



## The Role of ACE2 Receptor and its Age Related Immunity in Covid-19

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### ABSTRACT

World is facing the Coronavirus pandemic, which is resulting in large number of deaths and economic burden to the society. SARS-CoV-2 is the causative agent for COVID-19 infection. SARS-CoV-2 is a single stranded RNA molecule which enters the human through ACE2 receptor. ACE2 is widely expressed in the human tissues, primarily in the heart, kidney and testis and secondarily in the lungs, blood vessels and colon. Therefore, SARS-CoV-2 can infect the lungs and other organs as well leading to multiple organ damage. ACE2 receptor regulates the Renin Angiotensin System (RAS). Therefore, increasing SARS-CoV-2 infection decreases ACE2 receptor and results in dysfunction of RAS, imbalance of blood pressure and inflammation of airways. This provide direct link between the ACE2 receptor and COVID-19 infection. ACE2 expression and immune response may fluctuate throughout the life of human which accounts for variation of disease severity. ACE2 level decreases with age i.e. children have higher expression of ACE2 as compared to the older people and children also possess strong innate immunity leading to early control of the infection comparing to older people. Hence, children are found to be less susceptible to COVID19 infection then the older ones. The difference in ACE2 expression and host immune response to SARS-CoV-2 infection can explain the severity of disease progression in different age, gender and race.

**Keywords:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), immune response, ACE2 expression, Coronavirus pandemic, COVID-19, Renin angiotensin System (RAS).

### INTRODUCTION

COVID-19 is caused by the recently emerged Coronavirus (SARS-CoV-2), which was firstly reported in December 2019 in the city of Wuhan China. Like other coronaviruses (SARS-CoV-1 and MERS-CoV), human-to-human transmission is well established for this virus as well, which has now spread globally.<sup>1</sup> SARS-CoV-2 is an envelope, positive-sense single-stranded RNA virus, from beta coronavirus genera of coronaviridae family. SARS-CoV-2 shares 88% genetic identity to bats-derived SARS-like coronaviruses.<sup>2</sup> On March 11, 2020, the World Health Organization (WHO) declared the outbreak of SARS-CoV-2 a global pandemic, reporting community scale transmissions occurring in every continent outside Antarctica.<sup>3</sup> Respiratory tract is the main target of SARS-CoV-2 for infection leading to clinical signs like fever, dry cough, fatigue and dyspnoea. Acute respiratory disease syndrome characterised by difficulty in breathing and low blood oxygen level seen in COVID-19.<sup>4,5</sup> Risk factors include older age, male gender, high BMI and co-morbidities like obesity, hypertension cardiovascular disease, diabetes or chronic respiratory disease. In human corona virus enter via host cell surface enzyme ACE2 receptor by utilize their S protein for SARS-1 and 2. From person to person spread of virus via droplet form. Its incubation period is thought to be 5.1 days and onset of symptoms up to 14 days after exposure.<sup>6</sup> For screening for COVID-19 fever is the most

common symptom in addition to cough and shortness of breath may present as a decline in function.<sup>7</sup> After entering pneumocytes, SARS-CoV-2 down regulates ACE-2 expression, decreasing angiotensin-2 metabolism. Elevated angiotensin-2 increases pulmonary vascular permeability and inflammation, hence worsening the lung injury. Angiotensin-2 levels have been found to be increased in COVID-19 patients compared to healthy adults.<sup>5</sup> ACE2 is a cellular receptor in a similar way as SARS-CoV-1. Importantly, SARS-CoV-2 is more pathogenic, at least in part because of its 10- to 20-fold increased binding affinity to ACE2.<sup>6,7</sup> In this article we will discuss about the ACE 2 receptor and its role in the SARS-CoV-2 pandemic.

### ACE2 Receptor

Angiotensin-converting enzyme (ACE) 2 could be a potent negative regulator of Renin angiotensin system (RAS), which is critical for maintaining the homeostasis of RAS. The human ACE2 gene is found on chromosome Xp22 and includes 18exons. ACE2 is a homologue of ACE. In RAS, ACE2 degrades Angiotensin II, (vasoconstriction, pro-inflammation, and pro-fibrosis) and converts it into Ang (1-7) (vasodilatory, anti-proliferative and apoptotic). The Renin Angiotensin System (RAS) plays a key role in maintaining vital signs' homeostasis, as well as fluid and salt balance in mammals. Computational modelling and infection experiments using HeLa cells that express ACE2



protein from humans, Chinese horseshoe bats, civets, pigs, and mice provided evidence that ACE2 is the receptor for SARS-CoV-2 entry to the host cells during SARS-CoV infection.<sup>8</sup>

ACE2 receptors are primarily localised within the heart, kidneys and testes, and at a lower level in a variety of tissues of colon and lung. ACE2 also possess its significance in other organs like liver and intestines too. In the heart, ACE2 is expressed in the endothelium as well as cardiomyocytes. In kidney ACE2 distributes to the luminal surface of tubular epithelial cells and in testes, to the adult Leydig cells. ACE2 is enriched in the kidneys. In the renal cortex the activity of ACE2 is even more than that in the heart. The expression level of ACE2 decreased both in the acute kidney injury and in several models of chronic kidney disease induced by hypertension, diabetes and nephrosis, which disrupts the homeostasis of RAS in the kidneys and worsened the pathological changes in the kidneys. ACE2 regulates the amino acid absorption in the kidney and the gut and modulates the expression of transporters for amino acid.<sup>9</sup> ACE2 was identified as the receptor for SARS-CoV-2, which cause acute lung failure in humans. Hence ACE2 is vital for the viral entry to the host cells during SARS-CoV infection.<sup>8</sup> Epithelial cells of lung express high levels of ACE2. ACE2 has been implicated in acute lung injury by inducing an imbalance in the RAS. Evidence includes (1) a decrease in pulmonary ACE2 and an increase in Ang II levels occurs; (2) supplementation with ACE2 or inhibition of Ang II improves outcomes; and (3) a scarcity or decrease of pulmonary ACE2 aggravates viral-induced acute lung injury.<sup>3</sup> Together with respiratory tract, ACE2 has been observed in nasal and bronchial epithelial cells. Capillary endothelial cells also express high levels of ACE2. These data indicates that type II pneumocytes (targets of viral entry and replication) along with the related capillary endothelium could be a primary site of SARS-CoV-2 entrance. ACE2 upregulation has also been described in airways in patients with chronic respiratory disease who are smokers.<sup>11</sup>

From human organs Single-cell RNA sequencing data revealed that, cells that express ACE2 included 30% of ileum epithelial cells, 7.5 % of cardiomyocyte, 4 % of proximal tubular epithelial cells, 2.4 % of bladder urothelial cells, 1 % of esophageal epithelial cell, and 2 % of respiratory tract epithelial cells. SARS-CoV-2 may attack these cells after binding with ACE2.<sup>8,9</sup>

In a phase-2 clinical trial of recombinant ACE-2 infusion in adults with acute respiratory distress syndrome (ARDS), there was significant decrease in angiotensin-2 levels, and increase in Ang-(1-7) and surfactant protein-4 levels.<sup>2,10</sup>

### Relationship between ACE2 Receptor and SARS CoV 2

The nomenclature arises from the spike (S) protein present on the surface of the virus giving it a crown like appearance. S-protein has two subunits: S1 and S2. S1 contains amino- terminal domain and a receptor- binding domain (RBD) whereas S2 have a fusion peptide (FP) region

and two heptad repeat regions: HR1 and HR2.<sup>12-14</sup> The genetic sequence of SARS COV 2 is 88% close to two bat coronavirus accounts i.e bat-SLCoVZC45 and bat-SL-CoVZXC21 for the zoonotic origin (bat). SARS COV 2 shows 79% and 50% genetic similarity with SARSCoV-1 and MERS CoV, respectively.<sup>15</sup>

SARS COV2 enters the host cell through the target receptor i.e. Angiotensin Converting Enzyme-2(ACE 2). As the virus protein attached with the ACE2 receptor of the host through the receptor-binding domain (RBD) of the S1 and S2 domains of the spike protein.<sup>16</sup> The cellular entry is promoted by the proteolytic cleavage of ACE2 by transmembrane serine protease-2 (TMPRSS2). After cleavage virus releases its genetic material (RNA) into the host cell cytoplasm for further replication.<sup>17</sup> ACE 2 also regulates Renin Angiotensin System (RAS).<sup>18</sup> Increase in the viral load infection decrease the ACE 2 expression resulting in dysfunction of RAS, imbalance of blood pressure, fluid/electrolyte and increases vascular permeability and inflammation of airways.<sup>4</sup> In cohort study, 12 COVID 19 patients were compared with healthy subjects show the elevated level of circulating Ang II level in the COVID19 patients. Hence, it provides a direct link between the ACE2 down regulation, RAS imbalance and multi-organ damage with SARS-CoV-2.<sup>19, 11</sup> Therefore, the relation between ACE 2 receptor and SARS CoV 2 is evident for the COVID19 infection.

SARS-CoV also enters the host cell via ACE2 receptor. But the binding affinity of SARS CoV-2 is stronger with ACE2 receptor compared with SARS-CoV, therefore former accounts for higher rate of infection than the initial SARS-CoV.<sup>3</sup>

Potential therapies are available which prevents the binding of ACE2 receptor and SARS- CoV-2 by blocking the RBD of the S1 and S2 domain of the viral Spike protein or blocking of TMPRSS2. For example, a Janus kinase (JAK) inhibitor (baricitinib and ruxolitinib) are currently using for treatment of COVID 19 which are clinically approved for other indication.

Another treatment includes inhibition of viral entry or fusion by administration of monoclonal antibodies which targets S protein.<sup>4</sup>

CD 147 and glucose regulated protein are newly discovered secondary receptor for SARS CoV 2 entry in the host cell.<sup>20, 21</sup> Therefore it is still not confirmed that ACE2 is the sole receptor for viral entry.

### Fluctuations of ACE2 Receptors Throughout Life Span and How it Affects Human Body

ACE2 variants have several remarkable differences in the frequency of distribution. Ethnic and racial lines have been stated like Asian males might have bigger expression of tissue ACE2. It is also stated in results of studies that generally, adults have lower levels of ACE2 than children.<sup>22</sup> ACE2 has also been linked to neurodegenerative disease other than its role in immune response and it could also



show some supplementary benefits by further perceiving of its pleiotropic effects. ACE over-expression implies to supercharge the immune response.<sup>23</sup> The Human Protein Atlas database displayed that duodenum, gall bladder, testis, kidneys, small intestine, rectum, colon and adrenal gland had relatively higher expression levels of the ACE-2 protein. Hence, it is indicated that the tissues other than lungs may also get infected by SARS-CoV-2.<sup>5</sup> There is a difference observed in the mortality rate between males (2.8%) and females (1.7%) by COVID-19, and it is explained by the location where the ACE2 is located which is on X chromosome, where there might be alleles that negotiate resistance to COVID-19. The immune response and disease severity could also get influenced by the different immunoregulatory functions of oestrogen and testosterone sex hormones.<sup>4</sup> It is also stated in results of some studies that decreased ACE2-MasR axis might result in fibrosis, inflammation and oxidative strain of the thoracic aorta and the expanded vulnerability to vascular injury and cardiovascular disease in elderly population may also be explained with the altered expression of RAS components.<sup>24</sup> Accessible reports to date show that COVID-19 seems to be rare in children. Many factors like maturational changes in the axonal transport system, children having better innate immune response and healthier respiratory tract are suggested to be reasons for the less susceptibility of COVID-19 among children.<sup>25</sup> According to some studies the ACE2 levels in children (6 months to 17 years of age) is found to be 13-100 U/L compared with adults who have around 9-67 U/L.<sup>22</sup> Buniyavanich et al has evaluated in a study that the nasal epithelium is one of the first sites of infection with SARS-CoV2 and the younger children in the age group of 1-4 years have the higher ACE2 expression than compared to the age group of other children like 10-19 years and young adults and adults and the ACE2 has been proved to bind the SARS-CoV2 and promote its internalization of the virus into human cells which may conclude the factor that younger children are at low risk.<sup>26</sup> The patients who died from COVID-19 had lesser lymphocyte count when compared to the survivors, resulting in the probability of the correlation between lymphopenia and severity of COVID-19 infection.<sup>27</sup> The slower, less synchronized and not well organized immune responses of older adults make them more open to emerging infections. The key protection is likely to counterbalance antibodies directed at the spike protein binding site for the ACE2 receptor, although a challenge may be there because of the higher affinity of SARS-2S protein for ACE-2. Immunomodulatory and anti-viral treatments are currently an area of intense study in the future for vaccination strategies.<sup>7</sup>

### **Influence of ACE 2 Receptors on the Immune System**

ACE2 is the enzyme which keeps the balance between Ang II and Ang(1-7). Lung injury gets worsened when inflammation and pulmonary vascular permeability is caused due to upraised angiotensin-2. Angiotensin-2 levels have been found to be increased in patients suffering from COVID-19 when compared with the healthy individuals.

SARS-CoV-2 viral loads and lung injury severity do have crucially positive association with Angiotensin-2 levels possibly via ACE-2 down-regulation.<sup>2</sup> It has been stated in some articles that the potential targets of the SARS-CoV-2 infection are those tissues which are having greater expression of ACE-2 levels. The ACE-2 rich organs are known to be heart, testes and kidneys and is also widely present in the lungs, intestine, liver and brain. The primary organ where the SARS-CoV-2 attacks is found to be in the lungs.<sup>8</sup> As it has been suggested that the differential levels of ACE2 might be the partial responsible factor for the range of disease spread noticed among patients. Hence, in the context of this pandemic the capable use of ACE Inhibitors is a big issue to debate.<sup>28</sup> Luca Roncati et al pulled a hypothesis in their article that ACE Inhibitors and AngiotensinII receptor antagonist could get replaced by CC Blockers, Diuretics, Vasodilators or Adrenergic Receptor Blockers during this pandemic of COVID-19 as they might get the elderly people to be more susceptible of getting infected from the virus because these class of drugs can induce many elderly or middle aged people to be more at risk to the virus by expanding ACE2 receptors.<sup>29</sup> Whereas on the other hand it is also stated in many other articles that children are less susceptible to this virus because of having higher expression of ACE2 receptors, trained immunity and a constitutional higher lymphocyte count, this can relate to how the ACE2 receptors co-relate with the immunity system.<sup>30</sup> An article stated that immune signatures and ACE2 expressions was found negative in the lung tissue of females and younger persons but positive in males and older persons which collectively indicates that if the females and younger persons are the ones got infected by SARS-CoV-2 than they will have weaker immune signatures and on the other hand if males and older persons get infected by the SARS-CoV-2 they will possess stronger immune signatures. And that conclusively suggests that males and older people are likely to show excessive immune response with the infection.<sup>5</sup> Decreased ACE2 is the end result when a tumor gets infected by the SARS-CoV-2 which brings out decreased immune infiltration in the tumor microenvironment, which further could worsen the prognosis in UCEC and KIRP after SARS-CoV-2 infection.<sup>31</sup> Deficiency of ACE2 receptors is associated with many conditions like hypertension, diabetes etc. which make the person more vulnerable to infection.<sup>32</sup> The effects of the ACE substrates are the important areas of interest and have great promise for novel therapies as they elicit increased immune response and the downstream pathways that initiate these effects.<sup>23</sup>

### **CONCLUSION**

This study suggests that the role of ACE 2 in COVID 19 and understanding the correlation between age, gender, race with SARS CoV 2 pandemic. ACE 2 receptors are widely distributed in the human tissues. Therefore, SARS CoV 2 may also affect other tissues apart from lungs leading to multiple organ damage. The relationship between the immune signature and ACE 2 expression in the human may shows variation which results in difference of immune



response towards SARS CoV 2 infection. Although, the immune response of older person is less coordinated, less effective and slower comparing to children making them more susceptible to COVID-19 infection. Keeping these facts in mind, emerging treatment or vaccines are currently an area of intense study.

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