ТЕМА НОМЕРА ФИЗИОЛОГИЯ. ЭКСПЕРИМЕНТАЛЬНАЯ ФИЗИОЛОГИЯ
THEME OF THE ISSUE PHYSIOLOGY. EXPERIMENTAL PHYSIOLOGY

DOI 10.22363/2313-0245-2025-30-2-177-199
EDN GJBIWF

ОБЗОР
REVIEW

Deciphering the role of angiotensin converting enzyme2 in health and diseases

Shivani Sivasakthivel, Pratibha Ramani

Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, *Chennai, TamilNadu, India*
jsshivaninarayanan@gmail.com

Abstract. *Relevance.* Angiotensin converting enzyme 2 (ACE 2) is recognised as a significant regulator of cardiovascular and pulmonary homeostasis owing to its involvement in the renin-angiotensin system (RAAS). This extensive review addresses ACE 2's conventional role in converting Angiotensin II (Ang II) to the Angiotensin-(1–7) to its broader implications in cardiovascular illness, pulmonary pathology, metabolic diseases, and cancers. *Conclusion.* Recent research has shed light on ACE2's significance beyond its enzymatic capabilities, specifically as a cellular receptor of various pathogens. Furthermore, recent evidence shows that ACE2 is involved in inflammation, glucose metabolism, and gut microbiome modulation. The tissue distribution patterns, regulatory mechanisms, and therapeutic possibilities show its dual role as a protective factor in and a possible entryway for the viral infections. Understanding these multiple processes in health and disease state serves to be essential in establishing tailored treatments for the diseases. This review outlines the existing understanding of ACE 2 and emphasizes areas for further research, notably its potential as a therapeutic target. Furthermore, we have discussed the challenges and future directions in ACE2-based therapeutics.

Keywords: ACE2, angiotensin converting enzyme 2, health, ailments, physiology, CVS, pulmonary, renal, cancer, immuno, skin, gut, neuro, ocular

Funding. The authors received no financial support for the research, authorship, and publication of this article.

Author contributions. Shivani Sivasakthivel — conception, manuscript writing and writing the final manuscript text. Pratibha Ramani — checking the intellectual content of the manuscript, final approval of the version for publication. Shivani Sivasakthivel, Pratibha Ramani — checking the intellectual content of the manuscript. All authors made significant contributions to the conception, conduct of the study and preparation of the article, read and approved the final version before publication.

Conflicts of interest statement. The authors declare no conflicts of interest.

Ethics approval — not applicable.

Acknowledgment. The authors acknowledge the use of Microsoft PowerPoint for figure preparation, incorporating SmartArt graphics and design elements sourced from Medical Server Art to enhance the schematic representation of concepts presented in this review.

Consent for publication — not applicable.

Received 02.09.2025. Accepted 01.10.2025.

For citation: Sivasakthivel S, Ramani P. Deciphering the role of angiotensin converting enzyme2 in health and diseases. *RUDN Journal of Medicine*. 2026;30(2):177–199. doi: 10.22363/2313-0245-2026-30-2-177-199. EDN: GJBIWF

Significance/review highlights

- ACE2 regulates the Renin-Angiotensin System (RAAS), influencing cardiovascular, pulmonary, renal, and metabolic health.
- ACE2 serves as both a protective enzyme and a viral receptor, playing a crucial role in COVID-19 pathophysiology.
- ACE2 exhibits neuroprotective and endocrine regulatory functions, impacting brain health, insulin metabolism, and reproduction.
- ACE2 plays a dual role in cancer biology, with potential implications for tumour progression and therapeutic interventions.
- Therapeutic targeting of ACE2, including recombinant ACE2 and gene therapy, holds promise for multiple diseases.

Introduction

ACE 2 perform crucial role in the RAAS, that is essential for blood pressure regulation, electrolyte balance, fluid, along with systemic vascular resistance [1].The discovery of ACE 2 and the axis of ACE2/Ang (1–7)/Mas receptor has broadened our awareness of the RAAS's wider significance in health and illness, although it has traditionally been known for its function in cardiovascular physiology and pathophysiology. The global SARS-CoV and SARS-CoV-2 coronavirus outbreaks, along with the plethora of research findings as a response to subsequent COVID-19 pandemic, have revealed a fresh element of ACE 2's effects on living tissues and organs.

Donoghue et al. (2000) first characterized ACE 2 as a homolog of ACE (angiotensin-converting enzyme), highlighting its unique enzymatic properties [2]. Subsequent studies provided detailed crystallographic evidence of its molecular structure, revealing critical zinc-binding sites essential for its catalytic activity. A zinc-containing metalloenzyme is ACE 2 which is a membrane protein that occupies various organs that include the heart, gut, lungs, along with kidneys.

ACE 2 is extensively expressed in heart, kidneys, lungs, along with intestines, indicating its significant role in the cardiovascular, renal, respiratory, and gastrointestinal systems [3, 4]. ACE 2 is a transmembrane glycoprotein consisting of 805 amino acids that is a monocarboxypeptidase type I. It was identified in 2000 and shares sequence similarities with two other proteins,

collectrin and ACE. The highly polymorphic ACE 2 gene is found on Xp22 [5]. ACE 2 functions as a regulator for the RAAS system (Figure 1) to maintain homeostasis in addition to serving as an anchoring tool for SARS CoVs to attach to host cell membranes for fusion.

ACE 2 acts as a counterbalance to ACE, comprising an N-terminal peptidase domain (PD) along with a CLD (C-terminal collectrin-like domain), which terminates with a single transmembrane helix and an approximately 40 residue intracellular region, that makes up the full-length ACE 2. Through the PD, ACE2 cleaves Ang II to produce Ang-(1–7). Additionally, ACE 2 can cleave Ang I to create Ang-(1–9), that is subsequently transformed into Ang-(1–7) by other enzymes. This action not only minimizes levels of Ang II but also enhances levels of Ang (1–7), contributing to the balance of vasodilation and vasoconstriction [6].

ACE 2/Ang (1–7) axis exerts its physiological impact primarily through Mas receptor, a G protein-coupled receptor. This interaction promotes anti-fibrotic, vasodilation, anti-inflammatory, as well as anti-proliferative impact, which contrasts with the actions mediated by Ang II through AT1 receptor, causing vasoconstriction, inflammation, fibrosis, and cell proliferation. ACE 2/Ang (1–7) axis is also intricate in metabolic regulation, contributing to glucose and lipid metabolism [6–10].

ACE 2 being the RAAS regulator, we should be able to better understand how drugs like ACE inhibitors (ACEIs) along with ARBs (angiotensin receptor blockers) work. This would further deepen our comprehension of the pathophysiology connected to this biological system, like RAAS. In addition, the pandemic has increased the significance of immunohistochemistry-based morphological studies to pinpoint the location of ACE 2 positive cells and alterations in their distribution. Given the protective roles of ACE 2, there is significant interest in developing therapeutic strategies that enhance their functions. These include Ang (1–7) mimetics, ACE 2 activators, as well as Mas receptor agonists.

Thus, we undertook a review to provide a deep knowledge of ACE 2 that represents a vital counter-regulatory arm of the RAAS, with significant implications on health and diseases. And hence understanding the mechanisms and effects of

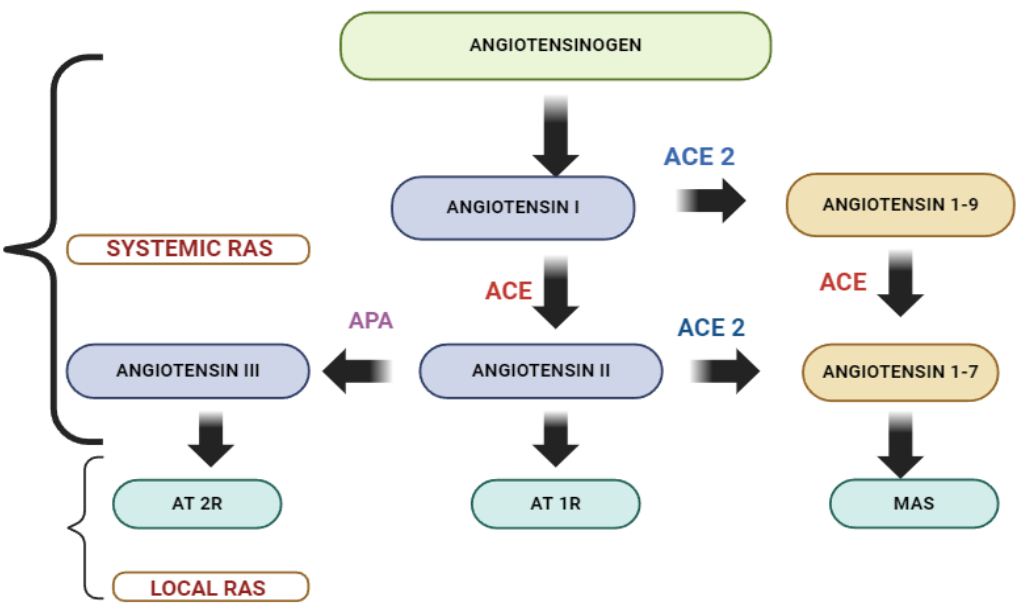

Fig.1. Cascade of Renin Angiotensin System (RAS)

ACE 2/Ang (1–7) axis continues to be an area of active research, with potential for developing new therapeutic strategies for range of diseases.

Cardiovascular functions of ACE 2 and linked diseases

As a component of the RAAS, ACE 2 is essential to cardiovascular physiology. The structural chimeric protein known as ACE 2 is the result of the 2 gene duplication: homology with ACE at the carboxypeptidase domain along with homology with Collectrin at the transmembrane C-terminal domain. ACE 2 is extremely expressed in heart [11], particularly in cardiomyocytes and fibroblasts. ACE 2 metabolises angiotensin II into Ang (1–7), shifting the balance from vasoconstriction and sodium retention (mediated by angiotensin II) towards vasodilation and natriuresis (Figure 2). This shift performs a vital role in blood pressure regulation, fluid balance, essential for both cardiovascular and renal health. ACE 2 undergoes three processes that contribute to ACE 2's protective benefits: (i) Ang I to Ang 1–9 degradation, which reduces amount of substrate available for the ACE activity; (ii) Ang II degradation, which lessens its harmful impact; and (iii) Ang 1–7 production that actually produces cardioprotective effects. The Ang II/AT1R axis is activated by decreased ACE 2 activity, which accelerates the progression of heart disease. Activation of ACE 2/Ang 1–9 and ACE 2/Ang 1–7 axes result from elevated ACE 2 level and activity, which protects against heart disease [12].

Significant roles are performed by the ACE 2 enzyme along with its product, the angiotensin (1–7) [Ang (1–7)], in the pathophysiology along with potential management of hypertension, a significant risk factor for cardiovascular diseases [13].Their actions provide a counter-regulatory mechanism to classical RAAS, which is recognized for controlling blood pressure through vasoconstriction, sodium retention, and aldosterone secretion. ACE 2 is extensively distributed in addition to other members of the systemic RAAS. Localised regions of ischemia/reperfusion (RAAS) are seen in cardiovascular tissues, and ACE 2 mRNA is expressed in diversity of cell types, such as coronary microcirculation.

Common mechanisms of ACE 2 in hypertension include *Vasodilation* where Ang (1–7) primarily exerts vasodilatory effects by the Mas receptor [13]. This action counters the vasoconstriction mediated by angiotensin

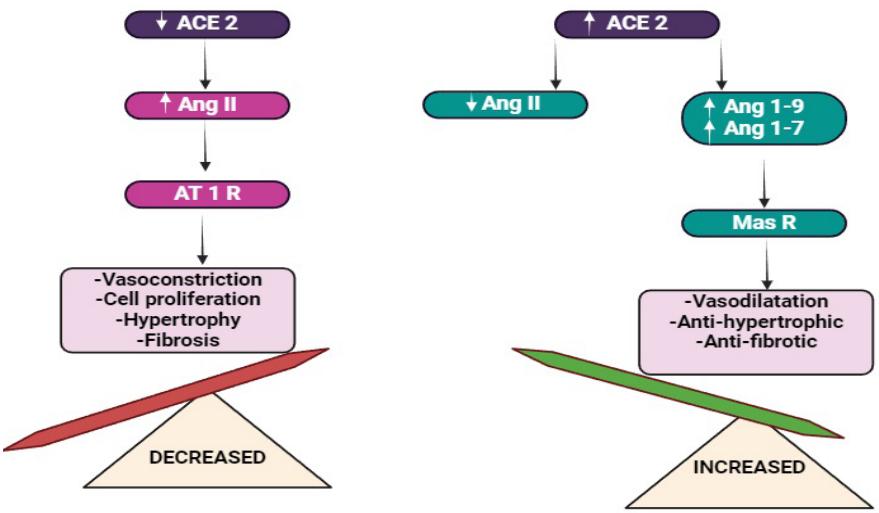

Fig. 2. ACE 2 shift paradigm. Decreased ACE 2 increases disease progression. Increased ACE 2 leads to protection from diseases

II (Ang II), thus contributing to blood pressure reduction [9, 13]; furthermore, Ang (1–7) reduces aldosterone secretion, which in turn decreases sodium and water retention, lowering blood pressure. The RAAS inhibition's impact on the renal sodium along with potassium excretion can be explained by the synergistic effects of Ang II and aldosterone on sodium along with potassium transport in distal nephron. Moreover, anti-fibrotic and anti-inflammatory effects of the Ang (1–7) reduce inflammation and fibrosis in cardiovascular system, which are pathophysiological mechanisms involved in hypertension and its complications [14] and in addition to all these mechanisms Ang (1–7) enhances endothelial function by promoting release of nitric oxide (NO), an effective endothelium-derived relaxing factor. Improved endothelial function is connected with better vasodilation and blood pressure regulation [14] Apelin, a crucial modulator of blood pressure and myocardium contractility, is one of the other vasoactive peptides that ACE 2 affects. ACE 2 mitigates myocardial remodelling and fibrosis by declining Ang II levels and rising Ang-(1–7), that acts through Mas receptor to inhibit hypertrophy and inflammation.

Given their roles in regulating blood pressure and vascular function, ACE 2 along with Ang (1–7) have therapeutic potential in hypertension management. ACE 2 Activators strategies to increase ACE 2 activity could enhance Ang II to the Ang (1–7) conversion, thus counteracting Ang II-mediated inflammation, protecting against oxidative stress along with endothelial dysfunction, shifting the balance towards vasodilation, reducing blood pressure both of which are implicated in conditions like hypertension and atherosclerosis. Ang (1–7) mimetics or Agonists can directly administer Ang (1–7) or drugs that mimic its action can be a therapeutic approach to harness its antihypertensive effects. Studies show that ACE2 prevents plaque instability by reducing inflammation in coronary vessels, offering potential therapeutic benefits for ischemic heart disease. Hence, circulating ACE2 levels may serve as biomarkers for early detection of cardiovascular dysfunctions, including heart failure and atherosclerosis.

Interestingly, Ang (1–9), a significant byproduct of ACE 2-mediated Ang I degradation, has newly demonstrated encouraging cardioprotective benefits [15] in the animal models of hypertension, myocardial infarction.

ACE 2 in pulmonary homeostasis and respiratory diseases

Over the years, the ACE2 has emerged as a critical molecular player in understanding lung physiology, inflammatory processes, and respiratory pathogenesis. The olfactory bulbs in the respiratory tract have the highest levels of ACE 2 gene expression, followed by the nasal respiratory epithelium, the bronchioles, and the alveoli. Research demonstrates that ACE2 expression in the lungs can be weakly detected at the protein level. By effects mediated through the Mas oncogene and the Ang (1–7) receptor, ACE-2 has been shown to have an established protective role in lung disease [16] Research shows that ACE2 protects against ALI (acute lung injury) and ARDS (acute respiratory distress syndrome) [17]. Experimental models of ALI demonstrate that downregulation of ACE 2 exacerbates lung damage, while its overexpression reduces oedema, inflammation, and oxidative stress. While ACE2/Ang-(1–7)/Mas axis, that inhibits the ACE/AngII/AT1R axis' activity, has been demonstrated to protect against the pulmonary fibrosis (PF), upregulation of the ACE/AngII/AngII type 1 receptor (AT1R) axis aggravates PF [17, 18]. Through balancing proapoptotic Ang II in addition to its antiapoptotic degradation product Ang 1–7 by its impact on Ang 1–7 and the MAS receptor, ACE-2 controls the survival of alveolar epithelial cells.

ACE 2 and SARS CoV infection: Ever since COVID-19 pandemic, the role of ACE2 has attracted a lot of attention and research. For virus that causes SARS CoV infections, ACE 2 serves as primary cellular receptor for the SARS-CoV-2 [19].Hence modulating ACE2/Ang (1–7) axis may have therapeutic benefits in ailment of illness.

Viral entry mechanism: The virus's spike S protein has a high affinity for ACE 2, facilitating its entry into cells (Figure 3). The interaction between the virus and ACE 2 performs a vital role in viral entry as well as subsequent infection. SARS-CoV-2's spike (S) protein

has a strong affinity for ACE 2. On host cell surface, S protein's RBD (receptor-binding domain) selectively binds with ACE 2 [20]. The SPIKE protein S is broken down into its S1, S2 subunits through host protease TMPRSS2 (transmembrane protease serine 2), this permits the virus to fuse its membrane with host cell's membrane [21].In order for the viral RNA to replicate in host cell's cytoplasm, this step is necessary.

It is demonstrated that interaction between SARS-CoV-2 and ACE 2 reduces ACE2 expression on cell surfaces. Although S2 subunit and ACE2 are responsible for membrane fusion and virus internalisation, the S1 subunit aids the virus in attaching to target cells in the epithelium. The expression of ACE 2 on the cell surface is significantly decreased when the extracellular juxta region of ACE 2 is cleaved, leading to internalisation and shedding [22, 23].The Ang II conversion into the protective Ang is slowed down by the reduction of ACE 2 expression at the cell surface brought on by ACE 2 internalisation (1–7). A rise in the Ang II to Ang (1–7) ratio exacerbates lung damage caused by SARS-CoV-2. Ang II causes tissue inflammation through the action of T-cells, mesangial cells, macrophages, dendritic cells, along with vascular smooth muscle cells. A deficit of ACE 2 has been identified in persons with several clinical disorders. Furthermore, the advancement of inflammation and thrombosis is favoured by the COVID-19 viruses binding to ACE2 receptors, membrane fusion, viral entrance into the cell, and subsequent downregulation of these receptors. This reduction in ACE2 can exacerbate imbalance among ACE/Ang II/AT1 receptor axis in addition to the ACE2/Ang (1–7)/Mas receptor axis, leading to increased inflammation, vascular permeability, and lung injury that include ARDS [24] hallmarks of severe COVID-19. Thus, interplay between ACE 2 and SARS viruses highlights its dual role in viral entry and disease progression, making it a crucial target for therapeutic interventions.

Renal functions and kidney diseases of ACE 2

Given its significant functions in RAAS balance, function of ACE2 in renal physiology and pathology has drawn interest, particularly in conditions for example CKD (chronic kidney disease), diabetic nephropathy, and hypertension-related kidney dysfunction [25]. Enzymatically ACE 2 converts Angiotensin II to the Ang (1–7) and is predominantly distributed in proximal tubular cells, glomerular endothelial cells, podocytes and

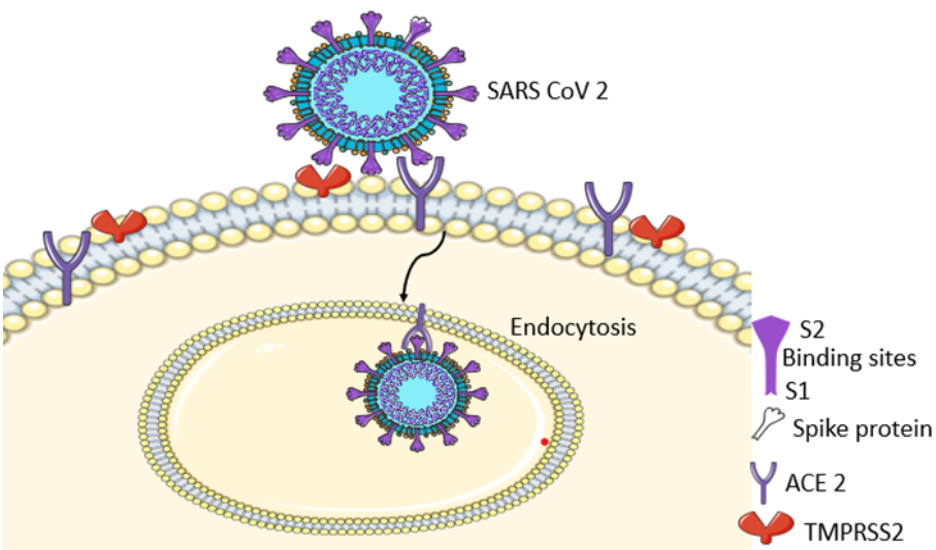

Fig. 3. Viral entry mechanism

in renal vasculature ACE 2 mitigates the impact of Ang II through reducing its concentration, thus preventing Ang II-mediated vasoconstriction of renal arterioles and promoting renal blood flow. Angiotensin-(1–7), the product of ACE2 activity, promotes natriuresis, diuresis, and vasodilation, all of which are protective for renal function [26].In renal tubular cells, ACE 2 modulates sodium and water reabsorption. This activity indirectly influences blood pressure regulation and fluid balance.

ACE 2 in Kidney Disease Pathology

Evidence shows that in healthy kidneys, high constitutive levels of ACE 2 and an increased ACE 2/ACE ratio are associated with a mechanism that is more important for breaking down Ang II than for producing it. This system is critical for maintaining the usual physiological and biological effects of Ang II [27]. The underlying causes of renal fibrosis and CKD progression are associated with abnormalities in RAAS, particularly ACE2/Ang (1–7) axis. A major contributor to the pathophysiology of CKD is ACE 2, which proposes potential therapeutic targets for condition's management and treatment. The characteristic of CKD is a steady decline in kidney function over time, which elevates blood pressure, causes waste products to build up in the body, and ultimately increases the chance of renal failure. Reduced ACE 2 expression exacerbates Ang II-mediated renal damage, contributing to inflammation, fibrosis, and glomerular hypertension. Animal studies have demonstrated that ACE 2 overexpression or supplementation with Ang-(1–7) can attenuate CKD progression [28].

Angiotensin II (Ang II), that stimulates vasoconstriction, fibrosis, inflammation, along with brine retention, is among the primary ways that the RAAS makes a contribution to CKD development [29].Angiotensin-(1–7), a product of ACE 2 (Figure 4) counteracts inflammation and fibrosis within the kidney, processes that are exacerbated by excessive Ang II activity in pathological conditions.ACE 2 functions as a counter-regulatory enzyme inside the RAAS. Through doing this, the detrimental impacts of Ang II on the kidneys are mitigated and renal function continues to improve.

Fibrosis, a condition where the kidneys' excessive connective tissue accumulates and impairs their function, is a defining feature of CKD. ACE 2 can reduce fibrosis through declining Ang II levels along with increasing Ang (1–7), that directly opposes fibrotic processes [30]. Inflammation contributes significantly to the progression of CKD. By declining Ang II levels whereas increasing Ang (1–7), ACE2 helps to dampen inflammatory responses in the kidney. Low expression of ACE2 might have contributed to the CKD progression, through

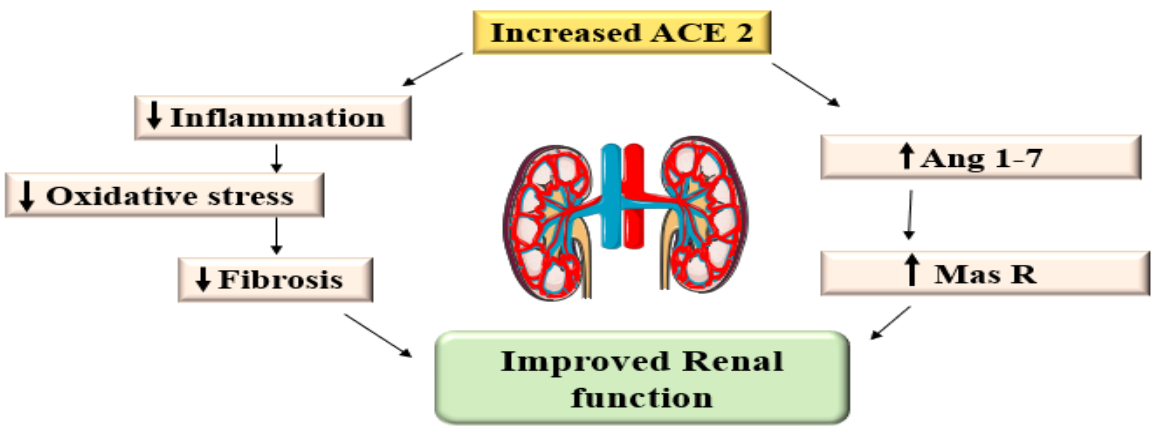

Fig. 4. Increased ACE 2's activity in renal wellness

improving early inflammation as well as contributing to the long-term fibrosis [29].High blood pressure is a cause while a consequence of the CKD. Dysregulated RAAS, with low ACE2 and high Ang II levels, made a contribution to the hypertension-induced renal injury development. ACE 2 improves kidney function by influencing glomerular hemodynamic, reducing glomerular hypertension, and thereby mitigating one of the key factors that contribute to CKD progression.

Furthermore, males had lower levels of ACE2 expression in both renal compartments than females [31]. ACE2 gene is situated on X chromosome; nonetheless, X inactivation is expected to mitigate any influence on ACE2 expression.One risk factor for CKD development is male sex. Though primarily linked to impact of the sex hormones on the kidney cells, variations in expression of ACE2 might also be partially responsible for this uneven risk [30].Acute Kidney Injury (AKI) is associated with a loss of ACE2 activity, leading to heightened Ang II activity and inflammatory responses. Experimental data suggest that restoring ACE 2 expression or activity may provide renal protection in AKI. The kidney-protective function of the ACE2/Ang (1–7)/MAS axis is supported by animal studies that demonstrate that vascular ACE 2-overexpression protects the kidney against ageing-induced decline in the kidney function [32].

ACE 2 in hormonal regulation

The ACE 2 has emerged as a crucial molecular mediator with profound implications across multiple endocrine systems. Originally characterized as a major component of the RAAS, recent research has unveiled its complex roles in hormonal regulation, metabolic homeostasis, and systemic physiology [33,34].The enzymatic activity of ACE 2 serves as a critical regulatory mechanism across multiple endocrine axes, demonstrating sophisticated molecular plasticity. Furthermore, ACE 2 performs complex interplay between hormonal systems and their variables between the individuals.

Aldosterone mechanism

Angiotensin-converting enzyme 2 has revealed complex regulatory mechanisms that significantly impact aldosterone secretion beyond traditional RAAS (renin-angiotensin-aldosterone system) paradigms. Traditionally, aldosterone secretion is mediated through: Angiotensin II (Ang II) stimulation, activation of AT1R (angiotensin II type 1 receptor), direct stimulation of zona glomerulosa cells in adrenal cortex. Whereas ACE 2 performs a critical role in modulating this classical pathway by enzymatic conversion of Ang II to the Ang (1–7), declining available Ang II for aldosterone stimulation creates a competitive inhibition and serves as a counter-regulatory mechanism. ACE 2 introduces numerous nuanced control mechanisms through Complex Regulatory Signalling. Acting as a molecular rheostat in aldosterone secretion ACE 2 provides dynamic, context-dependent regulation of zona glomerulosa cell responsiveness. Low tissue levels of the ACE-2 are not enough to generate enough Ang-(1–7) to regulate the release of cortisol and aldosterone, according to a study [35].Rodriguez, M., et al. discovered that ACE2 reduces pro-inflammatory signals in adrenal tissues thereby causing inflammatory modulation of Aldosterone secretion resulting in protective mechanisms against hyperaldosteronism [36].Precise molecular mechanisms of ACE 2 in aldosterone mechanism are currently uncertain.

Metabolic syndrome

Current investigation has offered more nuanced insights into metabolic implications of ACE2/Ang (1–7) signalling in insulin resistance. Chen et al. demonstrated that Ang (1–7) supplementation in animal models of metabolic syndrome significantly improved insulin sensitivity by enhancing mitochondrial function in adipose tissue, reduction in inflammatory markers associated with insulin resistance and modulating adipokine secretion [37].

Endocrine disruption and ACE 2 signalling

Emerging research has highlighted the vulnerability of the ACE2 axis to endocrine hormonal axis. Studies are investigating the impact of endocrine-disrupting chemicals on ACE 2 expression. Specific environmental toxins that downregulate ACE 2 activity demonstrated

potential mechanisms of hormonal axis disruption suggesting long-term metabolic consequences of chronic exposure [38].

Hypothalamus and pituitary system

Current investigations have highlighted ACE2's sophisticated interactions with the hypothalamic-pituitary system. Oliveira's animal model study demonstrates that corticotropin-releasing hormone cells exhibiting elevated ACE 2 expression were protected against hypoxia-induced pulmonary hypertension. Given that the majority of CRH expression takes place in brain nuclei for example the PVN (paraventricular nucleus of the hypothalamus) or else central nucleus of the amygdala (CeA), these findings imply that the protective effects of ACE 2 may be somewhat centrally mediated [39]. ACE 2 controls CRH (corticotropin-releasing hormone) release, that subsequently controls stress response mechanism and affects the neuroinflammatory processes in the hypothalamus. Evidences shows that increased expression of ACE 2 in the brain increases nitric oxide and antioxidant signalling, decreases oxidative stress as well as COX-mediated neuro-inflammation, slows the onset of neurogenic hypertension [40,41]. A number of investigations are currently underway to explore the molecular processes behind ACE2's potential in buffering hypothalamic inflammatory responses mediated by neuroendocrine stress adaptations.

Pancreatic Endocrine function and Insulin Resistance

Metabolic studies have revealed intricate ACE 2 connections in pancreatic endocrine regulation. ACE 2 is expressed by the islet microvasculature, pericytes, acinar, ductal, along with beta cells in the pancreas. Through essential enzymes, for example, ACE 2 and angiotensin, local RAAS in the pancreatic islet controls glucose homeostasis (1–7). Various physiological and endocrine roles of ACE 2 include upregulation of mitochondrial genes, mitochondrial metabolism in beta cells, secretion of insulin in existence of ROS, declines NADPH oxidase properties and ROS production, regulates rise in beta cell mass as well as adaptive hyperinsulinemia response to high-fat diet, enhance total insulin content in the islets, improves proliferation of beta cell along with prevents apoptosis[42,43,44]. ACE 2 /Ang (1–7)/Mas axis modulates Insulin secretion, protects from the oxidative stress thereby playing a pivotal in glucose homoeostasis [42]. Reduced ACE2 expression, which is prevalent in diabetes, increases RAAS activity and exacerbates fibrosis and inflammation [43]. A meta-analysis revealed that ACE 2 genetic variants correlate with increased risk of type 2 diabetes showing altered glucose metabolism and differential response to metabolic interventions.

Reproductive health

Preliminary studies and recent investigations have expanded our understanding of ACE2's role in reproductive physiology. ACE 2 is expressed in the testes and ovaries, and its activity influences the production of sex hormones such as testosterone and oestrogen [46,47,48,49].Decreased ACE2 expression correlates with age-related reproductive decline and also observed for potential protective mechanisms in ovarian aging and Implications of ACE 2 expression for fertility preservation strategies [48].

Growth Hormone regulation

Growth Hormone Regulation of ACE 2, while direct evidence is limited, the general influence of the RAAS on growth hormone (GH) secretion and the counter-regulatory effects of ACE 2 might suggest a role in modulating GH release.

Thyroid function and Inflammatory modulation

RAAS components, encompassing ACE2 and Ang (1–7), are expressed in thyroid gland, indicating potential roles in thyroid hormone synthesis and secretion [50]. Thyroid hormones are crucial for regulating metabolism, growth, and development. The precise impact of ACE2 and Ang (1–7) on thyroid function remains an area of active research. Advanced research has provided deeper insights into ACE2's inflammatory regulatory mechanisms. Studies demonstrate mechanistic links between RAAS components and thyroid inflammation. Study by Narayan et al examined the Thyroid tissue

ACE 2 expression and its potential utilization as a biomarker for the detection of thyroid cancer. ACE 2 were significantly increased in goitres, follicular adenomas, follicular thyroid carcinomas, papillary thyroid carcinomas, undifferentiated thyroid carcinomas [51]. ACE2 is regulated within thyroid benign and malignant tissues. The differentiation grade of thyroid cancer is correlated with increase in ACE 2. These complex mechanisms of ACE 2 suggest promising potential therapeutic implications for autoimmune thyroid diseases.

Immunomodulation

The role of ACE 2 extends by encompassing significant immunomodulatory effects. ACE 2 works on the MAS receptor, produces Ang (1–7) and declines the synthesis of pro-inflammatory cytokines and chemokines to produce anti-inflammatory effects. This modulation of the inflammatory response can be beneficial in conditions characterised by excessive inflammation [52]. ACE 2 regulates immune cell function through Ang (1–7) by modulating the function of various immune cells, that include neutrophils, macrophages, T cells. Macrophages perform a crucial role in the innate immunity, inflammation, and tissue repair. They exist in a spectrum of activation states, from pro-inflammatory (M 1) to the anti-inflammatory (M 2), depending on the cytokine environment and other signals [53]. Ang II tends to promote the M1 phenotype, which is characterized by the release of pro-inflammatory cytokines that include TNF-α, IL-6, and IL-1β, via acting on the AT1 receptor [54–56]. In contRAASt, ACE 2, has been shown to promote the M 2 phenotype [57], which is involved in tissue repair and inflammation resolution. This suggests that the balance among pro-inflammatory and anti-inflammatory macrophage phenotypes is modulated by ACE 2, thereby influencing the course of inflammatory responses. This aligns with the finding that monocyte/macrophage overreactions contribute to the hyperinflammation or cytokine storm observed in severe COVID-19 cases [58, 59].

T cells are central to adaptive immunity, with various subsets playing roles in immune regulation, cytotoxic responses, and help for B cells in antibody production. The RAAS, particularly through Ang II, has been shown to influence T cell function directly. Ang II can promote T cell proliferation and the cytokines production. ACE 2, by reducing Ang II levels, may indirectly modulate T cell responses, promoting a shift towards less inflammatory states [60].Additionally, Ang (1–7) can have direct effects on T cells, though this area requires further research to fully understand the mechanisms and implications. Key participants in the early stages of the inflammatory response are neutrophils, capable of rapid deployment to sites of infection or injury. While the direct effects of ACE 2 on neutrophils are less well characterised than those on macrophages and T cells, the overall anti-inflammatory milieu promoted by ACE 2 activity could lead to a modulatory effect on neutrophil recruitment and function [61]. For instance, reducing Ang II levels may decrease vascular permeability and adhesion molecule expression, potentially modulating neutrophil extravasation to inflamed tissues.

Beyond macrophages, T cells, and neutrophils, ACE 2 may also influence the function of other immune cells, for example, B cells, dendritic cells, along with NK (natural killer) cells [62].The overall anti-inflammatory and immunomodulatory effects of ACE 2 suggest that it could perform a role in shaping activities of an extensive variety of immune cells.

The relevance of ACE 2 in infectious diseases became prominently recognized during the COVID-19 pandemic, as ACE 2 is entry receptor for the SARS-CoV-2 [63].When SARS CoV-2 is present, the immunological responses of ACE 2 cause tissue and organ damage, coagulopathy, along with ARDS. These conditions then trigger the production of further proinflammatory cytokines and chemokines, causing an uncontrollable loop of inflammation and damage [64].While the interaction of the virus with ACE 2 can lead to downregulation of ACE 2 expression and enhanced lung injury, the immunomodulatory role of ACE 2 suggests that enhancing this pathway could potentially mitigate severe inflammatory responses associated with infections [65].

Deregulation of ACE 2 may enhance kinin activity while resulting in angioedema [66].Systemic kallikrein-kinin system activation can cause a "kinin storm," which can lead to vascular permeability, enhanced inflammation, effusion, along with eventual damage to organs [67].One of the main causes of endothelial damage, microthrombi development, and the ischemic symptoms that follow COVID-19 is RAAS dysregulation [68].

ACE2/Ang (1–7)/Mas axis may perform a role in modulating autoimmunity. Its anti-inflammatory properties suggest potential therapeutic benefits in autoimmune diseases by dampening inappropriate immune responses against self-tissues [69,70]. Through declining Ang II levels and improving Ang (1–7) levels, ACE 2 can reduce the inflammatory milieu that fosters autoimmune reactions, potentially mitigating the severity of autoimmune diseases. The exact impact of ACE 2 on specific autoimmune diseases that include, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, requires further research. However, the potential for ACE 2 to modulate immune responses suggests that enhancing ACE 2 activity or Ang (1–7) signalling could be a promising therapeutic strategy in autoimmunity.

ACE 2 in central nervous system

With all of its parts found in CNS (central nervous system), the brain has its own intrinsic RAAS [71]. Originally identified as a regulator of blood pressure along with cardiovascular homeostasis, ACE 2 also modulates brain function through its effects on neurovascular health, oxidative stress, and inflammatory pathways. The brainstem, hypothalamus, and cortex are among the areas of the brain where ACE 2 is expressed [72]. It performs a crucial role in neurovascular regulation by counteracting the effects of angiotensin II (Ang II), a peptide known for its pro-inflammatory and vasoconstrictive properties. ACE 2 boosts vasodilation, anti-inflammatory effects, along with neuroprotection by converting Ang II to angiotensin-1–7 (Figure 5) [73].

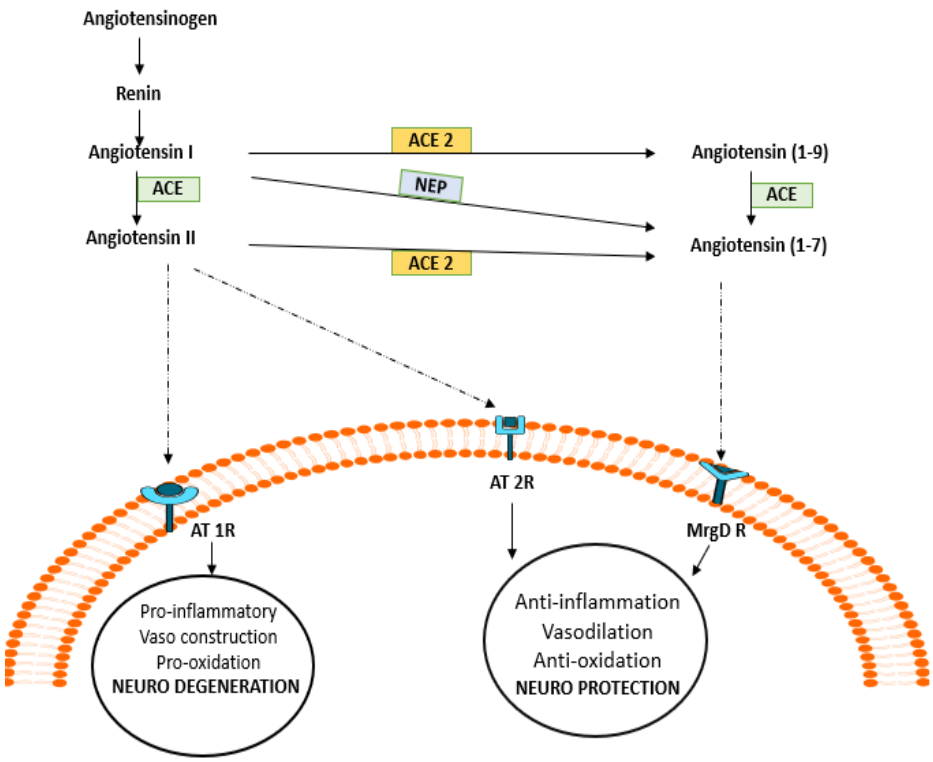

Fig. 5. Role of Renin Angiotensin System on the neurosystem

Along with these traditional RAAS pathways, few other channels are recognized that aid in the synthesis of various angiotensin and angiotensin fragments. Renin and pro-renin receptors have even been demonstrated to exhibit biological activity. In addition to Ang-(1–7), ACE 2 also generates alamandine, a peptide similar to Ang-(1–7) that selectively activates the MrgD receptor. These interactions are critical for maintaining neurovascular integrity and counteracting the detrimental impact of Ang II in the brain [74].

Neuroinflammation and oxidative stress are central to pathology of many neurodegenerative diseases (NDD), that include PD (Parkinson's disease), MS (multiple sclerosis), along with AD (Alzheimer's disease) [75]. ACE 2 reduces neuroinflammation by modulating the balance among pro-inflammatory along with anti-inflammatory pathways in the RAAS [76]. According to research on animals, ACE 2 activation can lower microglial activation and the generation of pro-inflammatory cytokines that include TNF-α, IL-6. MrgD activation decreases the pro-inflammatory cytokines production that includes, IL-6, TNF-α, whereas promoting anti-inflammatory cytokines that include IL-10. This modulation helps counteract neuroinflammatory effects of Ang II [77].

Overexpression of ACE 2 in the CNS has been shown in recent years to enhance GABA release in the presynapse, altering its neurotransmission and function to enhance mice's anxiety [78].The amygdala, paraventricular hypothalamic nucleus, nucleus of the solitary tract, along with ventrolateral medulla are among the brain regions that endogenously express both ACE 2 and MrgD (Figure 6). These regions regulate behavioral and physiological reactions to stress and anxiety [79]. The amygdala, a part of the brain that regulates the behavioural expressions of fear and anxiety, had more MasR mRNA when ACE2 was overexpression.Kehoe et al and his colleagues have found reduced ACE2 expression in brains of AD patients, causes increased Ang II activity and exacerbation of neuroinflammatory and neurotoxic pathways [78]. Angiotensin(1–7) has been shown to boost memory as well as decline amyloid-beta accumulation in the animal models of AD. On the same hand, ACE 2 protects dopaminergic neurons by reducing oxidative stress and inflammation. Studies suggest that enhancing ACE 2 activity may offer neuroprotective benefits in PD [77]. The MrgD receptor, through ACE2-derived peptides, reduces oxidative stress by enhancing antioxidant defense and lowering reactive oxygen species (ROS) levels. This mechanism is predominantly relevant in NDD for example AD and PD. In relation to ischaemic stroke, ACE2 has been extensively studied. Its activation lessens cerebral ischemia-reperfusion injury by lowering disruption of the BBB (blood-brain barrier), attenuating neuroinflammation, and triggering angiogenesis [79].

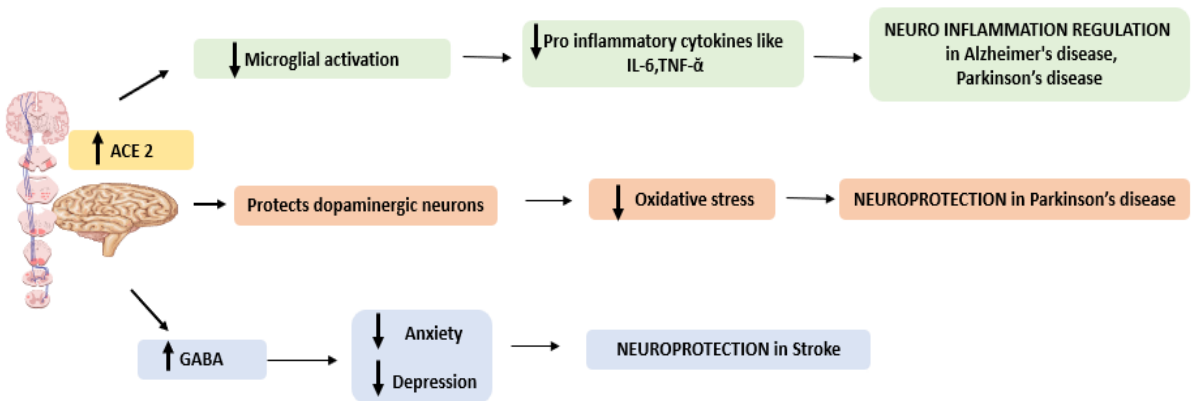

Fig. 6. Physiological process of ACE 2 -neuroprotection, neuroinflammation regulation plays an important role in AD, Parkinson's disease, stroke, anxiety and depression

ACE2 and gut

ACE2/Angiotensin-(1–7)/Mas receptor axis, as the renin–angiotensin–aldosterone system's (RAAS) non-canonical arm, plays a very important role for gastrointestinal homeostasis [80]. ACE2 controls the gut microbial balance and the nutrient absorption plus the immune responses and epithelial integrity, and ACE2 is expressed mainly on the enterocytes' luminal surface and on the intestinal epithelial cells' apical surface inside the intestinal tract. ACE2 presence within Paneth cells and within goblet cells implies secretory with immunological roles inside of the gastrointestinal tract.

ACE2 eases in a physiological way the uptake of neutral amino acids by way of transporter B^0AT1 plus particularly tryptophan (Figure 7). ACE2 greatly helps nutrient absorption within the healthy gut. Its control over the neutral amino acid transporter B^0AT1 (SLC6A19) stands out most [81]. For mucosal immunity along with gut-brain axis regulation, bioactive molecules from tryptophan metabolism are needed in epithelial regeneration. Tryptophan levels that are adequate secrete mucins with antimicrobial peptides, so they maintain intestinal epithelial defence as well as supporting gut mucosal immunity. For regulation of pancreatic insulin-producing β cells, amino acid Tryptophan activates enteroendocrine L cells so that they release GLP-1 and GIP. The GLP-1 and GIP do also inhibit glucagon-producing α cells with this having an effect upon plasma glucose levels [82, 83].

In addition, ACE2 converts pro-inflammatory angiotensin II into angiotensin-(1–7), through the Mas receptor exerting vasodilatory, anti-inflammatory, and cytoprotective effects within the gut. This conversion decreases the epithelial damage by helping tight junction protein expression and reducing intestinal permeability, thereby preserving the mucosal barrier. Angiotensin-(1–7) also promotes mucosal blood flow and attenuates the production of pro-inflammatory cytokines such as TNF-α and IL-6, while supporting the release of anti-inflammatory mediators. Through these mechanisms, the ACE2/Ang-(1–7)/Mas axis suppresses intestinal inflammation and supports tissue repair. This signalling pathway indirectly modulates the overall

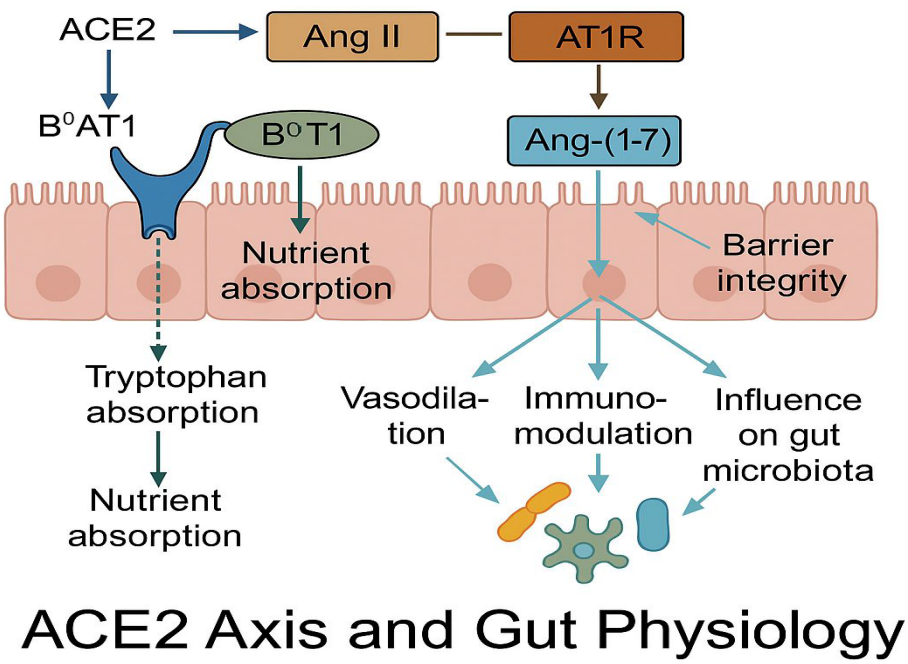

Fig. 7. ACE2 axis and gut physiology

composition and function of the gut microbiota by maintaining a favourable immune environment and controlling nutrient availability.

Reduced ACE2 expression causes dysregulation of this axis leading to excessive angiotensin II activity resulting in impaired barrier function, microbial dysbiosis, and chronic inflammation. Such disruptions have been implicated in a range of gastrointestinal disorders, including inflammatory bowel disease, ischemic colitis, and infection-associated enteropathies.

ACE2 in Gastrointestinal Disorders

Altered ACE2 expression is implicated in a spectrum of gastrointestinal diseases. In inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis [84, 85]. ACE2 dysregulation has been associated with increased inflammation and this intestinal inflammation is induced by epithelial damage disrupted barrier function, and altered cytokine profiles.

In Crohn's disease, ACE2 expression in the inflamed ileum was 60% lower than in healthy patients [86].However, colonic ACE2 expression was shown to be elevated in Crohn's disease patients. In Patients examined with inflammatory bowel disease (IBD), ACE2 and TMPRSS2 were found to be highly expressed in the ileum and colon. However, inflammation is associated with a considerable downregulation of epithelial ACE2 [86, 87].

Systemic infections like SARS-CoV-2, viral binding to the ACE2 receptor causes subsequent downregulation of ACE2 on gut epithelial surfaces. Symptoms such as diarrhoea, nausea, and intestinal inflammation have been reported during SARS CoV2 infections. These gastrointestinal symptoms were correlated with more severe pulmonary disease as patients required ventilatory support [86]. Altering ACE2 axis through genetic deletion, pharmacological inhibition, or disruptions by viral interactions such as SARS-CoV-2-mediated ACE2 internalization have been associated with increased intestinal inflammation, epithelial damage, and microbial imbalance [86].

ACE2 and the Gut Microbiome

The influence of ACE2 on the gut microbiome and metabolome profiles is now a higher concern. ACE2 regulates the microbial environment of the intestine through regulation of amino acid transport and immune mediators. Experimental models have demonstrated that ACE2 deficiency leads to microbial dysbiosis, characterized by a shift toward pathogenic species and a reduction in beneficial commensals. Studies have proved that upregulation of ACE2 may reverse these effects by improving stress state, mitochondrial dysfunction, and IRS-1/Akt/AMPK signalling [87]. Experimental study shows that ACE2 deficiency affects the microbiota and gut-vascular integrity by decreasing angiogenic bone marrow components in diabetes, perhaps inducing bacterial translocation [88].These findings collectively underscore the ACE2/Ang-(1–7)/Mas pathway as a critical regulator of gut physiology and a promising therapeutic target for inflammatory and infection-related gastrointestinal disorders.

ACE 2 in cancer biology

A growing understanding of the RAAS role in cancer biology has led to focus extensively on the role of ACE 2 in carcinogenesis. Although ACE 2 has been shown to be inhibitory, diminishing angiogenesis during tumour growth by preventing cell division and causing cell death, evidence also indicates that ACE 2 dysregulation may promote growth of tumour [89]. ACE 2 in cancer is complex and appears to be context-dependent, varying across different types of cancer. ACE 2 counter-regulates the impact of classical RAAS pathway, which is known to promote cell proliferation, angiogenesis, inflammation, and fibrosis [90].It seems that ACE 2 protects against the development of cancer; its up-regulation implies a favourable prognosis, and it is negatively linked to several important tumour development pathways, particularly proliferation and mismatch repair.

Research supporting the tumour-suppressive role of ACE 2 includes studies across several cancer types, that include lung, colorectal, breast, along with pancreatic cancers [91]. Higher expression levels of ACE 2 have

been associated with better survival outcomes in certain cancers. Conversely, a decline in ACE2 expression or activity, causing an unchecked angiotensin II signalling pathway, has been correlated with tumour growth, metastasis, and poor prognosis. Research has shown that ACE2 is down-regulated in a number of tumours, that include breast tumours [92], non-small cell lung cancer (NSCLC) [93], pancreatic ductal adenocarcinoma (PDAC) [94] along with gallbladder cancer [95]. Declined *ACE 2* expression had been also stated in Hepatocellular carcinoma.

RAAS pathway is inhibited through ACE 2 converting angiotensin II, a peptide that promotes proliferation and angiogenesis, into Ang (1–7), which has both antiproliferative and antiangiogenic properties. This switch shifts the balance from a pro-tumorigenic to a tumour-suppressive environment; Ang (1–7), a product of ACE 2 activity, inhibits cancer cell proliferation via the Mas receptor. This signalling pathway can promote apoptosis- programmed cell death, cause cell cycle arrest, and limit cancer cell proliferation, all of which contribute to tumour suppression [96].

Angiogenic factors often mediate tumour angiogenesis. ACE 2 also inhibits angiogenesis, that is new blood vessel formation, that tumours need for oxygen and nutrients to grow and metastasize [97]. The VEGFa/VEGFR2/ERK pathway may be involved in the mechanism through which ACE 2 inhibits the angiogenesis of cancer. By preventing phosphorylation of ERK1/2, ACE 2 reduces the production of VEGFa in the cancer cells, indicating that ERK signaling pathway controlled by ACE 2 was involved in the regulation of VEGFa [97]. It was established by research that VEGFa in tumour cells would attach to VEGFR2 on the nearby endothelial cells' membrane. This speeds up the phosphorylation and activation of VEGFR2, which in turn causes the ERK signaling pathway to becoming phosphorylated and activated. Following this, MEK1/2 is phosphorylated and activated by a cascade reaction from the ERK pathway, which in turn promotes phosphorylation and activation of ERK1/2. Consequently, nuclear translocation speeds up migration, differentiation, and proliferation, all of which support angiogenesis [98]. By limiting angiogenesis, ACE 2 activity can restrict tumour growth and spread. Through its anti-inflammatory and immunomodulatory effects, ACE 2/ang (1–7) axis might create a less favourable environment for tumour progression.

Beyond direct effects on tumour cells, ACE 2 also influences the tumour microenvironment, which includes extracellular matrix, immune cells, along with signalling molecules [99].The TME (tumour microenvironment), which affects growth, metastasis, along with response to treatment, is an essential factor in progression of cancer. It consists of various components, including stromal cells, cancer cells, signalling molecules, immune cells, n addition with extracellular matrix. Nature of ACE 2 influence is influenced by the specific tumour type and the balance of the RAAS components within tumour microenvironment [100, 101].

Understanding ACE 2's role in the TME involves examining its effects on cellular signalling, inflammation, angiogenesis, and the interplay between different cells within the tumour and its surroundings. ACE 2 influences the balance of angiotensin peptides in the TME, which can modulate inflammation — a key driver of tumour progression. ACE 2 acts by effect decreasing Ang II levels, thereby potentially limiting angiogenesis within the TME.

Several cancers, that include NSCLC, PDAC, clear cell renal carcinomas, thyroid carcinomas, colorectal adenocarcinoma, gastric adenocarcinoma, Oral Squamous cell carcinoma [102] shows decreased expression of ACE 2. This implies low levels of ACE 2 as the cancer progresses. In contrast, RT-PCR research revealed higher ACE2 mRNA expression levels in OSCC samples. These findings point to probable post-transcriptional regulation, protein degradation, or translational inhibitory mechanisms impacting ACE2 in oral squamous cell cancer.Invitro studies have shown that increased expression of ACE 2 may potentially suppress angiogenesis and invasion over the progression of cancer [103, 104].

Modulating ACE 2 activity levels could provide novel approaches for inhibiting tumour growth, reducing metastasis, and enhancing anti-tumour immunity [104]. However, developing such therapies

requires a nuanced understanding of the ACE 2 diverse roles in different cancers and their complexity.

ACE2 in ocular physiology

RAS components including ACE, ACE2 and Ang 1–7 has been shown to have significant levels of in several structures of the eye. Two key enzymes ACE and ACE2 being hot spots [105] in the renin-angiotensin system are highly expressed in epidermal basal cells and also detected in suprabasal and granular cells of the human aqueous humor [106]. ACE2 expression has also been detected in conjunctival cells and pterygium [107], an overgrowth of the subconjunctival tissue onto the corneal epithelium, multiple nonvascular neuroretinal cells, including the retinal ganglion cell layer, inner plexiform layer, inner nuclear layer, and photoreceptor outer segments in both nondiabetic and diabetic retinopathy specimens [108]. Ang II and ACE2 have been identified in both human limbal and corneal tissues. ACE2 being expressed in multiple ocular tissues, including the cornea, conjunctiva, aqueous humor, retina, and choroid, it plays a pivotal role in maintaining ocular homeostasis.

ACE2 in the anterior segment of the eye impacts aqueous humor dynamics and trabecular meshwork function, which has an effect on regulating intraocular pressure and protects against glaucomatous damage. In the posterior segment, ACE2 is highly expressed in retinal pigment epithelial (RPE) cells, Müller glia, and vascular endothelial cells. ACE/Ang II arm of the RAS system has been identified as the pro-inflammatory, pro-proliferative and pro-fibrotic axis in ocular physiology whereas ACE2/Ang 1–7 acts as counter-regulatory role as the anti-inflammatory, anti-proliferative and anti-fibrotic arm [109].Hence, the ACE2/Ang-(1–7)/Mas receptor axis modulates intraocular pressure, retinal blood flow, oxidative stress, and inflammatory signalling, thereby contributing to the preservation of visual function.

ACE2 plays regulatory role by regulating inflammation in varied ocular tissues. These anti-inflammatory effects of ACE2 are associated with the inhibition of MAPK, NF-κB and STAT3 pathways. An animal study by Wang et al shows that loss of ACE2 in the mouse cornea delayed the healing of corneal epithelial and the study suggest that ACE2/Ang1–7 axis has a translational potential in corneal re-epithelialization and also in preventing fibrosis [110]. Recent studies have proven that imbalance in Ang II/ACE2, might lead to increased inflammatory response in corneal epithelial and stromal tissues. Decreased ACE2 increases Ang II levels that leads to anti-fibrotic function in the cornea. Evidence shows that reduction in ACE2 levels causes also cloudy corneal haze which is accompanied by chronic inflammation, corneal edema and neovascularization.

Intraocular Pressure and ACE2

Studies have shown that intraocular RAS is involved in the regulation of intraocular pressure (IOP). In a study where the intrinsic ACE2 is pharmacologically activated has significantly decreased the Intraocular Pressure in glaucomatous rats. Hence, activation of intrinsic ACE2 may act as a potential therapeutic strategy to treat glaucoma [111].

Diabetic retinopathy

Increased activity of the ACE/ (Ang II)/AT1 receptor axis of the renin–angiotensin system (RAS) is associated with the pathogenesis of diabetic retinopathy. Studies have evaluated the retinal RAS gene expression in diabetic retinopathy shows decreased ACE2 expression that resulted in worsened pathophysiology of Diabetic Retinopathy. A study by Verma and colleagues [112] on rodent models showed that intravitreal administration of adeno-associated virus (AAV)- mediated gene transfer vector expressing ACE2 or Ang-1–7 peptide in the retina reduced diabetes-induced retinal pathophysiology.

Age-related macular degeneration

In an in vitro model study by Fu et al, overexpression of ACE2 reduces the inflammatory response in age-related macular degeneration (AMD) via inhibiting overproduction of cytokines such as IL-1β and CCL-2. By stimulating the ACE2/Ang-(1–7)/Mas axis in human RPE cells, overexpression of ACE2 reduces the inflammatory response brought on by Aβ [113].

All together ACE2 serves as a critical regulator of ocular vascular tone, neuroprotection, and anti-inflammatory signalling [120].And thus, targeting modulation of the ACE2/Ang-(1–7)/Mas axis represents a promising target for managing ocular pathologies ranging from glaucoma and diabetic retinopathy to viral conjunctivitis and AMD.

ACE2 in skin physiology

Angiotensin-converting enzyme 2 (ACE2) is an integral component of the cutaneous renin–angiotensin system (RAS) is expressed in several cells of the skin in keratinocytes, endothelial cells, fibroblasts, hair follicles, immune cells, lymphatic endothelial cells, melanocytes, and sweat gland cells. Hamming et al. [114] first showed the presence of ACE2 using immunohistochemistry staining in the skin, particularly in the basal cell layer of the epidermis extending to the basal cell layer of hair follicles. Smooth muscle cells surrounding sebaceous glands also shows positive forACE2 staining. ACE2 was weakly observed in sebaceous glands. The eccrine glands exhibit strong granular staining pattern for ACE2.

Functionally, ACE2 plays a significant role in modulating oxidative stress, inflammation, collagen degradation, and overall skin damage. ACE2 prevents oxidative stress by converting Ang II into Ang-(1–7). ACE2 reduces inflammatory mediators by downregulating Ang II by activating AT1 receptor. And also, ACE2 inhibits the matrix metalloproteinases (MMPs) activity through Ang-(1–7), and reducing collagen degradation [115].ACE2 also functions as a mechanosensitive protein.

Divergent ACE2 expression and activity has been associated with various dermatological pathologies. ACE2 protein expression was substantially upregulated in the epidermis of psoriasis lesions, especially in basal keratinocytes [116]. Increased *ACE2* expression in skin plaques was identified in psoriasis patients due to IL-17-mediated inflammation. In fibrotic conditions, including systemic sclerosis and keloids, impaired ACE2 signalling may promote fibroblast overactivation and excessive extracellular matrix deposition. Alterations in ACE2 protein affects skin soft tissue expansion, by changing cutaneous Ang II metabolism resulting from ACE2 modulation influence cellular function [117].

COVID skin manifestations

Cutaneous manifestations were increasingly observed during COVID-19. These cutaneous reactions may arise from both direct viral effects via ACE2-expressing epidermal keratinocytes, dermal vascular endothelial cells, and eccrine glands, as well as from indirect immune-mediated and microvascular injury mechanisms. They include upregulated innate immune human response, hypercoagulable state, and non- structural proteins in SARS-CoV-2 [118].They were presented as different dermatologic manifestations, which are maculopapular rash, papulovesicular rash, and livedo reticularis. Asymmetrical lesions like pernio-like (chilblain-like) acral lesions, often associated with microangiopathy and type I interferon responses; vesicular eruptions resembling varicella, suggestive of viral cytopathic activity; maculopapular (morbilliform) rashes linked to cytokine-mediated inflammation; and urticarial lesions driven by mast cell activation [119] were presented in many cases.

Emerging evidence shows ACE2 modulation to pigmentary changes through RAS-mediated effects on melanocyte biology. Studies suggests suggest that ACE2 activators, Ang-(1–7) analogs, or Mas receptor agonists may influence inflammation, accelerate wound closure, and reduce dermal fibrosis. However, experimental and clinical validation is required for targeting ACE2 axis in management of skin diseases.

Future perspectives

The outbreak of COVID-19 further expanded interest in ACE 2, for its potential as therapeutics. Hence this has fuelled the novel ACE2-based therapeutic strategies development, not only for viral infections but also for a range of cardiovascular, pulmonary, renal, cancer, and metabolic disorders.

a) Recombinant human ACE 2 (rhACE2) has been investigated as a treatment for cardiac disease, ARDS, ALI, and COVID-19. It reduces viral entry and restores RAAS balance by serving as an intermediary receptor

for SARS-CoV-2. Recombinant ACE 2 have shown several positive effects, including reversing pathological hypertrophy, improving endothelial dysfunction, reducing tissue inflammation and myocardial fibrosis, and correcting metabolic dysfunction. Recombinant human ACE 2 effectiveness in various disorders is being assessed in ongoing animal studies and clinical trials.

b) Synthetic novel compounds known as ACE 2 peptidomimetics mimic the structure and activity of Angiotensin Converting Enzyme 2. These compounds are being investigated for their potential in pulmonary hypertension, heart failure, hypertension, and SARS-CoV virus entry inhibitors.

c) Gene therapy-based approaches are gaining attention as innovative strategies to restore ACE 2 function in various diseases. This method involves the introduction of a functional ACE 2 gene into target cells to restore its protective effects. These techniques aim to either upregulate ACE 2 expression or deliver functional ACE 2 to counteract pathological conditions such as hypertension, heart failure, ARDS, and COVID-19 related complications.

d) mRNA-based strategies involve delivering synthetic mRNA encoding ACE 2 to cells, allowing temporary but effective expression of functional ACE 2. This strategy has gained momentum due to the success of mRNA vaccines in COVID-19. Lipid nanoparticles (LNPs), polymeric nanoparticles, and exosome-based delivery methods are some of the effective ways to deliver mRNA-based ACE 2.

ACE 2-based strategies have limitations despite their potential for treatment. These include the short half-life of recombinant ACE 2, which necessitates frequent administration, the possibility of off-target effects and immune reactions, the difficulty of efficiently delivering ACE 2-based gene therapies, and anticipates about viral mutations that could reduce the effectiveness of ACE 2-targeting treatments.

Conclusion

The review summarises recent discoveries on ACE 2 function and pathogenesis in diverse illnesses. ACE 2 is a double-edged sword, acting as both a preventive factor in different diseases and a receptor for viral infections, prompting researchers to investigate its eccentric role. Besides, this overview looked into ACE 2's therapeutic potential and research possibilities. Future research should focus on improving drug delivery strategies, developing long-lasting ACE2 activators, and exploring combination therapy for increased efficacy.

References/Список литературы

1. Mizuiri S, Ohashi Y. ACE and ACE2 in kidney disease. *World J Nephrol*. 2015;4(1):74–82. doi:10.5527/wjn.v4.i1.74
2. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A novel Angiotensin-Converting Enzyme–Related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1–9. *Circulation Research*. 2000;87(5): E1–9. doi:10.1161/01.res.87.5.e1
3. Ferreira AJ, Shenoy V, Yamazato Y. Evidence for angiotensin-converting enzyme 2 as a therapeutic target for the prevention of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179(11):1048–1054. doi:10.1164/rccm.200811-1678OC
4. Wiese O, Zemlin AE, Pillay TS. Molecules in pathogenesis: angiotensin converting enzyme 2 (ACE2). *J Clin Pathol*. 2021;74(5):285–290. doi:10.1136/jclinpath-2020-206954
5. Devaux CA, Camoin-Jau L. An update on angiotensin-converting enzyme 2 structure/functions, polymorphism, and duplicitous nature in the pathophysiology of coronavirus disease 2019: Implications for vascular and coagulation disease associated with severe acute respiratory syndrome coronavirus infection. *Frontiers in Microbiology*. 2022;13:1042200. doi:10.3389/fmicb.2022.1042200
6. Varagic J, Ahmad S, Nagata S, Ferrario CM. ACE2: Angiotensin II/Angiotensin-(1–7) balance in cardiac and renal injury. *Current Hypertension Reports*. 2014;16(3):420. doi:10.1007/s11906–014–0420–5
7. Magazine R, Chogtu B, Bhat A. Role of Angiotensin Converting Enzyme-2 and its modulation in disease: exploring new frontiers. *Medicine and Pharmacy Reports*. 2023;96(2):146–153. doi:10.15386/mpr-2345
8. Kazemi-Bajestani SMR, Patel VB, Wang W, Oudit GY. Targeting the ACE2 and Apelin pathways are novel therapies for heart failure: Opportunities and challenges. *Cardiology Research and Practice*. 2012;2012:1–11. doi:10.1155/2012/823193
9. Sevá Pessôa B, van der Lubbe N, Verdonk K, Roks AJ, Hoorn EJ, Danser AH. Key developments in renin-angiotensin-aldosterone system inhibition. *Nat Rev Nephrol*. 2013;9(1):26–36. doi:10.1038/nrneph.2012.249
10. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/Angiotensin 1–7 Axis of the Renin-Angiotensin System in Heart Failure. *Circ Res*. 2016;118(8):1313–1326. doi:10.1161/CIRCRESAHA.116.307708
11. Santos RA, Ferreira AJ. Angiotensin-(1–7) and the renin-angiotensin system. *Curr Opin Nephrol Hypertens*. 2007;16(2):122–128. doi:10.1097/MNH.0b013e328031f362
12. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin-Converting enzyme 2: SARS-COV-2 receptor and regulator of the Renin-Angiotensin system. *Circulation Research*.2020;126(10):1456–1474. doi:10.1161/circresaha.120.317015
13. Kuriakose J, Montezano AC, Touyz RM. ACE2/Ang-(1–7)/Mas1 axis and the vascular system: vasoprotection to COVID-19-associated vascular disease. *Clinical Science*. 2021;135(2):387–407. doi:10.1042/cs20200480
14. Norambuena-Soto I, Lopez-Crisosto C, Martinez-Bilbao J, Hernandez-Fuentes C, Parra V, Lavandero S, Chiong M. Angiotensin-(1–9) in hypertension. *Biochemical Pharmacology*. 2022;203:115183. doi:10.1016/j.bcp.2022.115183

15. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436(7047):112–116. doi:10.1038/nature03712

16. Morganstein T, Haidar Z, Trivlidis J, Azuelos I, Huang MJ, Eidelman DH, Baglole CJ. Involvement of the ACE2/ANG-(1–7)/MASR axis in pulmonary fibrosis: Implications for COVID-19. *International Journal of Molecular Sciences*. 2021;22(23):12955. doi:10.3390/ijms222312955

17. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *European Journal of Clinical Microbiology & Infectious Diseases*. 2021;40(5):905–919. doi:10.1007/s10096–020–04138–6

18. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *Journal of Virology*. 2020;94(7). doi:10.1128/jvi.00127-20

19. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426(6965):450–454. doi:10.1038/nature02145

20. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*. 2020;395(10224):565–574. doi:10.1016/s0140-6736 (20) 30251–8

21. Sun G, Xue L, He Q, Zhao Y, Xu W, Wang Z. Structural insights into SARS-CoV-2 infection and therapeutics development. *Stem Cell Research*. 2021;52:102219. doi:10.1016/j.scr.2021.102219

22. Suh SH, Kwon S MA, Kim SW, Bae EH. Angiotensin-converting enzyme 2 and kidney diseases in the era of coronavirus disease 2019. *The Korean Journal of Internal Medicine*. 2020;36(2):247–262. doi:10.3904/kjim.2020.355

23. Williams VR, Scholey JW. Angiotensin-converting enzyme 2 and renal disease. *Current Opinion in Nephrology & Hypertension*. 2017;27(1):35–41. doi:10.1097/mnh.0000000000000378

24. Sun X, Wang M, Xu C, Wang S, Li L, Zou S, Yu J, Wei Y. Positive effect of a Pea–Clam Two-Peptide composite on hypertension and organ protection in spontaneously hypertensive rats. *Nutrients*. 2022;14(19):4069. doi:10.3390/nu14194069

25. Sanad AM, Qadri F, Popova E, Rodrigues AF, Heinbokel T, Quach S, Schulz A, Bachmann S, Kreutz R, Alenina N, Bader M. Transgenic angiotensin-converting enzyme 2 overexpression in the rat vasculature protects kidneys from ageing-induced injury. *Kidney International*. 2023;104(2):293–304. doi:10.1016/j.kint.2023.04.007

26. Maksimowski N, Williams VR, Scholey JW. Kidney ACE2 expression: Implications for chronic kidney disease. *PLoS ONE*. 2020;15(10): e0241534. doi:10.1371/journal.pone.0241534

27. Bosso M, Thanaraj TA, Abu-Farha M, Alanbaei M, Abubaker J, Al-Mulla F. The two faces of ACE2: the role of ACE2 receptor and its polymorphisms in hypertension and COVID-19. *Molecular Therapy — Methods & Clinical Development*. 2020;18:321–327. doi:10.1016/j.omtm.2020.06.017

28. Komatsu T, Suzuki Y, Imai J, Sugano S, Hida M, Tanigami A, Muroi S, Yamada Y, Hanaoka K. Molecular cloning, mRNA expression and chromosomal localization of mouse angiotensin-converting enzyme-related carboxypeptidase (MACE2). *DNA Sequence*. 2002;13(4):217–220. doi:10.1080/1042517021000021608

29. McClements L, Kautzky-Willer A, Kararigas G, Ahmed SB, Stallone JN. The role of sex differences in cardiovascular, metabolic, and immune functions in health and disease: a review for "Sex Differences in Health Awareness Day." *Biology of Sex Differences*. 2025;16(1):33. doi:10.1186/s13293-025-00714-7

30. Zheng J, Hao H. Targeting renal damage: The ACE2/Ang-(1–7)/mas axis in chronic kidney disease. *Cellular Signalling*. 2024;124:111413. doi:10.1016/j.cellsig.2024.111413

31. Young MJ, Clyne CD, Chapman KE. Endocrine aspects of ACE2 regulation: RAAS, steroid hormones and SARS-CoV-2. *Journal of Endocrinology*. 2020;247(2): R45-R62. doi:10.1530/joe-20-0260

32. Caroccia B, Vanderriele PE, Seccia TM, Piazza M, Lenzini L, Prisco S, Torresan F, Domenig O, Iacobone M, Poglitsch M, Rossi GP. Aldosterone and cortisol synthesis regulation by angiotensin-(1–7) and angiotensin-converting enzyme 2 in the human adrenal cortex. *Journal of Hypertension*. 2021;39(8):1577–1585. doi:10.1097/hjh.0000000000002816

33. Acevedo-Rodriguez A, Kauffman AS, Cherrington BD, Borges CS, Roepke TA, Laconi M. Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. *Journal of Neuroendocrinology*. 2018;30(10): e12590. doi:10.1111/jne.12590

34. Chen F, Chen Y, Ke Q, Wang Y, Gong Z, Chen X, Cai Y, Li S, Sun Y, Peng X, Ji Y, Zhang T, Wu W, Cui L, Wang Y. ApoE4 associated with severe COVID-19 outcomes via downregulation of ACE2 and imbalanced RAS pathway. *Journal of Translational Medicine*. 2023;21(1):103. doi:10.1186/s12967-023-03945-7

35. Rath S, Perikala V, Jena AB, Dandapat J. Factors regulating dynamics of angiotensin-converting enzyme-2 (ACE2), the gateway of SARS-CoV-2: Epigenetic modifications and therapeutic interventions by epidrugs. *Biomedicine & Pharmacotherapy*. 2021;143:112095. doi:10.1016/j.biopha.2021.112095

36. Oliveira AC, Karas MM, Alves M, He J, De Kloet AD, Krause EG, Richards EM, Bryant AJ, Raizada MK. ACE2 overexpression in corticotropin-releasing-hormone cells offers protection against pulmonary hypertension. *Frontiers in Neuroscience*. 2023;17:1223733. doi:10.3389/fnins.2023.1223733

37. Sriramula S, Xia H, Xu P, Lazartigues E. Brain-targeted angiotensin-converting enzyme 2 overexpression attenuates neurogenic hypertension by inhibiting cyclooxygenase-mediated inflammation. *Hypertension*. 2015;65(3):577–586. doi:10.1161/HYPERTENSIONAHA.114.04691

38. Li J, Kong X, Liu T, Xian M, Wei J. The role of ACE2 in neurological disorders: From underlying mechanisms to the neurological impact of COVID-19. *International Journal of Molecular Sciences*. 2024;25(18):9960. doi:10.3390/ijms25189960

39. Memon B, Abdelalim EM. ACE2 function in the pancreatic islet: Implications for relationship between SARS-CoV-2 and diabetes. *Acta Physiol (Oxf)*. 2021;233(4): e13733. doi:10.1111/apha.13733

40. Wang L, Liang J, Leung PS. The ACE2/ANG-(1–7)/MAS axis regulates the development of pancreatic endocrine cells in mouse embryos. *PLoS ONE*. 2015;10(6): e0128216. doi:10.1371/journal.pone.0128216

41. Shoemaker R, Yiannikouris F, Thatcher S, Cassis L. ACE2 deficiency reduces β-cell mass and impairs β-cell proliferation in obese C57BL/6 mice. *Am J Physiol Endocrinol Metab*. 2015;309(7): E621-E631. doi:10.1152/ajpendo.00054.2015

42. Shukla AK, Awasthi K, Usman K, Banerjee M. Role of renin-angiotensin system/angiotensin converting enzyme-2 mechanism and enhanced COVID-19 susceptibility in type 2 diabetes mellitus. *World J Diabetes*. 2024;15(4):606–622. doi:10.4239/wjd.v15.i4.606

43. Mukherjee A, Wanjari U, Gopalakrishnan A, Kannampuzha S, Murali R, Namachivayam A, Ganesan R, Renu K, Dey A, Vellingiri B, Prabakaran D. Insights into the Scenario of SARS-CoV-2 Infection in Male Reproductive Toxicity. *Vaccines*. 2023;11(3):510. doi:10.3390/vaccines11030510

44. Achua JK, Chu KY, Ibrahim E, Khodamoradi K, Delma KS, Iakymenko OA, Kryvenko ON, Arora H, Ramasamy R. Histopathology and ultrastructural findings of fatal COVID-19 infections on testis. *The World Journal of Men S Health*. 2020;39(1):65. doi:10.5534/wjmh.200170

45. Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, Fei C. Potential influence of COVID-19/ACE2 on the female reproductive system. *Molecular Human Reproduction*. 2020;26(6):367–373. doi:10.1093/molehr/gaaa030

46. Zafari Zangeneh F. Interaction of SARS-CoV-2 With RAS/ACE2 in the Female Reproductive System. *J Family Reprod Health*. 2022;16(1):1–8. doi:10.18502/jfrh.v16i1.8588

47. Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST, Villani L, Magri F, Latrofa F, Chiovato L. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. *Journal of Endocrinological Investigation*. 2020;44(5):1085–1090. doi:10.1007/s40618-020-01436-w

48. Narayan SS, Lorenz K, Ukkat J, Hoang-Vu C, Trojanowicz B. Angiotensin converting enzymes ACE and ACE2 in thyroid cancer progression. *Neoplasma*. 2020;67(2):402–409. doi:10.4149/neo_2019_190506N405

49. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. *EMBO Mol Med*. 2010;2(7):247–257. doi:10.1002/emmm.201000080

50. Binesh A, Devaraj SN, Devaraj H. Expression of chemokines in macrophage polarization and downregulation of NFκB in aorta allow macrophage polarization by diosgenin in atherosclerosis. *J Biochem Mol Toxicol*. 2020;34(2):e22422. doi:10.1002/jbt.22422

51. Cortez-Retamozo V, Etzrodt M, Newton A, Ryan R, Pucci F, Sio SW, Kuswanto W, Rauch PJ, Chudnovskiy A, Iwamoto Y, Kohler R, Marinelli B, Gorbatov R, Wojtkiewicz G, Panizzi P, Mino-Kenudson M, Forghani R, Figueiredo JL, Chen JW, Xavier R, Swirski FK, Nahrendorf M, Weissleder R, Pittet MJ. Angiotensin II drives the production of Tumor-Promoting macrophages. *Immunity*. 2013;38(2):296–308. doi:10.1016/j.immuni.2012.10.015

52. Zhou S, Lu H, Chen R, Tian Y, Jiang Y, Zhang S, Ni D, Su Z, Shao X. Angiotensin II enhances the acetylation and release of HMGB1 in RAW264.7 macrophage. *Cell Biology International*. 2018;42(9):1160–1169. doi:10.1002/cbin.10984

53. Yunna C, Mengru H, Lei W, Weidong C. Macrophage M1/M2 polarization. *European Journal of Pharmacology*. 2020;877:173090. doi:10.1016/j.ejphar.2020.173090

54. Song X, Hu W, Yu H, Zhao L, Zhao Y, Zhao Y, Zhao X, Xue H, Zhao Y, Zhao Y. Little to no expression of angiotensin-converting enzyme-2 on most human peripheral blood immune cells but highly expressed on tissue macrophages. *Cytometry Part A*. 2020;103(2):136–145. doi:10.1002/cyto.a.24285

55. Jafarzadeh A, Chauhan P, Saha B, Jafarzadeh S, Nemati M. Contribution of monocytes and macrophages to the local tissue inflammation and cytokine storm in COVID-19: Lessons from SARS and MERS, and potential therapeutic interventions. *Life Sci*. 2020;257:118102. doi:10.1016/j.lfs.2020.118102

56. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. *The Journal of Experimental Medicine*. 2020;217(6). doi:10.1084/jem.20200678

57. Welch JL, Xiang J, Chang Q, Houtman JCD, Stapleton JT. T-Cell Expression of Angiotensin-Converting Enzyme 2 and Binding of Severe Acute Respiratory Coronavirus 2. *J Infect Dis*. 2022;225(5):810–819. doi:10.1093/infdis/jiab595

58. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clinical Infectious Diseases*. 2020;71(15):762–768. doi:10.1093/cid/ciaa248

59. Bhari VK, Kumar D, Kumar S, Mishra R. SARS-CoV-2 cell receptor gene ACE2 -mediated immunomodulation in breast cancer subtypes. *Biochemistry and Biophysics Reports*. 2020;24:100844. doi:10.1016/j.bbrep.2020.100844

60. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *European Journal of Clinical Microbiology & Infectious Diseases*. 2021;40(5):905–919. doi:10.1007/s10096–020–04138–6

61. Song Y, Myers R, Mehl F, Murphy L, Brooks B, Wilson JM, Kadl A, Woodfolk J, Zeichner SL. ACE-2-like enzymatic activity is associated with immunoglobulin in COVID-19 patients. *mBio*. 2024;15(4): e0054124. doi:10.1128/mbio.00541-24

62. Merad M, Blish CA, Sallusto F, Iwasaki A. The immunology and immunopathology of COVID-19. *Science*. 2022;375(6585):1122–1127. doi:10.1126/science.abm8108

63. Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I. COVID-19 cytokine storm: The anger of inflammation. *Cytokine*. 2020;133:155151. doi:10.1016/j.cyto.2020.155151

64. Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. *eLife*. 2020;9. doi:10.7554/elife.59177

65. Alabsi S, Dhole A, Hozayen S, Chapman SA. Angiotensin-Converting enzyme 2 Expression and severity of SARS-COV-2 infection. *Microorganisms*. 2023;11(3):612. doi:10.3390/microorganisms11030612

66. McMillan P, Dexhiemer T, Neubig RR, Uhal BD. COVID-19—A theory of autoimmunity against ACE-2 explained. *Frontiers in Immunology*. 2021;12:582166. doi:10.3389/fimmu.2021.582166

67. Mohammed M, Berdasco C, Lazartigues E. Brain angiotensin converting enzyme-2 in central cardiovascular regulation. *Clinical Science*. 2020;134(19):2535–2547. doi:10.1042/cs20200483

68. Cui H, Su S, Cao Y, Ma C, Qiu W. The altered anatomical distribution of ACE2 in the brain with Alzheimer's disease pathology. *Frontiers in Cell and Developmental Biology*. 2021;9:684874. doi:10.3389/fcell.2021.684874

69. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. *Journal of Biological Chemistry*. 2000;275(43):33238–33243. doi:10.1074/jbc.m002615200

70. Pop D, Dădârlat-Pop A, Tomoaia R, Zdrenghea D, Caloian B. Updates on the Renin–Angiotensin–Aldosterone system and the cardiovascular continuum. *Biomedicines*. 2024;12(7):1582. doi:10.3390/biomedicines12071582

71. Li J, Kong X, Liu T, Xian M, Wei J. The role of ACE2 in neurological disorders: From underlying mechanisms to the neurological impact of COVID-19. *International Journal of Molecular Sciences*. 2024;25(18):9960. doi:10.3390/ijms25189960

72. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. *Journal of Neurochemistry*. 2008;107(6):1482–1494. doi:10.1111/j.1471-4159.2008.05723.x

73. Labandeira-Garcia JL, Rodríguez-Perez AI, Garrido-Gil P, Rodriguez-Pallares J, Lanciego JL, Guerra MJ. Brain Renin-Angiotensin system and microglial polarization: Implications for aging and neurodegeneration. *Frontiers in Aging Neuroscience*. 2017;9:129. doi:10.3389/fnagi.2017.00129

74. Chen Q, Gao Y, Yang F, Deng H, Wang Y, Yuan L. Angiotensin-converting enzyme 2 improves hepatic insulin resistance by regulating GABAergic signaling in the liver. *Journal of Biological Chemistry*. 2022;298(12):102603. doi:10.1016/j.jbc.2022.102603

75. Becker ES, Rinck M, Türke V, Kause P, Goodwin R, Neumer S, Margraf J. Epidemiology of specific phobia subtypes: Findings from the Dresden Mental Health Study. *European Psychiatry*. 2006;22(2):69–74. doi:10.1016/j.eurpsy.2006.09.006

76. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2006;292(1):R373-R381. doi:10.1152/ajpregu.00292.2006

77. Kim JE, Dager SR, Lyoo IK. The role of the amygdala in the pathophysiology of panic disorder: evidence from neuroimaging studies. *Biology of Mood & Anxiety Disorders*. 2012;2(1):20. doi:10.1186/2045–5380–2–20

78. Kehoe PG, Passmore PA. The Renin-Angiotensin system and antihypertensive drugs in Alzheimer's disease: Current standing of the angiotensin hypothesis? *Journal of Alzheimer S Disease*. 2012;30(s2):S251-S268. doi:10.3233/jad-2012-111376

79. Barzegar M, Stokes KY, Chernyshev O, Kelley RE, Alexander JS. The role of the ACE2/MASR axis in Ischemic Stroke: New insights for therapy. *Biomedicines*. 2021;9(11):1667. doi:10.3390/biomedicines9111667

80. Penninger JM, Grant MB, Sung JJY. The role of angiotensin converting enzyme 2 in modulating gut microbiota, intestinal inflammation, and coronavirus infection. *Gastroenterology*. 2020;160(1):39–46. doi:10.1053/j.gastro.2020.07.067

81. Qin W h., Liu C l., Jiang Y h., Hu B, Wang H y., Fu J. Gut ACE2 expression, tryptophan deficiency, and inflammatory responses the potential connection that should not be ignored during SARS-COV-2 infection. *Cellular and Molecular Gastroenterology and Hepatology*. 2021;12(4):1514–1516.e4. doi:10.1016/j.jcmgh.2021.06.014

82. Li J, Yan Y, Fu Y, Chen Z, Yang Y, Li Y, Pan J, Li F, Zha C, Miao K, Ben L, Saleemi MK, Zhu Y, Ye H, Yang L, Wang W. ACE2 mediates tryptophan alleviation on diarrhea by repairing intestine barrier involved mTOR pathway. *Cellular & Molecular Biology Letters*. 2024;29(1):90. doi:10.1186/s11658-024-00603-8

83. Perrotta F, Matera MG, Cazzola M, Bianco A. Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter? *Respiratory Medicine*. 2020;168:105996. doi:10.1016/j.rmed.2020.105996

84. Nowak JK, Lindstrøm JC, Kalla R, Ricanek P, Halfvarson J, Satsangi J. Age, inflammation, and disease location are critical determinants of intestinal expression of SARS-COV-2 receptor ACE2 and TMPRSS2 in inflammatory bowel disease. *Gastroenterology*. 2020;159(3):1151–1154.e2. doi:10.1053/j.gastro.2020.05.030

85. Burgueño JF, Reich A, Hazime H, Quintero MA, Fernandez I, Fritsch J, Santander AM, Brito N, Damas OM, Deshpande A, Kerman DH, Zhang L, Gao Z, Ban Y, Wang L, Pignac-Kobinger J, Abreu MT. Expression of SARS-COV-2 entry molecules ACE2 and TMPRSS2 in the gut of patients with IBD. *Inflammatory Bowel Diseases*. 2020;26(6):797–808. doi:10.1093/ibd/izaa085

86. Neurath MF. COVID-19: biologic and immunosuppressive therapy in gastroenterology and hepatology. *Nature Reviews Gastroenterology & Hepatology*. 2021;18(10):705–715. doi:10.1038/s41575-021-00480-y

87. Song L, Ji W, Cao X. Integrated analysis of gut microbiome and its metabolites in ACE2-knockout and ACE2-overexpressed mice. *Frontiers in Cellular and Infection Microbiology*. 2024;14:1404678. doi:10.3389/fcimb.2024.1404678

88. Duan Y, Prasad R, Feng D, Beli E, Calzi SL, Longhini ALF, Lamendella R, Floyd JL, Dupont M, Noothi SK, Sreejit G, Athmanathan B, Wright J, Jensen AR, Oudit GY, Markel TA, Nagareddy PR, Obukhov AG, Grant MB. Bone Marrow-Derived cells restore functional integrity of the gut epithelial and vascular barriers in a model of diabetes and ACE2 deficiency. *Circulation Research*. 2019;125(11):969–988. doi:10.1161/circresaha.119.315743

89. Afsar B, Afsar RE, Ertuglu LA, Kuwabara M, Ortiz A, Covic A, Kanbay M. Renin-angiotensin system and cancer: epidemiology, cell signaling, genetics and epigenetics. *Clinical & Translational Oncology*. 2020;23(4):682–696. doi:10.1007/s12094–020–02488–3

90. Zhang Z, Li L, Li M, Wang X. The SARS-CoV-2 host cell receptor ACE2 correlates positively with immunotherapy response and is a potential protective factor for cancer progression. *Computational and Structural Biotechnology Journal*. 2020;18:2438–2444. doi:10.1016/j.csbj.2020.08.024

91. Feng H, Wei X, Pang L, Wu Y, Hu B, Ruan Y, Liu Z, Liu J, Wang T. Prognostic and immunological value of Angiotensin-Converting enzyme 2 in Pan-Cancer. *Frontiers in Molecular Biosciences*. 2020;7:189. doi:10.3389/fmolb.2020.00189

92. Zhang Q, Lu S, Li T, Yu L, Zhang Y, Zeng H, Qian X, Bi J, Lin Y. ACE2 inhibits breast cancer angiogenesis via suppressing the VEGFa/VEGFR2/ERK pathway. *Journal of Experimental & Clinical Cancer Research*. 2019;38(1):173. doi:10.1186/s13046–019–1156–5

93. Wan. The angiotensin-converting enzyme 2 in tumor growth and tumor-associated angiogenesis in non-small cell lung cancer. *Oncology Reports*. 2010;23(4):941–948. doi:10.3892/or_00000718

94. Zhou L, Zhang R, Yao W, Wang J, Qian A, Qiao M, Zhang Y, Yuan Y. Decreased Expression of Angiotensin-Converting Enzyme 2 in Pancreatic Ductal Adenocarcinoma Is Associated with Tumor Progression. *The Tohoku Journal of Experimental Medicine*. 2009;217(2):123–131. doi:10.1620/tjem.217.123

95. Zong H, Yin B, Zhou H, Cai D, Ma B, Xiang Y. Loss of angiotensin-converting enzyme 2 promotes growth of gallbladder cancer. *Tumor Biology*. 2015;36(7):5171–5177. doi:10.1007/s13277-015-3171-2

96. Xu J, Fan J, Wu F, Huang Q, Guo M, Lv Z, Han J, Duan L, Hu G, Chen L, Liao T, Ma W, Tao X, Jin Y. The ACE2/Angiotensin-(1–7)/MAS receptor axis: Pleiotropic roles in cancer. *Frontiers in Physiology*. 2017;8:276. doi:10.3389/fphys.2017.00276

97. Huang WJ, He WY, Li JD, He RQ, Huang ZG, Zhou XG, Li JJ, Zeng DT, Chen JT, Wu WZ, Dang YW, Chen G. Clinical significance and molecular mechanism of angiotensin-converting enzyme 2 in hepatocellular carcinoma tissues. *Bioengineered*. 2021;12(1):4054–4069. doi:10.1080/21655979.2021.1952791

98. Song T, Choi CH, Kim MK, Kim ML, Yun BS, Seong SJ. The effect of angiotensin system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) on cancer recurrence and survival: a meta-analysis. *European Journal of Cancer Prevention*. 2016;26(1):78–85. doi:10.1097/cej.0000000000000269

99. Yu C, Tang W, Wang Y, Shen Q, Wang B, Cai C, Meng X, Zou F. Downregulation of ACE2/Ang-(1–7)/Mas axis promotes breast cancer metastasis by enhancing store-operated calcium entry. *Cancer Letters*. 2016;376(2):268–277. doi:10.1016/j.canlet.2016.04.006

100. Errarte P, Beitia M, Perez I, Manterola L, Lawrie CH, Solano-Iturri JD, Calvete-Candenas J, Unda M, López JI, Larrinaga G. Expression and activity of angiotensin-regulating enzymes is associated with prognostic outcome in clear cell renal cell carcinoma patients. *PLoS ONE*. 2017;12(8): e0181711. doi:10.1371/journal.pone.0181711

101. Bernardi S, Zennaro C, Palmisano S, Velkoska E, Sabato N, Toffoli B, Giacomel G, Buri L, Zanconati F, Bellini G, Burrell LM, De Manzini N, Fabris B. Characterization and significance of ACE2 and Mas receptor in human colon adenocarcinoma. *Journal of the Renin-Angiotensin-Aldosterone System*. 2011;13(1):202–209. doi:10.1177/1470320311426023

102. Sivasakthivel S, Ramani P, Krishnan RP. Systematic Review and Meta-Analysis on Angiotensin Converting Enzyme 2 in Head and neck region. *Cureus*. 2023;15(1): e33673. doi:10.7759/cureus.33673

103. Wan H. Overexpression of ACE2 produces antitumor effects via inhibition of angiogenesis and tumor cell invasion in vivo and in vitro. *Oncology Reports*. 2011;26(5):1157–1164. doi:10.3892/or.2011.1394

104. Cheng Q, Zhou L, Zhou J, Wan H, Li Q, Feng Y. ACE2 overexpression inhibits acquired platinum resistance-induced tumor angiogenesis in NSCLC. *Oncology Reports*. 2016;36(3):1403–1410. doi:10.3892/or.2016.4967

105. Holappa M, Valjakka J, Vaajanen A. Angiotensin(1–7) and ACE2, "The hot spots" of Renin-Angiotensin system, detected in the human aqueous humor. *The Open Ophthalmology Journal*. 2015;9(1):28–32. doi:10.2174/1874364101509010028

106. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine*. 2020;8(4):420–422. doi:10.1016/s2213-2600(20)30076-x

107. Ma D, Chen CB, Jhanji V, Xu C, Yuan XL, Liang JJ, Huang Y, Cen LP, Ng TK. Expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in human primary conjunctival and pterygium cell lines and in mouse cornea. *Eye*. 2020;34(7):1212–1219. doi:10.1038/s41433–020–0939–4

108. Zhou L, Xu Z, Guerra J, Rosenberg AZ, Fenaroli P, Eberhart CG, Duh EJ. Expression of the SARS-COV-2 receptor ACE2 in human retina and Diabetes — Implications for Retinopathy. *Investigative Ophthalmology & Visual Science*. 2021;62(7):6. doi:10.1167/iovs.62.7.6

109. Colin M, Delaitre C, Foulquier S, Dupuis F. The AT1/AT2 Receptor Equilibrium Is a Cornerstone of the Regulation of the Renin Angiotensin System beyond the Cardiovascular System. *Molecules*. 2023;28(14):5481. doi:10.3390/molecules28145481

110. Foureaux G, Nogueira JC, Nogueira BS, Fulgêncio GO, Menezes GB, Fernandes SOA, Cardoso VN, Fernandes RS, Oliveira GP, Franca JR, Faraco A a. G, Raizada MK, Ferreira AJ. Antiglaucomatous effects of the activation of intrinsic Angiotensin-Converting enzyme 2. *Investigative Ophthalmology & Visual Science*. 2013;54(6):4296. doi:10.1167/iovs.12-11427

111. Verma A, Shan Z, Lei B, Yuan L, Liu X, Nakagawa T, Grant MB, Lewin AS, Hauswirth WW, Raizada MK, Li Q. ACE2 and ANG-(1–7) confer protection against development of diabetic retinopathy. *Molecular Therapy*. 2011;20(1):28–36. doi:10.1038/mt.2011.155

112. Fu X, Lin R, Qiu Y, Yu P, Lei B. Overexpression of Angiotensin-Converting enzyme 2 ameliorates amyloid B-Induced inflammatory response in human primary retinal pigment epithelium. *Investigative Ophthalmology & Visual Science*. 2017;58(7):3018. doi:10.1167/iovs.17-21546

113. Kaplan N, Gonzalez E, Peng H, Batlle D, Lavker RM. Emerging importance of ACE2 in external stratified epithelial tissues. *Molecular and Cellular Endocrinology*. 2021;529:111260. doi:10.1016/j.mce.2021.111260

114. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, Van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology*. 2004;203(2):631–637. doi:10.1002/path.1570

115. Li RJ, Wu CY, Ke HL, Wang XP, Zhang YW. Qing Fei Hua Xian Decoction ameliorates bleomycin-induced pulmonary fibrosis by suppressing oxidative stress through balancing ACE-AngII-AT1R/ACE2-Ang-(1–7)-Mas axis. *Iran J Basic Med Sci*. 2023;26(1):107–113. doi:10.22038/IJBMS.2022.67042.14700

116. Liu X, Liu X, Li M, Zhang Y, Chen W, Zhang M, Zhang M, Zhang C, Zhang M, Zhang M. Mechanical stretch induces smooth muscle cell dysfunction by regulating ACE2 via P38/ATF3 and post-transcriptional regulation by MIR-421. *Frontiers in Physiology*. 2021;11:540591. doi:10.3389/fphys.2020.540591

117. Csekes E, Račková L. Skin aging, cellular senescence and natural polyphenols. *International Journal of Molecular Sciences*. 2021;22(23):12641. doi:10.3390/ijms222312641

118. Xue X, Mi Z, Wang Z, Pang Z, Liu H, Zhang F. High expression of ACE2 on keratinocytes reveals skin as a potential target for SARS-COV-2. *Journal of Investigative Dermatology*. 2020;141(1):206–209.e1. doi:10.1016/j.jid.2020.05.087

119. Pho DM. ACE2 Receptor in the skin and Cutaneous Manifestations of SARS-Cov-2: A Review of the Literature. *Bioscientia Medicina Journal of Biomedicine and Translational Research*. 2020;5(1):204–211. doi:10.32539/bsm.v5i1.209

Расшифровка роли ангиотензинпревращающего фермента 2 в норме и при заболеваниях

Ш. Сивасактивел ✉, П. Рамани

Стоматологический колледж больницы Савита, Институт медицинских и технических наук Савита, *г. Ченнаи, Тамилнад, Индия*

✉ jsshivaninarayanan@gmail.com

Аннотация. *Актуальность*. Ангиотензинпревращающий фермент 2 (АПФ 2) признан важным регулятором сердечно-сосудистого и легочного гомеостаза благодаря его участию в РААС (ренин-ангиотензиновой системе). В этом обширном обзоре рассматривается как традиционная роль АПФ 2 в превращении ангиотензина II (Ang II) в ангиотензин-(1–7), так и его более широкое значение в сердечно-сосудистых заболеваниях, легочной патологии, метаболических заболеваниях и раке. Выводы. Недавние исследования пролили свет на значение АПФ 2, выходящее за рамки его ферментативных возможностей, в частности, как клеточного рецептора различных патогенов. Кроме того, недавние исследования показывают, что ACE2 участвует в воспалении, метаболизме глюкозы и модуляции микробиома кишечника. Распределение в тканях, механизмы регуляции и терапевтические возможности демонстрируют его двойную роль: защитного фактора и возможного пути проникновения вирусных инфекций. Понимание этих множественных процессов в состоянии здоровья и болезни имеет важное значение для разработки персонализированных методов лечения заболеваний. В данном обзоре изложено существующее понимание ACE2 и выделены области для дальнейших исследований, в частности, его потенциал в качестве терапевтической мишени. Кроме того, обобщены проблемы и будущие направления в терапии на основе ACE2.

Ключевые слова: ACE2, ангиотензин превращающий фермент 2, здоровье, заболевания, физиология, сердечно-сосудистая система, легочная система, почечная система, рак, иммунология, кожа, кишечник, нейрофизиология

Информация о финансировании. Авторы не получали финансовой поддержки для проведения исследования, написания и публикации данной статьи.

Вклад авторов. Шивани Сивасактивел — разработка концепции, написание рукописи и написание окончательного текста рукописи. Пратибха Рамани — проверка интеллектуального содержания рукописи, окончательное утверждение версии для публикации. Шивани Сивасактивел, Пратибха Рамани — проверка интеллектуального содержания рукописи. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочитали и одобрили окончательную версию перед публикацией.

Информация о конфликте интересов. Авторы заявляют об отсутствии конфликта интересов.

Этическое одобрение — неприменимо.

Благодарности. Авторы выражают благодарность за использование Microsoft PowerPoint для подготовки рисунков, включая графику SmartArt и элементы дизайна, взятые из Medical Server Art, для улучшения схематического представления концепций, представленных в этом обзоре.

Информированное согласие на публикацию — неприменимо.

Поступила 02.09.2025. Принята 01.10.2025.

Для цитирования: *Sivasakthivel S., Ramani P.* Deciphering the role of angiotensin converting enzyme2 in health and diseases // Вестник Российского университета дружбы народов. Серия: Медицина. 2026. Т. 30. № 2. С. 177–199. doi: 10.22363/2313-0245-2026-30-2-177-199. EDN: GJBIWF

Corresponding author: Shivani Sivasakthivel — Doctor of Dental Surgery, Researcher,Department of Oral and Maxillofacial Pathology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai-600077, TamilNadu, India. Email: jsshivaninarayanan@gmail.com
Sivasakthivel S. ORCID 0000-0003-2021-4906
Ramani P. ORCID 0000-0002-5426-3506

Ответственный за переписку: Шивани Сивасактивел — доктор стоматологической хирургии, научный сотрудник, кафедра челюстно-лицевой патологии, Стоматологический колледж и больницы Савита, Институт медицинских и технических наук Савита, г. Ченнаи-600077, Тамилнад, Индия. Электронная почта: jsshivaninarayanan@gmail.com
Сивасактивел Ш. ORCID 0000-0003-2021-4906
Рамани П. ORCID 0000-0002-5426-3506