]	Vascular Dysfunction	ACE2-/y male mice	Impairment of vascular function	Reduction in eNOS expression, reduced •NO concentrations, urine nitrite and lower plasma concentration, increased lipid peroxidation, decreased superoxide dismutase activity	Vascular homeostasis is maintained in part by ACE2.
[32]	Improper intestinal absorption of amino acids	$ACE2^{-/y}$ mice	Weight loss occurred after weaning, and Malabsorption	The ileum lumen should receive more L-tryptophan and other neutral amino acids. Plasma and muscle levels of glycine and L-tryptophan were significantly decreased in ace2 null mice	Mice lacking intestinal amino acid transport is ACE2-dependent mice without intestine amino acid transport is Ace2-dependent

Volume 6, Issue 2, 2025 | https://doi.org/10.53576/bashir.006.02.0260

[22]	Changed blood pressure	$ACE2^{-/y}$ mice with C57BL/6 and 129/SvEv genetic backgrounds	Increase in blood pressure	Increased Ang II levels and a pronounced renal Ang II buildup	The renin-angiotensin system's functional component ACE2 metabolises Ang II and controls blood pressure.
[29]	Pressure overload-induced heart failure	ACE2 knockout (ACE2 KO, $Ace2^{-/y}$), $p47^{phox}$ knockout ($p47^{phox}$KO, $p47^{phox-/-}$), and ACE2/$p47^{phox}$ double KO mice	Pathological hypertrophy increased and systolic function deteriorated	Angiotensin II (Ang II) levels in the myocardium rose whereas Ang 1-7 levels dropped. Increased expression and phosphorylation of $p47^{phox}$, NADPH oxidase activity, and superoxide generation	Mice carrying the ACE2KO gene cause significant myocardial dysfunction and remodeling.
[33]	Pressure overload-induced heart failure	$ACE2^{-/y}$	Cardiac hypertrophy and dilatation with decreased cardiac contractility	Increased activity of MAP kinases and cardiac angiotensin II concentration	ACE2 lessens the angiotensin II-mediated hypertrophic response to overload pressure. ACE2 disruption could hasten cardiac hypertrophy. ACE2 exerts cardio- and vascular-protective effects under pathological conditions
[24]	Cardiac dysfunction	ACE2 KO mice	Heart weight/body weight ratio, increased left ventricular wall thickness, typical cardiomyocyte cross-sectional area, and hypertrophic cardiomyopathy	Elevated levels of MIP 1 (macrophage inflammatory protein 1) in the aorta	
[24]	Failure of the heart caused by pressure overload	ACE2 KO mice	Systolic dysfunction and increased left ventricular wall dysfunction,	Extracellular signal-regulated kinase 1/2, signal transducer and activator of transcription 3, Akt, and glycogen synthase kinase 3 are all phosphorylated, as well as protein kinase C. NADPH oxidase activity is up	Irbesartan, an AT1R blocker, plus Ang 1-7 therapy reduced cardiac remodelling and stopped cardiac hypertrophy.
[34]	Diabetic cardiovascular complications	ACE2 KO mice (Akita/$ACE2^{-/y}$)	Impaired diastolic function	Increased activation of protein kinase C, NADPH oxidase and metalloproteinases. Loss of Akt and phosphorylation of endothelial nitric oxide synthase.	Treatment with the AT1R blocker irbesartan and Ang 1-7 rescued systolic dysfunction

Volume 6, Issue 2, 2025 | https://doi.org/10.53576/bashir.006.02.0260

[35]	Cardiac dysfunction and obesity	ACE2 KO mice	Reduced weight gain, increased glucose intolerance, and inflammation of the epicardial adipose tissue	Increased proinflammatory phenotypic polarization of macrophages	ACE2 have an important role heart disease associated with obesity

Expanding Our Understanding of ACE2: Bridging the Knowledge Gap and Finding Priorities for Future Research

ACE2 (angiotensin-converting enzyme 2) manipulation holds potential therapeutic applications in hypertension management due to its role in the renin-angiotensin-aldosterone system (RAAS) and the regulation of blood pressure. Here are some of the potential therapeutic applications of ACE2 manipulation in hypertension management. Angiotensin II is a potent vasoconstrictor and plays a central role in the development and progression of hypertension. ACE2 functions as a negative regulator of the RAAS by metabolizing angiotensin II into angiotensin-(1-7), a vasodilator and counter-regulatory peptide. By enhancing ACE2 activity or increasing ACE2 expression, the balance between angiotensin II and angiotensin-(1-7) can be shifted, potentially leading to improved blood pressure control [36]. Hypertension is often associated with chronic inflammation and increased oxidative stress, which contribute to vascular dysfunction and end-organ damage. ACE2 has been shown to have anti-inflammatory and antioxidant properties. Manipulating ACE2 activity may help reduce inflammation and oxidative stress, thereby preventing or ameliorating hypertension-related complications [37]. Endothelial dysfunction, characterized by impaired nitric oxide availability and vasodilation, is a common feature in hypertension. ACE2 promotes the production of nitric oxide, a potent vasodilator, by enhancing the bioavailability of its precursor, L-arginine [38]. By enhancing ACE2 activity, endothelial function can be improved, leading to better blood vessel dilation and blood pressure control. Chronic hypertension can lead to damage in various organs, including the heart, kidneys, and blood vessels. ACE2 manipulation may provide protection against end-organ damage by mitigating the deleterious effects of angiotensin II, reducing inflammation, and improving endothelial function. This could help prevent or delay the development of hypertension-related complications, such as heart failure and kidney disease [39].

Challenges in ACE2 gene studies:

ACE2 gene exhibits genetic variability, including single nucleotide polymorphisms (SNPs) and structural variations, which can impact its expression, function, and susceptibility to diseases. Studying the functional implications of these genetic variants and their association with disease susceptibility is a challenge [40]. ACE2 expression is not uniform across all tissues and cell types. It is highly expressed in the lungs, heart, kidney, and gastrointestinal tract, among others. Understanding the tissue-specific regulation of ACE2 expression and its implications in various diseases requires comprehensive studies across multiple organ systems. ACE2 gene expression is regulated by complex molecular mechanisms, including transcriptional and post-transcriptional processes [36]. Explaining the working of these regulatory mechanisms is essential to understand ACE2 expression patterns and its role in disease pathogenesis accurately. ACE2 interacts with various molecular pathways, such as the renin-angiotensin system, Wnt/β-catenin signaling, and others [41]. Understanding the association of ACE2 with these pathways and their combined effects on disease development and progression is a challenge.

Potential future research directions:

Investigating the genetic variants within the ACE2 gene and their association with disease susceptibility or severity can provide insights into individual variability in disease outcomes. Large-scale genomic studies and comprehensive functional characterization of these variants can help identify potential therapeutic targets and personalize treatment approaches. Understanding the tissue-specific regulation of ACE2 expression and its implications in different diseases is crucial. Future research can focus on comprehensive profiling of ACE2 expression across various tissues and cell types to unravel its role in organ-specific pathophysiology and identify novel therapeutic strategies. Epigenetic modifications, such as DNA methylation and histone modifications, play a significant role in gene regulation. Investigating the epigenetic landscape of the ACE2 gene and its impact on gene expression can provide insights into disease susceptibility and potential therapeutic interventions.

Further characterization of ACE2 protein structure, interactions with other molecules, and downstream signaling pathways will enhance our understanding of its role in disease processes. Exploring the functional consequences of ACE2 genetic variants and their impact on protein structure, stability, and binding affinity can provide valuable insights into disease

Volume 6, Issue 2, 2025 | https://doi.org/10.53576/bashir.006.02.0260

mechanisms. Identifying novel therapeutic targets that modulate ACE2 expression or its downstream signaling pathways can have significant clinical implications. Future research can focus on developing targeted therapies to manipulate ACE2 expression or activity to prevent or treat diseases associated with dysregulation of ACE2.

CONCLUSION

ACE2 plays a critical role in regulating various physiological and pathophysiological processes, including the renin-angiotensin system, inflammation, and autophagy. However, ACE2 expression is altered in many diseases, including hypertension, resulting in dysregulated RAS signaling and disease progression. Therefore, ACE2 is a promising therapeutic target for various diseases. ACE2-null mice have been used to study the role of ACE2 in different organ systems, including the heart, lungs, and kidneys, providing valuable insights into the physiological and pathophysiological functions of ACE2. Despite our current understanding of ACE2's importance, there are still significant research gaps that need to be addressed to achieve a comprehensive understanding of its role in hypertension, stroke risk, brain-gut-lung communication, and lipidome remodeling. The insights gained from such studies could potentially lead to new therapeutic options for the treatment of hypertension and related conditions. Future research should focus on developing novel ACE2-targeted therapies and exploring the role of ACE2 in different organ systems.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTION

HQ and AH conceived and designed the study. HQ, AH, and MH performed the experimental work and data acquisition. SR contributed to data analysis and interpretation. AM provided technical support and critical input during the study. HQ and AH drafted the manuscript, while SR, AM, and MH critically revised it for important intellectual content. All authors read and approved the final manuscript.

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