

# Molecules in pathogenesis: angiotensin converting enzyme 2 (ACE2)

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## ABSTRACT

The renin–angiotensin system is mainly associated with the regulation of blood pressure, but recently many other functions of this system have been described. ACE2, an 805-amino acid monocarboxypeptidase type I transmembrane glycoprotein, was discovered in 2000 and has sequence similarity to two other proteins, namely ACE and collectrin. The ACE2 gene is located on Xp22 and is highly polymorphic. ACE2 is expressed in numerous tissues especially the lung alveolar epithelial cells, heart, kidney and gastrointestinal tract. Animal studies have found that ACE2 is central in diseases affecting almost all organ systems, among other cardiac, respiratory, renal and endocrine functions. ACE2 was identified as the cellular contact point for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the global pandemic (COVID-19), and is a potential drug target. SARS-CoV-2 infection has several effects on the renin–angiotensin system and conversely, regulation of this receptor may affect the progress of infection. We describe the genetics and functions of ACE2, explore its various physiological functions in the renin–angiotensin system and discuss its role in the pathophysiology of disease. ACE2 opposes the vasopressor ACE pathway of the renin–angiotensin system by converting angiotensin (Ang) I to Ang (1–9) and Ang II to Ang (1–7) which initiates the vasodilatory pathway. ACE2 may have a protective effect in the lung and kidney as knockout mice display susceptibility to acute respiratory distress and hypertensive nephropathy. Binding of SARS-CoV-2 and the subsequent fusion and downregulation of this pathway during SARS-CoV-2 infection may explain some of the unusual sequelae seen in COVID-19.

## INTRODUCTION

Not since its discovery in 2000,<sup>1,2</sup> has the ACE2 receptor attracted as much attention as currently. The receptor has been identified as the cellular docking point for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),<sup>3</sup> the causative agent of COVID-19,<sup>4</sup> which was declared a pandemic by the WHO<sup>5</sup> and at the time of writing has infected more than 13 million people globally, and more than 580 thousand deaths.<sup>6</sup>

The renin–angiotensin system is a central mechanism for blood pressure regulation through a diverse system of hormones and receptors (figure 1).

The vasopressive actions of this ‘classical’ pathway is opposed by the actions of ACE2, a key component of the ‘protective (vasodilatory)’ arm which converts angiotensin (Ang) II to Ang (1–7). Thus, the system is central in a number of pathological processes ranging from cardiovascular and

respiratory diseases, to amino acid absorption in the gut and kidney. Understanding the role of ACE2 has shed light on the pathogenesis of COVID-19 and may potentially explain the myriad of unusual biochemical findings.

## ACE2 GENE

### Location and gene product

ACE2 was discovered independently by two groups in 2000 by homology cloning from a heart failure ventricular complementary DNA (cDNA) library and a lymphoma cDNA library, respectively.<sup>1,2</sup>

The ACE2 gene is 39.98 kB in size, located on Xp22 and contains 18 exons and 20 introns.<sup>7</sup> The gene is highly polymorphic<sup>8–10</sup> and variations may account for differences in enzymatic activity.<sup>9</sup> The gene undergoes alternative splicing to produce six variants.<sup>10</sup>

The final product is an 805 amino acid, 120 kDa monocarboxypeptidase type I transmembrane glycoprotein. The first 17 amino acids make up the N-terminal signal peptide followed by a HEXXH zinc-binding metalloprotease motif, a C-terminal collectrin domain and an insulin-like domain that includes a ferredoxin-like neck domain ending with a 22 amino acid hydrophobic transmembrane region anchoring it in the cell membrane<sup>7,10</sup> (figure 2).

Location on the X-chromosome implies that expression could be impacted by differences in parental imprinting and escape of X-inactivation in females resulting in dosage discordance in ACE2 expression between males and females.<sup>11</sup> Interestingly, analysis of renin–angiotensin metabolites shows a 27% higher plasma renin activity in males.<sup>12</sup> ACE2 shares significant sequence identity with two other proteins, ACE and collectrin (figure 3).

### Angiotensin converting enzyme

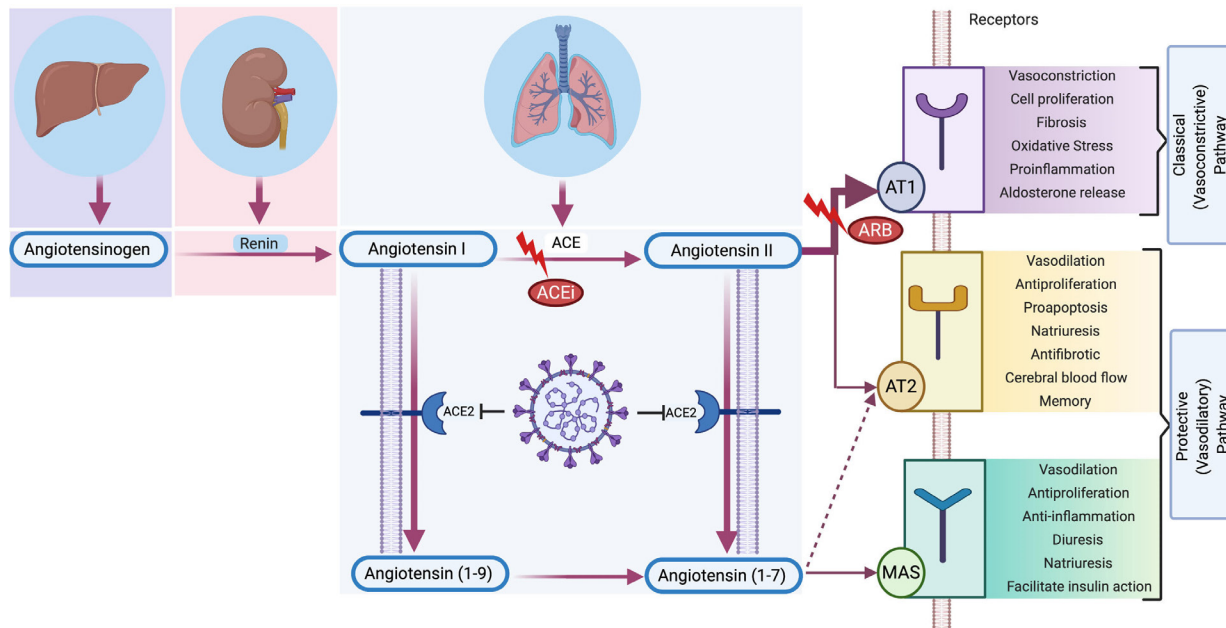
The significant homology, 42% amino acid sequence similarity in the catalytic domains, and the conservation of exon and intron organisation suggest that ACE and ACE2 genes originated from a common ancestor. The ACE gene is located on chromosome 17, spans 21 kB with 26 exons and 25 introns, and codes for a 180 kDa protein anchored to the plasma membrane by a single carboxy-terminal transmembrane domain.<sup>13</sup> Two differentially spliced forms are known. The single domain testicular form plays an important role in male fertility, and the two-domain somatic form is essential in regulating cardiovascular functions.<sup>14</sup>

Although it was initially thought that ACE and ACE2 have similar functions, this is not the case. The carboxydipeptidase activity of ACE removes

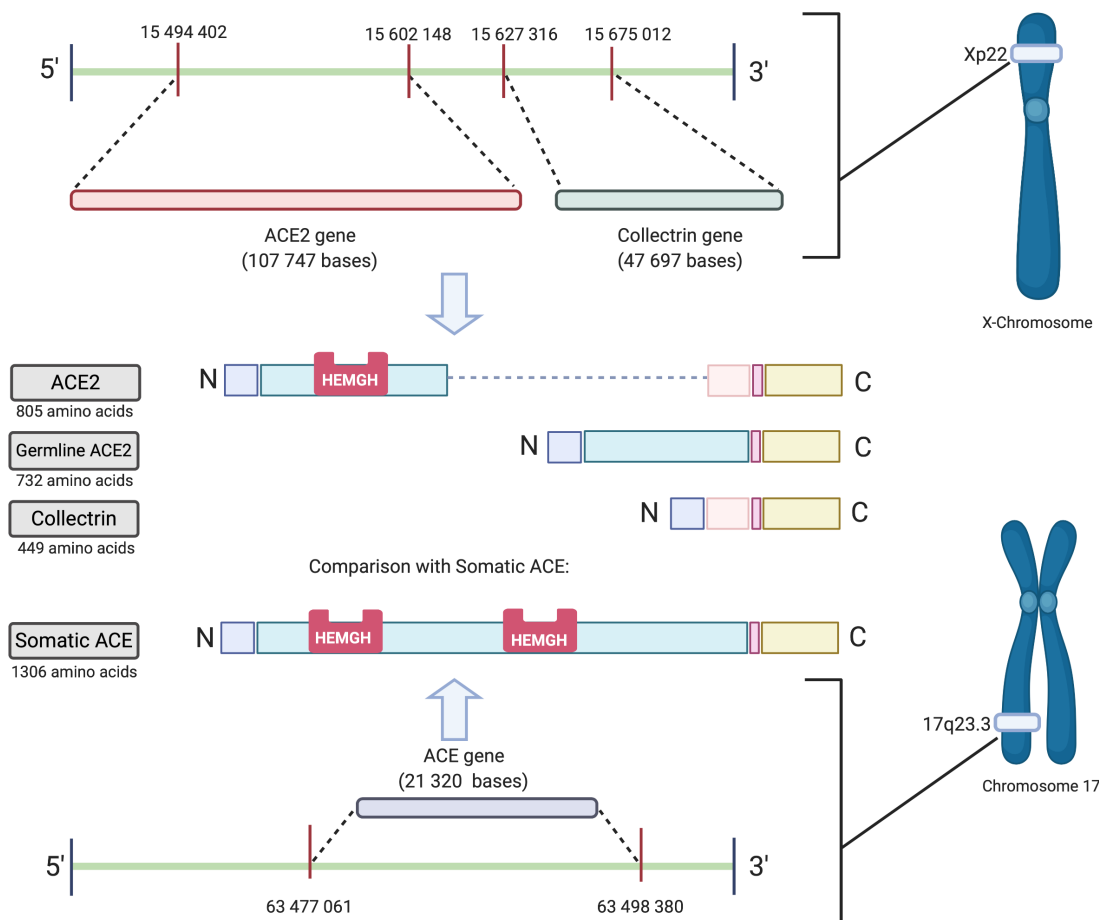


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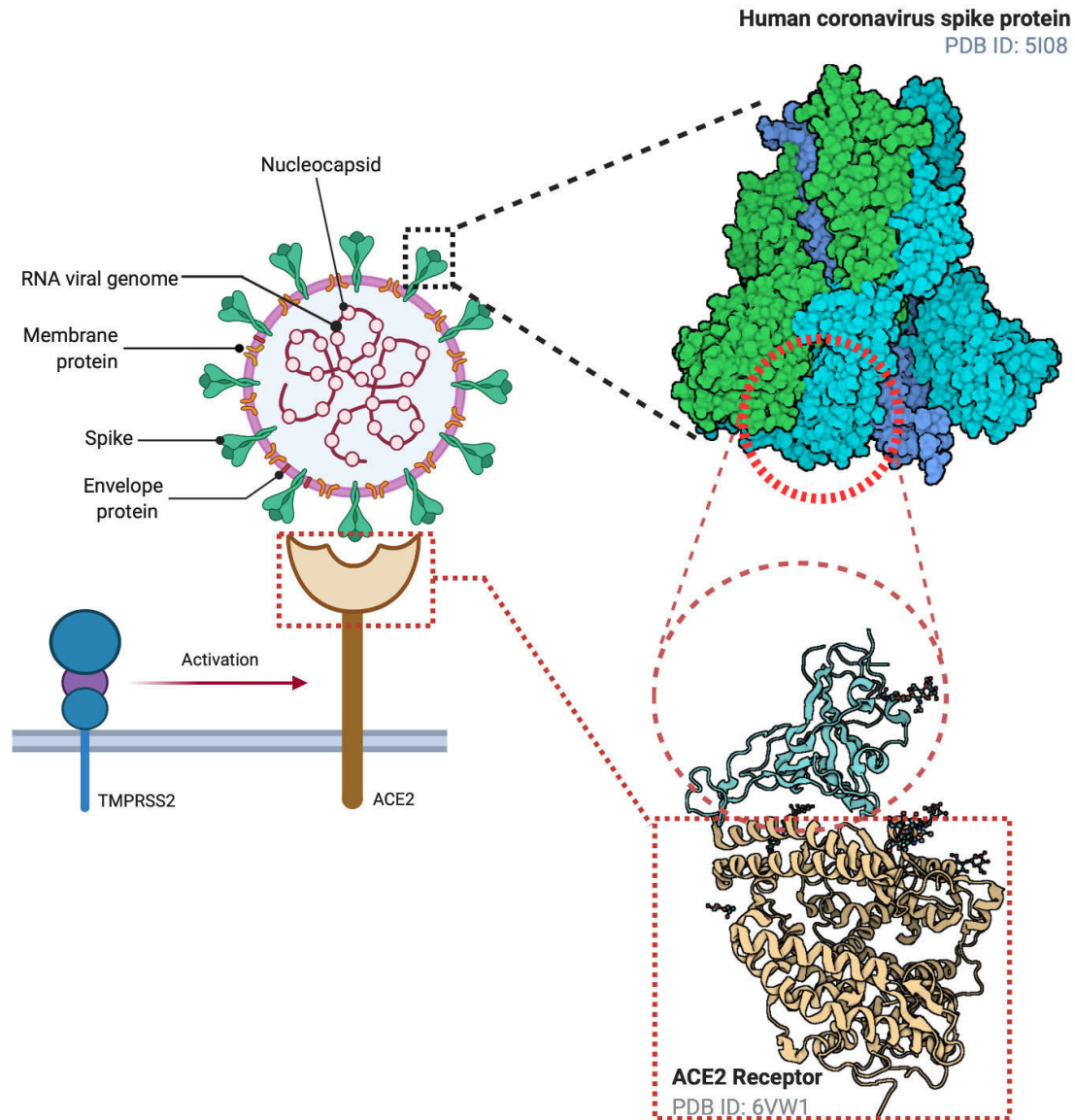
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**Figure 1** Central role of the renin–angiotensin system in blood pressure homeostasis. The cascaded system involves a number of enzymes and receptors. Angiotensinogen produced by the liver is converted to angiotensin I (Ang I) by renin secreted by the kidney. ACE2 is important in the conversion of Ang I to angiotensin (1–9) and angiotensin II (Ang II) to angiotensin (1–7). Ang II and angiotensin (1–7) exert a number of actions by binding to AT1, AT2 and MAS receptors. ACEi, ACE inhibitor; AT1, angiotensin type 1; AT2, angiotensin type 2.



**Figure 2** Gene structure of ACE2 compared with ACE and collectrin. HEMGH illustrates the zinc-binding motifs—the active sites of the protein. The exact locations of the genes are indicated. (Adapted from: Clarke and Turner).<sup>53</sup>



**Figure 3** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel member of the *Betacoronavirus* genus, and like other coronaviruses, has the characteristic appearance of spikes 'crowning' a lipid membrane enveloped viral particle containing the non-segmented positive-sense single-stranded RNA genome.<sup>44 45</sup> Each monomer of the trimeric spike (S)-glycoprotein consists of two subunits, namely S1 and S2, that allows binding to the ACE2 receptor and subsequent fusion of the viral and host cell membranes, respectively. The serine protease, TMPRSS2, plays an integral part in the activation and induction of a conformational change of the S-protein–ACE2 receptor complex to allow the virus particle to fuse with the host cell.

the C-terminal dipeptide from the decapeptide Ang I to form the octapeptide Ang II. Ang II binds the angiotensin type 1 (AT1) receptors and has a well-established vasopressor role in regulating blood pressure (BP), fluid and electrolyte balance (via aldosterone).<sup>11</sup> ACE inhibitors do not affect the ACE2 activity directly but may have indirect effects on ACE2 expression.<sup>15</sup> Furthermore, ACE plays an important role in the kinin–kallikrein system by inactivating the vasodilator bradykinin.<sup>16</sup>

#### Collectrin

Collectrin has 47.8% sequence similarity to the C-terminal region of ACE2 including the non-catalytic extracellular, trans-membrane and cytosolic domains of the protein, but lacks the catalytic domain.<sup>17</sup> Collectrin plays an important role in vesicle transport and membrane fusion. This is important in the exocytosis of insulin and other membrane proteins and is therefore an

attractive possible treatment target for diabetes mellitus, polycystic kidney disease and hypertension.<sup>17</sup> The collectrin gene is regulated by hepatocyte nuclear factor-1 $\beta$ , and disruption of this factor leads to maturity onset diabetes of the young (MODY) type 5 diabetes mellitus.<sup>17</sup>

#### Sites of expression

ACE2 is expressed in a number of tissues but most abundantly in lung alveolar epithelial cells, kidney, heart, gastrointestinal tract and testes.<sup>13 18</sup> Soluble ACE2, a form lacking membrane anchors, is shed at very low levels into the circulation following the cleavage action of sheddases ADAM (A Disintegrin and Metalloprotease) 10 and ADAM 17 between amino acids 716 and 741. This form does not reflect tissue levels and has a very short half-life.<sup>19</sup>

## ROLE OF ACE2 IN PHYSIOLOGY AND PATHOPHYSIOLOGY

ACE2 regulates the levels of Ang I and Ang II by converting Ang I to Ang (1–9), and Ang II to Ang (1–7) which bind the MAS and AT2 receptors forming the ‘protective arm’ of the renin–angiotensin system resulting in vasodilation, increased nitric oxide synthesis, anti-inflammatory and antifibrotic effects. This counterbalances the ‘classical’ vasoconstrictive, proinflammatory and profibrotic effects of the Ang II/AT1 arm<sup>20–22</sup> (figure 1).

ACE2 also plays an integral role in neutral amino acid transport as a chaperone for the sodium-dependent amino acid transporter B<sup>0</sup>AT1 in the intestine.<sup>23</sup> Mutations in this system lead to Hartnup disease, an autosomal recessive inborn error of metabolism affecting the absorption of non-polar amino acids characterised by pellagra, cerebellar ataxia and psychosis.<sup>23</sup>

### Evidence from mouse models

#### ACE2 gene knockout (KO)

KO mouse models have provided some evidence for the role of ACE2 but results have been divergent, depending on the mouse background used. For example, in C57BL/6 KO mice a moderate increase in BP was noticed, whereas in 129/SvEv KO mice no difference in BP was noted.<sup>24</sup>

ACE2 appears to be important for normal cardiac function and contractility.<sup>20</sup> The hearts of the KO mice showed clear structural abnormalities with contractility defects and a reduction in BP was also noticed with no hypertrophic or fibrotic changes.<sup>20</sup>

Other studies reported contrasting findings with no morphological changes and normal cardiac function.<sup>24,25</sup> They also noted normal fertility and a normal lifespan in their experimental animals. It is therefore postulated that ACE2 has limited effects on cardiac function and BP control and that other genetic and possibly environmental factors may be important for the function of ACE2. The difference in findings may be due to the mice strains used, and results therefore remain controversial.<sup>24</sup>

In lung tissue, ACE2 KO mice had significantly worse outcome in induced acute respiratory distress syndrome with increased vascular permeability and pulmonary oedema. Treatment with recombinant ACE2 rescued this phenotype, underlining the protective role of ACE2 in contrast with the disease-promoting effects of ACE, Ang II and AT1 receptor stimulation.<sup>25</sup>

ACE2 KO in renal disease showed exacerbation of existing hypertension-induced kidney disease.<sup>20,24</sup> Furthermore, ACE2 appears to play a protective role in diabetic kidney disease.<sup>20,24</sup>

#### Overexpression of ACE2 gene in transgenic models

There are limited data from transgenic models. When overexpressed in heart tissue, ventricular tachycardia and sudden death was observed.<sup>26</sup> In the kidney, overexpression of ACE2 appeared to be protective against diabetic kidney disease.<sup>27,28</sup> Transgenic mice were also found to be more susceptible to SARS-CoV infection.<sup>28</sup>

### Function of ACE2 and polymorphisms in disease

#### Cardiovascular system

ACE2 expression was found to be decreased in patients with heart failure and levels correlated with disease severity.<sup>29</sup> It was postulated that higher ACE2 levels may be cardioprotective, as cardiac dysfunction was noted in ACE2 KO mice.<sup>30</sup> ACE2 deficiency upregulates mediators of atherogenesis and ACE2 suppresses vascular inflammation with subsequent development of atherosclerosis.<sup>31</sup> ACE2, via Ang (1–7), increases nitric oxide which has vasodilatory and antithrombotic effects.<sup>32</sup>

The apelin peptide family protects against the development of cardiovascular disease. Apelin KO mice have reduced ACE2 messenger RNA and ACE2 protein levels.<sup>33</sup> Apelin deficiency can potentially lead to cardiovascular disease including heart failure and hypertension with impaired contractility and hypertrophy.<sup>33</sup> When AT1 was also inhibited in apelin KO mice, the induced phenotype was rescued. This was accompanied by an increase in ACE2 underlining its possible protective traits.<sup>34</sup>

Studies investigating the effects of single nucleotide polymorphisms (SNPs) of ACE2 in hypertension showed mixed results. A number of SNPs of the ACE2 gene are associated with essential hypertension (EH) in humans, as the gene is located in area on the X chromosome<sup>20,35</sup> known to be associated with hypertension disorders on the X-chromosome. ACE2 downregulation results in BP dysregulation.<sup>33</sup> ACE2 deletion in rats led to impaired baroreflex sensitivity and autonomic dysfunction.<sup>36</sup>

ACE2 polymorphisms in dyslipidaemia have also been studied. A variant ACE2 rs4646188 was found to be a potential marker of susceptibility for EH, dyslipidaemia and related ischaemic stroke in Asian communities.<sup>37</sup> However, another study found that this variant was not correlated with a dyslipidaemia in Uyghur communities.<sup>8</sup> Therefore, variant effects differ in various populations and environmental and genetic factors are important.

#### Respiratory system

The role of ACE2 in COVID-19 is now well established and there is intense interest in how it influences the unusual pathophysiology seen. Lung ACE2 levels decline with age in rat models<sup>36</sup> and this decline is higher in males. This supports the observation that older men are more susceptible to SARS-CoV-2 infection.

Certain variations in ACE2 may increase individual susceptibility to COVID-19 infection, but these are very rare.<sup>38</sup> It has been postulated that downregulation of ACE2 may reduce the susceptibility to COVID-19, but in animal models it was found that lower levels of ACE2 were also associated with lung oedema and worsening acute lung injury.<sup>39</sup>

#### Endocrine system and metabolism

Some polymorphisms of ACE2 may be useful markers for type 2 diabetes mellitus and some polymorphisms are associated with cardiovascular complications in this setting.<sup>40</sup> In the pancreas, ACE2 has glycaemia-protective properties,<sup>41</sup> and in the kidney low ACE2 levels are associated with worsening diabetic nephropathy.<sup>42</sup> Diabetic retinopathy is associated with the activation of the classical arm of the renin–angiotensin system and the proinflammatory, profibrotic and activation of oxidative stress of this arm can be counteracted by ACE2/Ang (1–7).<sup>43</sup>

ACE2 also plays an important role in the browning of adipose tissue leading to favourable metabolic effects and weight loss.<sup>33</sup>

#### Renal system

ACE2 is extensively expressed in tubular epithelial cells and also the vascular components and glomerular epithelium.<sup>44</sup> In hypertensive kidney disease, ACE2 levels were decreased.<sup>20</sup> Although ACE inhibitors and angiotensin receptor blockers do not affect the enzymatic activity of ACE2, they increase ACE2 gene expression in animal studies.<sup>45</sup>

In diabetic kidney disease, ACE2 is protective and overexpression of ACE2 in podocytes reduces diabetic kidney disease in animal models.<sup>27</sup>

### Neurological system

The ability of ACE and ACE2 to cleave amyloid- $\beta$ -peptidase and the use of inhibitor drugs of the renin-angiotensin system and their role in the development Alzheimer's disease have been investigated with no concrete conclusions at this stage.<sup>46</sup>

### Gastrointestinal system

ACE2 is important in regulating intestinal amino acid transportation and plays a vital role in the expression of antimicrobial peptides and prevention of gut dysbiosis.<sup>47</sup> ACE2 deficiency resulted in increased susceptibility for intestinal inflammation.<sup>47</sup> In the liver, ACE2 is protective against the development of fibrosis via Ang (1-7).<sup>48</sup> In ACE2 KO mice, there was significant worsening of liver fibrosis in chronic induced liver conditions. Interestingly, this was not observed in acute liver injury.<sup>48</sup>

### Neoplasms

Overexpression of ACE2 and DNA hypomethylation was observed in tumours including colon adenocarcinoma, kidney papillary cell adenocarcinoma, pancreatic, rectum, stomach and rectum adenocarcinoma.<sup>49</sup> Lung adenocarcinoma had significant upregulation of ACE2 RNA expression.<sup>49</sup> Furthermore, histone modification and glycosylation may be involved in abnormal ACE2 expression in tumour development.<sup>49</sup>

### Pregnancy and fertility

ACE2 and Ang (1-7) are present in uteroplacental tissue and are important in placentation of normal pregnancy via vasoactive regulatory action. ACE2 and Ang (1-7) expression is similar in uncomplicated and pre-eclamptic pregnancies.<sup>50</sup> ACE2 also appears to be important in the regulation of renal adaptations in pregnancy by enhancing the increased expression of renal Ang (1-7).<sup>51</sup>

## CONCLUSION

ACE2 plays a complex role in disease that has relevance beyond the cardiovascular and respiratory systems. Its role in the pathophysiology of COVID-19 is a source of ongoing research and makes it an attractive possible therapeutic target. Of recent interest is the effect of tobacco smoking on ACE2 expression in the lung which implies that smoking could increase the susceptibility to lung infection by SARS-CoV-2.<sup>52</sup> It is clear that further studies of its genetic and physiological roles will be required to fully understand how it could be therapeutically modulated in disease.

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