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ACE2 Nascence, Trafficking and SARS-CoV-2 Pathogenesis: The Saga Continues

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Abstract

With the emergence of the novel corona virus SARS-CoV-2 since December 2019, more than 43 million cases have been reported worldwide. This virus has shown high infectivity and severe symptoms in some cases leading to over 1 million deaths globally. Despite the collaborative and concerted research efforts that has been made, no effective treatment for COVID-19 (corona virus disease-2019) is currently available. SARS-CoV-2 uses the angiotensin converting enzyme 2 (ACE2) as an initial mediator for viral attachment and host cell invasion. ACE2 is widely distributed in human tissues including the cell surface of lung cells which represent the primary site of the infection. Inhibiting or reducing cell surface availability of ACE2 represents a promising therapy for tackling COVID-19. In this context, most ACE2–based therapeutic strategies have aimed to achieve this through the use of angiotensin converting enzyme (ACE) inhibitors or neutralizing the virus by exogenous administration of ACE2. However, through this review, we present another perspective focusing on the subcellular localization and trafficking of ACE2. Membrane targeting of ACE2, shedding and its cellular trafficking pathways including internalization are not well elucidated. Therefore, hereby we present an overview on the fate of newly synthesized ACE2, its post translational modifications, what is known of its trafficking pathways. In addition, we highlight the possibility that some of the identified ACE2 missense variants might affect its trafficking efficiency and localization and hence may explain some of the observed variable severity of SARS-CoV-2 infections. Extensive understanding of these processes is necessary to evaluate the potential use of ACE2 as a credible therapeutic target.

Keywords: Angiotensin converting enzyme 2 (ACE2), trafficking, localization, SARS-CoV-2, COVID-19.

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Introduction

Following the discovery of Renin and Angiotensin converting enzyme (ACE) in 1898 and 1956, respectively [1, 2], the understanding of the renin angiotensin system (RAS) has been greatly improved by the uncovering of associated receptors, enzymes and protein complexes. Twenty years ago, in an approach of searching for human ACE homologues, two independent groups have identified angiotensin converting enzyme 2 (ACE2) that shares a common ancestor with ACE, with 42% sequence identity [3, 4]. ACE2 expression disruption studies have identified ACE2 as an important regulator of blood pressure and cardiovascular functions through its role in the renin angiotensin system that counteracts ACE functions [5].

With the emergence of the severe acute respiratory syndrome (SARS), significant attention has been given to ACE2 due to its involvement as the host's cellular receptor that mediates the initiation of the viral infection. Consequently, since 2002, approximately 4000 ACE2 – related articles have been published where the majority correspond to 2020 as revealed by a PubMed database search. In 2019, a novel corona virus has emerged, known as SARS-CoV-2, causing the new coronavirus disease 2019 (known as COVID-19) and leading to unprecedented economic and health burden world-wide. Similar to its predecessor SARS-CoV and unlike MERS-CoV, the spike S protein of SARS-CoV-2 mediates the viral attachment and entry into the host cell by binding to its target receptor, the ACE2 [6, 7]. The accumulated acquired knowledge of ACE2 led to several therapeutic interventions such as the introduction of recombinant ACE2 protein as a hypertensive therapeutic target in 2009 [8] and a potent therapeutic target for SARS-related viruses [9–11]. However, some discrepancies and unknowns still exist, and further investigations are therefore required. In this context, throughout this review we will present and discuss what is currently known about ACE2 biogenesis, regulation and polymorphism with emphasize on the gaps in our understanding of its intracellular trafficking and the potential on its use as a therapeutic target for COVID-19.

ACE2 structure, tissue distribution and multiple functions

ACE2 is 40 kb gene mapped to chromosome Xp22 and constitutes 22 introns and 18 exons with remarkable resemblance to ACE's first 17 exons [4]. *ACE2* gene encodes a 120 kDa typical zinc-metalloproteinase type 1 transmembrane protein composed of 805 amino acids. ACE2 protein possess a unique N-terminal catalytic domain on the extracellular surface and a C-terminal domain serving as a membrane anchor. Despite the considerable similarity between them, ACE and ACE2 don't function similarly and significant differences in their substrate specificities have been observed (**Figure 1**). Structural protein studies have shown that both proteins exhibit a highly conserved catalytic domain and share similar mechanism of action with a different substituted amino acid in the binding pocket [12, 13]. This substitution sterically hinders the access of the substrates to ACE2 binding site leading to the elimination of ACE-like dipeptidase activity. Like carboxypeptidases, ACE removes C-terminal dipeptide to yield Ang II with injurious effects whereas ACE2 removes only one amino acid residue to produce Ang (1-7) and Ang (1-9) counterbalancing Ang II sequels [5]. Unexpectedly, the C-terminal cytoplasmic domain of ACE2 has high homology with the renal protein, collectrin, mapped on chromosome Xp22 as well,

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which acts as a molecular chaperone that binds to amino acid transporters, like the neutral amino acid transporter B^0AT1 and regulate the trafficking of amino acids in the proximal tubules [14–16]. ACE2 was later shown to resemble a similar chaperone function. It heterodimerizes with B^0AT1 in a tissue specific manner and regulates membrane trafficking in the intestine where collectrin is absent [17–19].

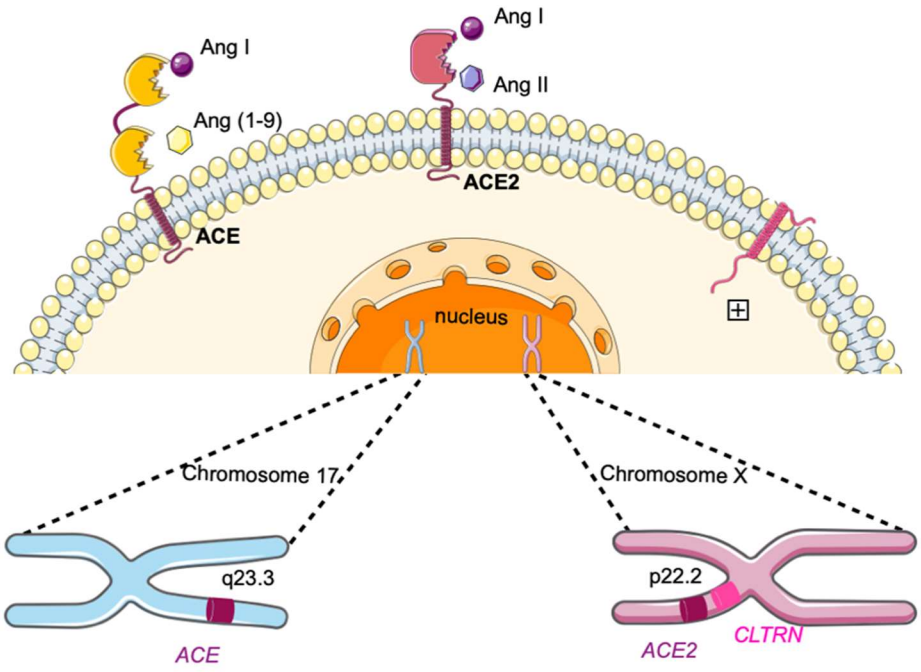

Figure 1: ACE2 and its homologous chromosomal and cellular localizations.
The 3 type I transmembrane proteins ACE, ACE2 and collectrin located in the plasma membrane with activity differences. ACE acts as a dipeptidyl carboxypeptidase with 2 catalytic active sites for angiotensin I (Ang I) and angiotensin (1-9) (Ang (1-9)), whereas ACE2 acts as a monocarboxypeptidase possessing one active site that cleaves Ang I and angiotensin II (Ang II). However, collectrin lacks a catalytic activity in its extracellular domain. ACE2 and collectrin gene (CLTRN) are both mapped to chromosome Xp22.2 were ACE is located on chromosome 17q23.3.

Moreover, two human ACE2 forms have been reported, the larger form corresponding to the full length ACE2 with 18 exons and 805 amino acids and the shorter one corresponding to the soluble form of ACE2 (sACE2) which is 555 amino acids in size. sACE2 is obtained by shedding of the protein mainly through a disintegrin and metalloproteinase 17 (ADAM17) which is demonstrated to maintain its enzymatic activity and play a role in partially attenuating viral entry to the cells [20]. 3D structure analysis of ACE2 reveals a signal peptide sequence composed of 18 amino acids, an extracellular sequence (18-740) which contains the active carpoxypeptidase domain, a transmembrane domain (741-761) and a cytoplasmic domain (762-805) which together the latter two form the collectrin homology domain (**Figure 2a**).
In addition, 4 different transcript variants of human ACE2 are available in the GeneBank corresponding to 3 ACE2 isoforms. Aside from the full-length isoform (805 amino acids), two others have been reported. ACE2 isoform 2 is a 786 amino acid protein, based on blast sequence

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alignment it is 100% identical with the full-length ACE2, where it is truncated at the cytoplasmic domain and lacks a collectrin homology domain. Whereas, the third ACE2 isoform (isoform 3) is composed of 695 amino acids and is 95% identical to ACE2 where some deletions occurring in the collectrin homology domain (**Figure 2b**). It is worth noting that the role of these isoforms in the SARS viral infections remains unidentified.

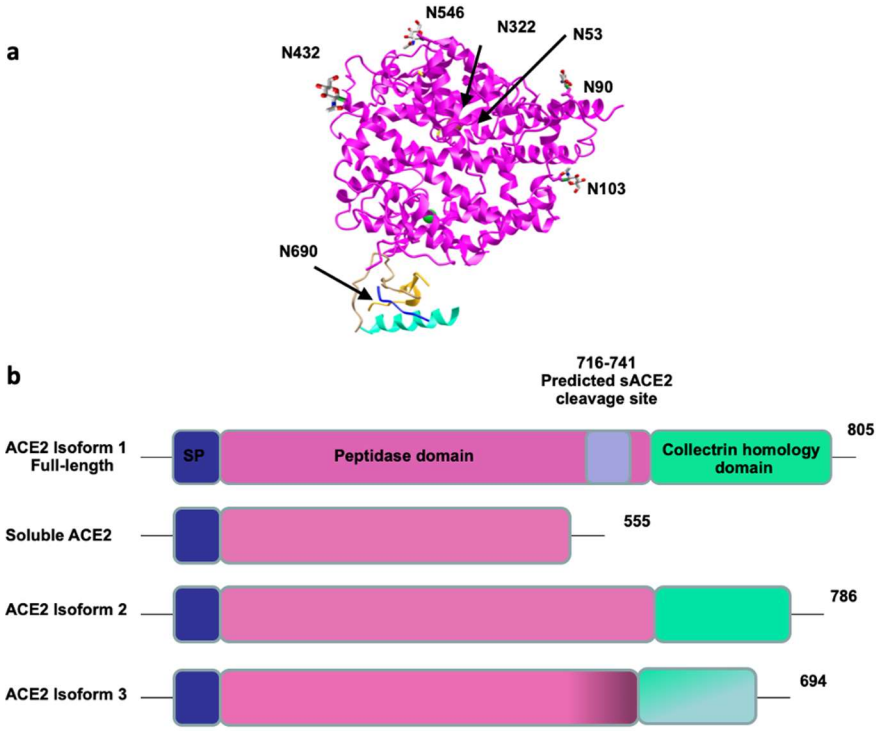

Figure 2: **ACE2 3D-structure and isoforms**.
(**a**) 3D structure of ACE2 adopted from Towler et al [13] and drawn in iCn3D using PBD ID: 1R4L. The structure was modified based on the newly identified N-glycosylation sites labelled in black. (**b**) ACE2 exists in 3 different isoforms along with a soluble form cleaved at residues 716-741 and constitutes 555 amino acids lacking the transmembrane collectrin homology domain. GeneBank ACE2 isoform 2 show a truncation of the full length ACE2 with 100% homology in the 786 residues. ACE2 isoform 3 displays deletions in the transmembrane and collectrin homology domains leading to 95% similarity with ACE2 represented by gradient color in the corresponding domains. SP: signal peptide.

ACE2 belongs to a family of transmembrane proteins that has wide tissue distribution. The observed difference in the cytoplasmic C-terminal sequence between ACE and ACE2 could explain the preferential localization of ACE2 on the apical membrane of polarized cells whilst ACE being localized on both the apical and basolateral membrane of epithelial cells [21]. Initial analysis has indicated that ACE2 expression is mainly in the rodent's heart [3] and more precisely in cardiomyocytes and fibroblasts [22, 23]. However, detailed transcriptional profiling of ACE2 has shown that transcribed ACE2 is expressed in 72 human tissues with higher expression in cardiovascular and renal systems [24]. Furthermore, protein expression of ACE2 was initially identified in the heart, kidney and testis [3–5], where immunolocalization studies of ACE2 have later demonstrated that ACE2 also exists on the surface of cells that are in contact with the

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cellular environment like the lung's alveolar epithelial cells and the small intestine's enterocytes [25]. ACE2 was also localized in the brain [26], islets of Langerhans of the pancreatic tissue [27] and bone [28] with no significant expression in the lymphatic system and lymphoid organs [25, 29].

ACE2 polymorphic footprint in health and disease

In order to find association with disease, genetic variable signature has been extensively studied in different populations through single nucleotide polymorphisms (SNPs). SNPs were found to significantly contribute to the outcome of diseases, noting that they are highly affected by different factors like age and ethnicity. In this setting, ACE2 polymorphism and its association with hypertension was reported in different populations including the Chinese population with three major ACE2 variants (rs4830542, rs4240157 and rs4646155) [30], the Canadian population with another three different variants (rs233575, rs2074192 and rs2158083) [31], the Brazilian population with ACE2 G8790A mutation in combination with ACE I/D [32], and the Indian population with the ACE2 rs2106809 mutant [33].

In an attempt to discover association between COVID-19 and ACE2 polymorphic variations, being its major host cellular receptor, Cao and colleagues have investigated 1700 ACE2 coding variants collected from the China Metabolic Analytics Project and 1000 Genome Project databases. Their results demonstrated that no natural resistance mutations for SARS-CoV-2 S binding protein were detected in the studied populations. In addition, 32 variants were identified to potentially affect the amino acid sequence of ACE2 with 7 hotspot variations unevenly distributed in different populations (Lys26Arg, Ile468Val, Ala627Val, Asn638Ser, Ser692Pro, Asn720Asp, and Leu731Ile/Leu731Phe) [34]. Notably, in another large populations study, authors have identified natural ACE2 variants that might affect host susceptibility to SARS-CoV-2. Interestingly, they have also demonstrated that some variants potentially enhance susceptibility while others showed reduced binding to SARS-CoV-2 [35]. Among the ones that enhanced ACE2 affinity for the S protein is K26R missense mutation. K26R along with another mutation, the N720D, were characterized by Al-Mulla and colleagues as the most frequent missense variants of ACE2 in different global datasets [36]. Conversely, these results do not apply to an Italian COVID-19 positive population, where Novelli and colleagues have shown that no significant association is present between ACE2 and SARS-CoV-2 severity, speculating that susceptibility related variants might be located in the non-coding region and contributing to the regulation of ACE2 activity [37]

Epigenetic variation of ACE2

The localization of *ACE2* gene on the X chromosome raise the question of balance in the expression profiles between genders. Various studies have shown significant differences between males and females in ACE2 expression [38–41]. These findings were explained by identifying ACE2 as an escapee gene that undergoes incomplete X inactivation and shows a heterogenous sex-bias profile that is often shared across tissues [42]. X chromosome inactivation

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was shown to be greatly affected by epigenetic variations like the DNA-methylation that also affects ACE2 expression profile [43].

Modifications in the DNA and chromatin structures are marked as epigenetic variations that were shown to play an important role in several human diseases like cardiovascular ones [44, 45]. Interestingly, recent studies have suggested that ACE2 production rate is controlled by its epigenetic modifications, where methylation of ACE2 gene near the transcription start site is found to be associated to the age and gender dependent variation of ACE2 with the lowest rate of methylation in the lungs and the highest in neurons where ACE2 protein is not detected [46]. Along these findings, ACE2 profiles were also shown to display significant correlation with histone modification related genes in human lungs [47]. Additionally, the results of another study have previously demonstrated that ACE2 promoter was hypermethylated in hypertensive patients with significant difference between males and females [48], where COVID-19 patients as well have displayed differential methylation pattern in ACE2 of blood samples [49] which further requires testing in the respiratory samples.

Aside from the pre-transcriptional regulation, ACE2 mRNA level displays an epigenetic signature through the putative short non-coding micro-RNAs regulation network. Several studies have reported new miRNAs that are involved with ACE2 expression either via hampering its translation or through degrading its corresponding protein. A recent bioinformatic study has identified 1954 miRNAs involved in the ACE2 regulating network [50]. miRNAs were either directly regulating ACE2 like miR-421, miR-125b and miR-483-3p via having a putative site in its 3'UTR region [45, 51, 52] or indirectly affecting ACE2 expression like miR-181a and miR-4262 through affecting RAS components and target proteins (apoptotic Bcl2), respectively [53, 54].

In addition, other factors like smoking and sex hormone can also induce epigenetic modifications in the genome. Several studies conducted on sex hormone have shown correlation with ACE2 expression level which could also contribute to the sex-biased susceptibility of COVID-19. The female sex steroid 17β-estradiol (E_2) was shown to regulate ACE2 expression, where it induces downregulation in the kidney and the differentiated airway epithelial cells [40, 55]. Conversely, in the atrial heart tissue ACE2 expression was upregulated through the E2- Estrogen receptor alpha activated pathway [56]. In addition, another a study on the male hormone, testosterone, was reported to upregulate ACE2 expression [57]. Furthermore, cigarette smoking was demonstrated to enhance ACE2 expression which also presented a risk factor for the progression of COVID-19 with more severe complications [58, 59].

Subcellular localization and intracellular trafficking of ACE2

Among the 10% proteins that are destined to the plasma membrane [60], nascently biosynthesized ACE2 traffic to its intended location in the cell via a highly regulated machinery that includes different subcellular compartments. Translated proteins are inserted into the endoplasmic reticulum (ER) via their signal peptides, where they undergo folding into their correct conformations. Post-translational modifications of the proteins such as attaching

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carbohydrate moieties, a process named glycosylation which is a common modification of secretory pathway targeted proteins, is initiated in the ER. In order to exit the ER, proteins need to be fully folded and assembled (in case of multi-subunit complexes) before they are allowed to exit the ER. Misfolded proteins and orphaned subunits of protein complexes are retained in the ER and transported to the cytosol where they are degraded by the proteasome through ERAD (Endoplasmic Reticulum-associated protein degradation) degradation process [61, 62]. At the ER exist sites, folded proteins are transported from the ER by transport vesicles into the Golgi apparatus through the cis Golgi network. Proteins are further processed in the Golgi including carbohydrate remodeling, sulfation, proteolysis and phosphorylation. Processed proteins then sorted and exit the Golgi through the trans Golgi network via the secretory pathway in which they are secreted or targeted to subcellular compartments such as the plasma membrane [63].

Generally, proteins composed of more than 100 amino acids, including ACE2, undergo co-translational translocation into the ER while being translated. Unlike the small proteins that cross the ER membrane, newly synthesized ACE2 is targeted to the translocon (ER membrane channel) via its 17 amino acid N-terminal signal sequence. As translation proceeds, ACE2 binds to the channel and passes to the ER membrane where the ribosome is dissociated [64]. Once ACE2 is well folded and N-glycosylated in the ER, it exits through transport vesicles and enters the Golgi apparatus through its cis face. In the Golgi, ACE2 undergoes further modifications and packaging and is then transported to the plasma membrane by vesicular transport (**Figure 3a**) [65]. Several glycosylation sites have been identified on ACE2. In fact, seven Asparagine residues were detected to undergo N-glycosylation in human ACE2 (N53, N90, N103, N322, N432, N546, and N690) (**Figure 2a**) [66]. The same study has suggested that glycosylation of ACE2 had no effect on its binding affinity with the S protein of SARS-CoV-2. However, these data contradict other studies that have reported N90 and N322 glycosylation to be interfering with the binding and contributing significantly to the infectivity of the virus [67, 68]. Proper N-glycosylation is expected to be important for efficient trafficking of the receptor to the plasma membrane. However, a study by Zhao and colleagues showed that inhibiting ER resident glucosidases, responsible for trimming sugars prior to protein folding, altered the glycan structure of ACE2. This alteration didn't affect neither ACE2 cellular expression nor its binding to SARS-CoV, but it showed impaired ability in the viral induced membrane fusion [69]. Similarly, in the context of glycosylation, a study by Vincent and colleagues have demonstrated that effective doses' treatments of chloroquine and NH_4CL, not only affected the viral proteins, but also induced impaired terminal glycosylation of ACE2 and increased intracellular mobility in the ER and the Golgi. However, these modifications displayed no effect on ACE2 localization to the cellular surface [70]. Moreover, modifications other than glycosylation like methylation have also been identified on human ACE2 at different sites, unlike phosphorylation and acetylation post translational modifications that were not detected [66].

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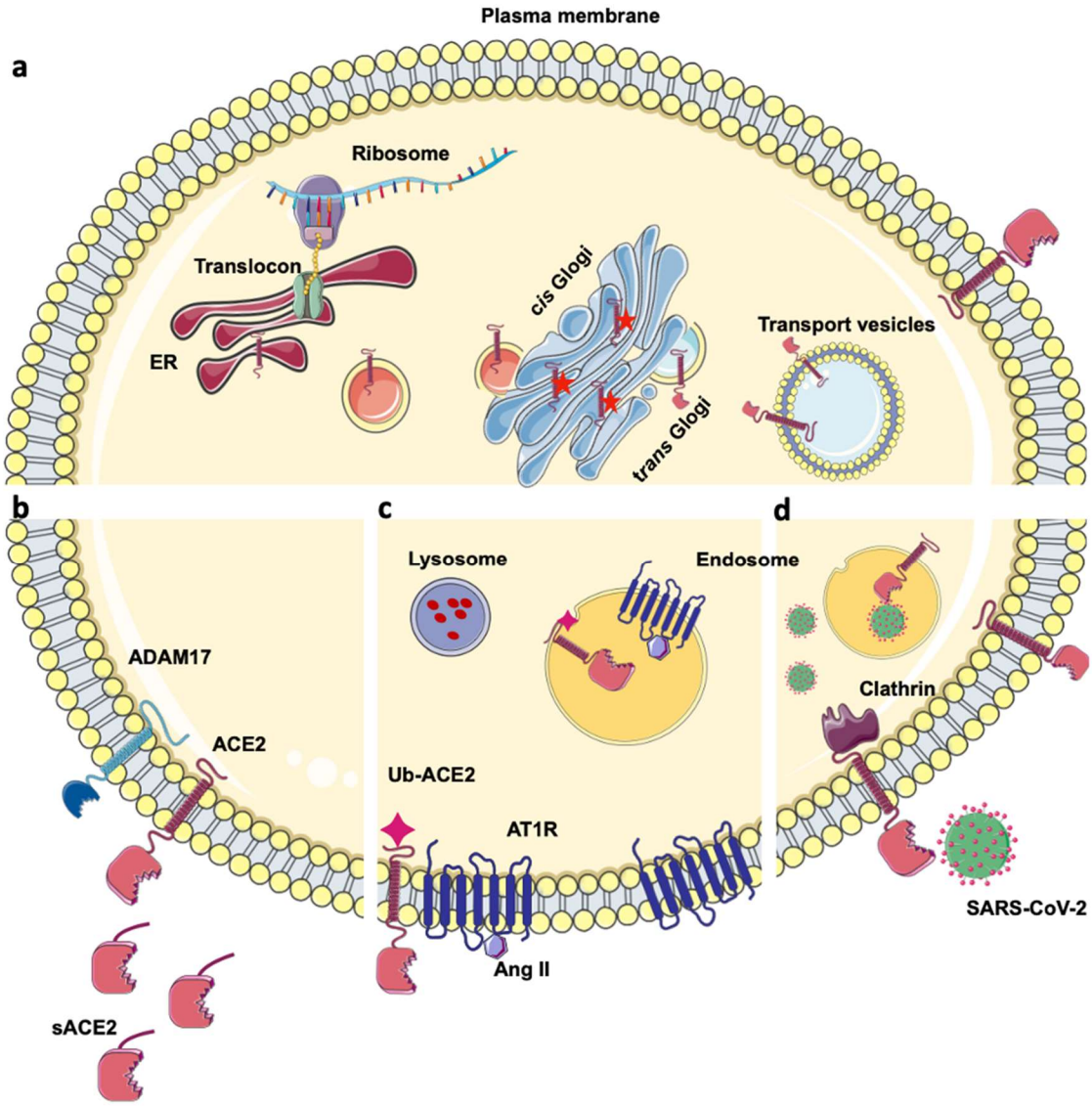

Figure 3: **ACE2 synthesis, trafficking, proteolysis and internalization**.
(**a**) Synthesis of ACE2 protein and its translocation to the endoplasmic reticulum (ER) through Golgi apparatus towards the plasma membrane via transport vesicles. Red stars correspond to post-translational modifications. (**b**) Truncation of ACE2 by ADAM17 and the release of soluble ACE2 (sACE2) into the extracellular environment. (**c**) Internalization of ACE2 in response to increased angiotensin II (Ang II) via ubiquitylation of ACE2 and interaction with angiotensin type I receptor (AT1R). The latter complex is endocytosed where, ACE2 is degraded by the lysosome and AT1R is recycled and transported back to the membrane. (**d**) ACE2 internalization in response to SARS-CoV-2 binding via clathrin-mediated endocytosis. ACE2 is recycled and transported to the membrane and SARS-CoV-2 is replicated inside the host cell.

Type I transmembrane proteins are subjected to shedding, also known by proteolytic cleavage, where the protein's ectodomain is cleaved by a protease and is released extracellularly in order to control the protein's expression and function [71]. ACE2 is catalytically cleaved by ADAM17, a metalloprotease family member, near the transmembrane domain, between the residues 716 and 741, leading to an enzymatically active soluble ACE2 (**Figure 3b**) [20, 72]. Interestingly, a

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mutation at the 584 residue has inhibited the shedding activity but didn't affect the trafficking of the mutant ACE2 to the cell surface, noting that several mutations at different residues has displayed no effect (580, 581, 582, 583 and 604) neither on ACE2 shedding nor surface targeting [20]. The shedding event of ACE2 is regulated by different stimuli. Increased soluble ACE2 levels have been reported in cardiovascular diseases contributing to higher blood pressure [73]. In addition, spike protein binding to the ACE2 receptor induces its cleavage, however, it doesn't augment the viral infectivity [74]. TMPRSS2, type II transmembrane serine protease, was demonstrated to have a competitive cleavage activity that removes a C-terminal fragment of ACE2 and contribute to further virulence during SARS-CoV infections [74–76].

Furthermore, ACE2 was shown to display an internalization pattern under different stimulations. During hypertension, decreased ACE2 protein expression level contributed to an internalization compensatory mechanism in response to increased Ang II, mediated through the Angiotensin II type I receptor (AT1R) [77]. ACE2 displayed enhanced ubiquitination and interacted with AT1R, where the latter is recycled and transported back to the membrane via endosomes, whereas ACE2 was degraded in the lysosome (**Figure 3c**). In addition, ACE2 was also internalized during SAR-CoV-1 and SARS-CoV-2 infections via a clathrin mediated endocytosis [78, 79] in which it was suggested that ACE2 is recycled back to the cell surface and the virus is further replicated in the cell (**Figure 3d**) [78].

ACE2 as therapeutic target

Given the protective effect that it displays, ACE2 represents a potent therapeutic target to prevent and treat several cardiovascular diseases such as hypertension. Strategies that aim to enhance the protective role of ACE2 like ACE inhibitors and angiotensin-receptor blockers (ARB) have shown effectiveness in treating high blood pressure and some other cardiovascular issues. In this context, treatments were based on activating ACE2. However, researchers have developed a new strategy based on exogenous administration of ACE2 in which recombinant human ACE2 (rhACE2) was used and demonstrated encouraging cardioprotective, anti-fibrotic effects and protection against lung injury [8, 80, 81].

Paradoxically, ACE2 acts as a double-edged sword where this protective effect is abolished in the presence of SARS viral infections. Conversely, therapeutic strategies could aim to decrease ACE2 expression or alter its binding affinity to SARS S protein and consequently reduce the viral entry to host cells. Pharmacologic RAS inhibition through ACE inhibitors or ARBs were hypothesized to upregulate ACE2 in diabetic and hypertensive patients which will subsequently amplify the viral infection [82]. However, the concerns regarding the potential harmful effect of ACE inhibitors and ARBs were not confirmed to be true. A study by Peng and colleagues has shown that the use of ACEI/ARBs don't affect the mortality rate in cardiovascular patients infected with COVID-19 [83]. Furthermore, another study has demonstrated that RAS inhibition significantly contribute to lower virulence [84]. Interestingly, the administration of rhACE2 to SARS-CoV-2 patients could display a positive approach due to its hypothetical dual function. Increasing ACE2 availability could contribute to slowing down viral entry through its competitive binding to the viral S protein

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and could protect the lung against the subsequent injury through its classical protective role [85]. Monteil and colleagues have previously demonstrated that soluble rhACE2 was able to alter the early infection stages of SARS-CoV-2 in engineered human kidney organoid [86]. Noting that it wasn't tested in any animal model [87], the use of recombinant human ACE2 was remarkably tolerated at different doses in healthy human subjects and patients with acute respiratory distress syndrome [9, 10]. To date, rhACE2 (APN01) is being assessed as a treatment for patients with SARS-CoV-2 infection. Currently, the pilot clinical study has 200 participants and is in phase 2 clinical trial [11].

Additionally, in a new nanotechnology approach, it was suggested that ACE2 nanoparticles applied to the protective personal equipment (masks, gloves and clothes) could present an effective strategy in tackling the virus and preventing its entry to the host cells [88]. Moreover, none of these strategies has been approved yet and further studies are still required.

Discussion

Given the multifunction, complexity and dynamic nature of ACE2, the present understanding of its structure and function represent the beginning of guidance into therapeutic solutions. The presence of conflicting data highlight the importance of systems biology studies of the viral infections that includes different variables to provide a holistic perspective of how our system interacts and responds to SARS-CoV-2 infection, noting its wide distribution in human tissues [24, 89]. Reductionist studies of ACE2 have led to a massive accumulation of data, however, unfortunately, no effective medication for COVID-19 is currently available to date. After its synthesis, ACE2 is subjected to different interactions and regulations that might be occurring simultaneously and not separately, affecting its cellular trafficking, localization and expression. These interactions might differ between individuals based on their genetic signature and consequently may lead to variable virulence and infectivity.

The presence of genetic variations in the host cellular receptor could greatly contribute to the observed variable susceptibility of SARS-CoV-2 infection. Their occurrence in the promoter region of ACE2 gene could consequently lead to decreasing its cellular expression. Moreover, the presence of these variants in the coding region would probably lead to altering its amino acid sequence that might modify its structure and alter its plasma membrane targeting and as a result reduce the interaction with SARS-CoV-2 S protein. Compared to ACE2, a point mutation on the 1069 residue of ACE, located in the C-terminal domain, is reported to be responsible for autosomal Renal Tubular Dysgenesis (RTD) disease. This mutation has led to retaining ACE in the ER and increased its degradation leading consequently to its decreased cell surface localization [90]. Besides, ACE was reported to interact with immunoglobulin-binding protein (BiP) chaperone that resides in the ER, its overexpression leads to the retention of ACE in the ER and decrease its cell surface expression which suggests transient interaction with BiP for optimal transport. This study has demonstrated that BiP affect exclusively the transport of ACE rather than its synthesis [91]. Moreover, using pharmacological chaperones and proteasome inhibitors prevented intracellular degradation and rescued mutant ACE to the plasma membrane [92]. Additionally, in the context of RTD, several mutations at different residues were evaluated. Missense (at 594 and

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828 residues) and truncated mutants (at 1136 and 1145 residues) were also retained in ER and displayed no plasma membrane expression, where another mutant at 1180 has displayed partial ER retention and delayed cell surface expression compared to wild type-ACE [93]. Whether the different identified mutations and isoforms of ACE2 could modify its trafficking and lead to cellular retention is not tested yet. In addition, a combination of these mutants could also occur together leading to a further decreased ACE2 membrane expression. In a deep mutagenesis study involving the soluble ACE2, combining different engineered single mutations together showed higher binding to the spike protein of SARS-CoV-2 [94]. Understanding the trafficking and secretory pathways of classical and mutated ACE2 shall provide potential trafficking modulators that can be targeted to improve clinical outcomes.

Conclusion

In summary, “in every angel a demon hides and in every demon an angel strides”. The angelic protective role of ACE2 is interchanged with the emergence of SARS viral infections and the evil ACE2 as a host cellular receptor can potently be reciprocated and act as a therapeutic target to treat COVID-19 patients. Through this review, we highlight the importance of further mutational screening, trafficking assessment and systems biology studies of ACE2 and their role in characterizing novel therapeutic strategies for tackling COVID-19.

List of abbreviations

ACE	Angiotensin Converting Enzyme
ACE2	Angiotensin Converting Enzyme 2
ACEI	Angiotensin Converting Enzyme Inhibitor
ADAM17	A DIsintegrin and metalloproteinase 17
Ang II	Angiotensin II
Ang(1-7)	Angiotensin (1-7)
Ang(1-9)	Angiotensin (1-9)
ARB	Angiotencin Receptor Blocker
AT1R	Angiotensin II Type I receptor
B^0AT1	Neutral amino acid transporter
BiP	Binding Immunoglobulin Protein
CLTRN	Collectrin
COVID-19	Corona Virus Disease - 2019
ER	Endoplasmic Reticulum
I/D	Insertion/Deletion
RAS	Renin Angiotensin System
rhACE2	Recombinant Human Angiotensin Converting Enzyme 2

RTD	Renal Tubular Dysgenesis
sACE2	Soluble Angiotensin Converting Enzyme 2
SARS-CoV-2	Severe Acute Respiratory Syndrome - Corona Virus 2
SNP	Single Nucleotide Polymorphism
SP	Signal Peptide
TMPRSS2	Type II Transmembrane Serine Protease

Declarations:

Ethics Approval and Consent to participate
Not applicable

Consent for Publication
Not applicable

Availability of Data and Materials
Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors Contributions
SB conducted the literature and data base searches, wrote the manuscript draft and prepared the diagrams. BA conceived the idea of the review, refined and edited drafts of the manuscript and approved the final version.

Conflict of interest statement
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