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Overview of ACE-2 Receptor, Its Structure and Polymorphism and its Susceptibility to SARS-Cov-2, Influences of COVID-19 on Multi-Organs Cardiovascular Comorbidities, and COVID-19 Disease Outcome

Srinjoy Chattopadhyay[1], Vanshika Saini[2]

Abstract: ***Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects human cells via binding a "spike" protein on its surface to angiotensin-converting enzyme 2 (ACE2) within the host. ACE2 is crucial for maintaining tissue homeostasis and negatively regulates the renin-angiotensin-aldosterone system (RAAS) in humans. We employed our basic understanding of bioinformatics to give an overview of ACE-2 receptor, its structure and polymorphism and its susceptibility to SARS-Cov-2, influences of COVID-19 on multi-organs cardiovascular comorbidities, and COVID-19 disease outcome. This study may help in the significant understanding of the ongoing pandemic due to SARS-CoV-2 infection.***

Keywords: ACE-2 receptor, SARS Cov-2, Spike glycoprotein, Receptor binding domain, dimers, transmembrane helix, virions, Collectrin like domain, polymorphism, RAAS, disintegrin, ARDS, TYK2 gene

1. Introduction

The world had witnessed the deadliest destruction of lives within the single year 2020. Still, we haven't yet been stabilised on the commencement of a new year from the riling ravage that wreaked havoc throughout the world. Despite being baffled by a single infinitesimally small virus a horde of scientists and research enthusiasts have abnegated themselves in finding a cure which is quite a tough challenge. A new human viral disease called severe acute respiratory syndrome (SARS) first appeared in humans in Guangdong Province in China in the fall of 2002. A doctor who treated these patients travelled to Hong Kong on February 21, 2003, and checked into a hotel. He became ill and died in the hospital the very next day. During his stay in the hotel, the virus was transmitted to 10 other residents, who subsequently flew to Singapore, Vietnam, Canada, and the United States before symptoms were evident. A major viral epidemic was spread by air travel. This small number of infected people efficiently transmitted the new SARS coronavirus to other individuals around the world, such that 8, 000 people in 29 countries became infected in less than a year. The case-fatality ratio was almost 1 in 10, a chilling statistic that activated health organizations worldwide. The scientific community mobilized with unprecedented speed and cooperation, and the causative agent was identified within only a few months. The SARS pandemic of 2002–2003 is believed to have been caused by a bat coronavirus that first infected a civet and was then passed onto humans. The isolation of a new SARS-like coronavirus from bats suggests that the SARS coronavirus could have infected humans directly from bats. A single colony of horseshoe bats (*Rhinolophus* sinicus) in Kunming, Yunnan Province, China, was sampled for coronavirus sequences over 1 year.

The SARS-Cov-2 variant has spread globally across many countries/territories and has caused over three million deaths. has now spread to a large number of countries/territories and has caused over three million deaths. The virus has been mutating and adapting during this period. Significant effort has been spent on identifying these variations and their impact on transmission, virulence and pathogenicity of SARS-CoV-2.

Binding of the SARS-CoV-2 spike protein to the angiotensin-converting enzyme 2 (ACE2) promotes cellular entry. Therefore, human ACE2 variations are supposed to influence susceptibility or resistance to the virus. A deeper understanding of the evolution and genetic variations in SARS-CoV-2 and ACE2 could contribute to the development of effective treatment and preventive measures. (Antony and Vijayan) [1]

Recent studies reveal the angiotensin-converting enzyme 2 (ACE2) has been identified as a functional and active receptor for the SARS coronavirus (SARS-CoV) and its binding site on the SARS-CoVS glycoprotein has been found between two amino acid residues 303 and 537. ACE2 is a homolog of the metalloprotease angiotensin-converting enzyme ACE and was an essential heart function regulator. (Laboratory of Experimental and Computational Biology, CCR, NCI-Frederick, NIH, Frederick, MD 21702-1201, USA) [2]

The recent outbreak of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has severely damaged the natural flow of life (Amanat Ali & Ranjit Vijayan) [3]. Genomic studies have established that SARS-CoV-2 belong to the betacoronavirus genus, which also includes SARS-CoV and MERS-CoV that were associated with previous outbreaks of relatively smaller scale 4-6. These coronaviruses attach to the host cell with the aid of the spike (S) glycoprotein present on its envelope. Coronavirus S

glycoprotein is composed of two subunits—the S1 subunit is important for binding to the host cell receptor and the S2 subunit is responsible for the fusion of the virus and the host cell's membrane. Angiotensin-converting enzyme 2 (ACE2), an enzyme located on the outer surface of a wide variety of cells, is the primary host cell target with which the S protein of SARS-CoV and SARS-CoV-2 associates[7-9]. The receptor-binding domain (RBD) of the S1 subunit of these viruses binds to the outer surface of the claw-like structure of ACE2.

This article mainly focuses on the overview of SARS-Cov-2 and ACE-2 receptors, a correlation between them and the susceptibility that arises due to the polymorphic property of the ACE-2 receptor and some related diseases from a medical point of view.

SARS-Cov-2: A brief account

As the origin suggests, coronavirus is a single positive-stranded RNA virus that belongs to the family Coronaviridae which contains a large non-segmented genome (containing about 30, 000 nucleotides). It also contains a large surface glycoprotein gene, an integral membrane protein gene, and a nucleocapsid protein gene. These genes are arranged on the genome in a specific order (in the 5' ~3' direction) but maybe interspersed with additional genes encoding further structural or non-structural proteins. There is also a virion envelope bearing pronounced surface accession projections. These projections are composed of the large surface glycoprotein (200 k Da) that characteristically exhibits a coiled structure. The prototype of the coronavirus genus is the avian infectious bronchitis virus. The name "coronavirus" is derived from the solar corona-like (lain-corona-crown like) appearance of virus particles in negatively stained electron micrographs. We can focus on some characteristic morphological features of coronavirus that differ it from torovirus (genera that share the same family with coronavirus).

A newly emerged strain of novel SARS-CoV-2 variant VOC 202012/01 in southeast England in November 2020 raised an alarming emergency. VOC 202012/01 is defined by 17 mutations (14 non-synonymous mutations and 3 deletions), among which eight are located in the spike protein. Minimum three mutations have a potential biological significance. Mutation N501Y is one of the staple contact residues in the receptor-binding domain (RBD) and has been reported to enhance binding affinity to human ACE2 receptors. The function of mutation P681H is ambiguous, but it is located immediately adjacent to the furin cleavage site in spike, a known region of importance for infection and transmission.

The recent coronavirus disease 2019 (COVID-19) pandemic is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

By 29 June 2020, there had been 9, 962, 193 laboratory-confirmed SARS-CoV-2 infections globally, leading to 498, 723 deaths. As of 4 November 2020, there were no approved therapeutics or vaccines against SARS-CoV-2 and other human-infecting coronaviruses.

The spike (S) glycoprotein of SARS CoV-2 is a membrane-fusion machine, facilitates receptor recognition and viral entry into cells and is the primary target of the humoral immune response during infection [11, 12]. The S protein is a homotrimeric class I fusion protein that forms large protrusions from the virus surface and undergoes a substantial structural rearrangement to fuse the viral membrane with the host-cell membrane once it binds to a host-cell receptor [13, 14]. The S protein ectodomain consists of a receptor-binding subunit S1 and a membrane-fusion subunit S2 [12, 15, 16]. Two major domains in coronavirus S1 have been identified, including an N-terminal domain (NTD) and a C-terminal domain (CTD) also called receptor-binding domain (RBD). In RBD, S1 also contains two subdomains (SD1 and SD2) [15]. The S2 contains a variety of motifs, starting with the fusion peptide (FP). The FP is conserved across the viral family and composed of mostly hydrophobic residues, which inserts in the host-cell membrane to trigger the fusion event [12, 17]. Previous cryo electron microscopy (cryo-EM) studies on the stabilized ectodomain of SARS-CoV-2 S protein revealed a closed state of the S trimer with three RBD domains in "down" conformation, and an open state with one RBD in the "up" conformation, corresponding to the receptor-accessible state [15, 16]; these two states have also been observed in the recent cryo-EM structures of full-length wild-type S trimer[18] and other stabilization constructs of the ectodomain of S trimer ([18, 19]. Moreover, the mutation SARS-CoV-2 spike D614G has been reported to promote the infectivity of SARS-CoV-2 and enhances viral transmissibility in multiple human cell types, while the underlying structural basis remains not fully understood [19, 20].

ACE-2 Receptor

ACE2 is a transmembrane protein with an extracellular carboxypeptidase domain, located at the cell membrane in a variety of epithelial cells, including lung and airways, olfactory system, heart, kidneys, liver, pancreas and intestine[21]. ACE2 processes Angiotensin II to Angiotensin 1–7 (DRVYIHP) and Angiotensin I to Angiotensin 1–9 (DRVYIHPFH), both enhancing vasodilatation and reducing blood pressure. Hence ACE2 is protective in multiple cardiovascular diseases.2[4]

ACE2 is cleaved at the cell membrane by the ADAM17 protease (tumour necrosis alpha convertase, TACE), and by other proteases such as TMPRSS2, HAT and hepsin. The cleavage by ADAM17, in a process termed shedding, releases catalytically active soluble forms of ACE2 into the circulation, with a still unclear physiological function. Recombinant human ACE2 18-740 (rhACE2; i. e. GSK2586881/APN01) is being tested in clinical trials for diverse disorders including lung injury and pulmonary arterial hypertension. GSK2586881/APN01, and also B38-CAP, a bacterial-derived carboxypeptidase, which cleaves both Ang I and Ang II to Ang 1–7, are also in clinical trials for the treatment of SARS-CoV-2 infections. ACE2 expression is enhanced by interferon IFNα in human airway epithelial cells. ACE-2. Allostery and allosteric interaction might also be shown by ACE-2. Allostery can be defined as the structural and dynamic communication between at least two sites of a protein molecule, assume site P and Q, in such a way that any change in site P affects the conformation of

site B, rendering a response. This also approves that allostery is bi-directional (ChemMedChem 10.1002/cmdc.202000368) [21].

Biochemical studies reveal that ACE2 consists of a catalytic domain (Protease catalytic Domain, PD) and a Collectrin-like domain (CLD) that includes a neck domain, a single transmembrane sequence and a cytoplasmic 43 amino acid tail. The Spike protein is a trimer. Though, recent studies show that a monomeric form of the PD (ACE2 18-640) binds efficiently to the isolated RBD from Spike, but does not properly bind with full-length Spike trimer, while the PD (18-640)-Fc dimer can bind full-length Spike trimers with reduced on-rate but also reduced off-rate. CryoEM studies with SARS-CoV virions show that it binds to three soluble ACE2-Fc molecules. After interaction with ACE2, the Spike trimer undergoes conformational changes that promote membrane fusion. It is not yet known whether ACE2 must also undergo conformational changes to enable infection. It is shown that ACE2 is a dimer. Dimers provide additional probabilities for cooperative-allosteric effects, although these have not been described in ACE2. In the full-length solved structure, B°AT1 supports the formation of dimers by stabilizing the Neck Domain and the transmembrane helix of ACE2. This is in agreement with previous work showing that ACE2 constructs comprising the extracellular regions, Neck Domain and PD, are dimers. Dimers of ACE2 comprising PD fused to the Fc domain of antibodies have also been employed in research. The cryoEM solved the structure of full-length ACE2 and revealed the existence of two types of dimers: “closed-dimer” and “open-dimer”. For sake of convenience, the “open” and “closed” conformations of the PD can be designated as tight-dimer and loose-dimer respectively. In the tight-dimer conformation, the dimerization interface consists of a strong interaction between the CLD Neck domain and a second interaction between the two PDs. Interestingly, when the authors investigated by cryoEM the structure of full-length ACE2 in the presence of the RBD, they identified only the ACE2 tight-dimer in complex with RBD (in the presence of 10 mM leucine). In the loose-dimer confirmation, Accession occurs between the CLD and the PD which breaks the dimer interaction between the PDs and separates both domains about 25 Å. As a result, the PDs do not interact, while the dimer remains stable, mediated by the interface within the Neck domain. More notably, the cryoEM structure of the full-length ACE2 reveals that the PD can be stabilized in a new structural “twisted” conformation. In this new conformation, the PD claw-like surface shows changes which include the shifting of residues involved in the interaction with the RBD, most notably at the α1 helix of ACE2, the main point of interaction with the viral protein. In this figure below shown is RBD/ACE2-B0AT1 complex.2[1]

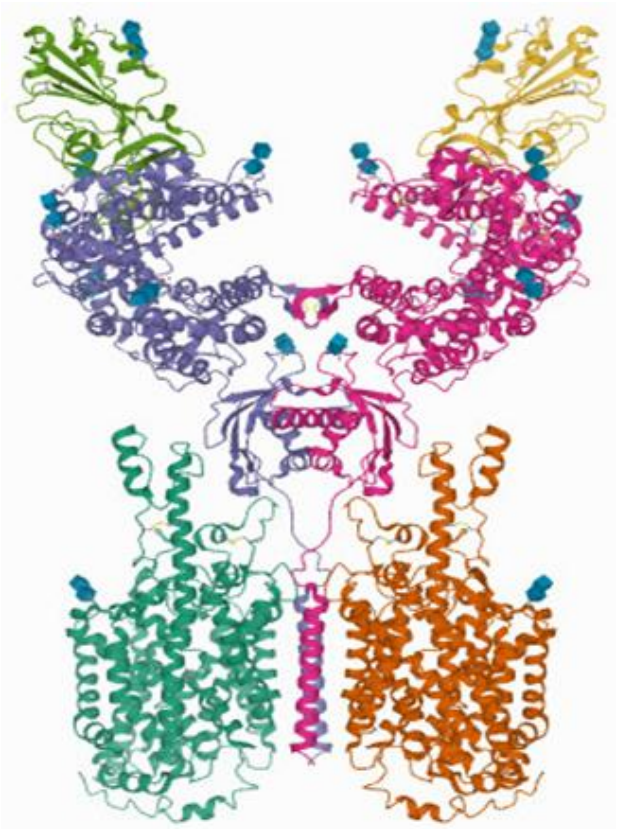

Figure 1: RBD/ACE2-B0AT1 complex. (source-RCSB PDB-Accession.-6M17) Structural basis for the recognition of SARS-CoV-2 by full. . .-Science

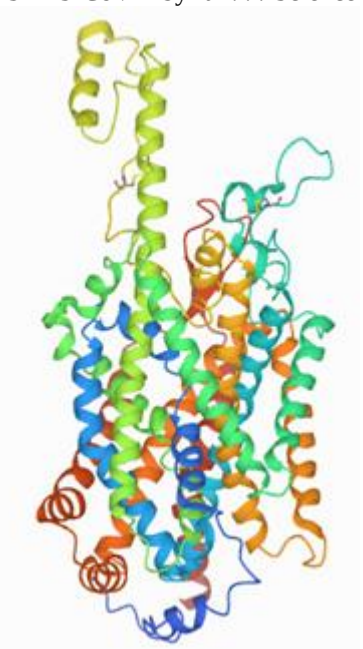

Figure 2: Sodium-dependent neutral amino acid transporter B (0) AT

Figure 3: Angiotensin-converting enzyme 2

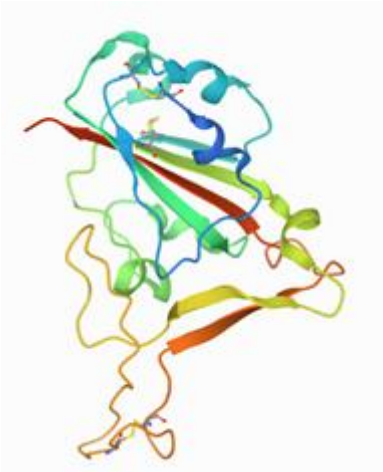

Figure 4: Accession rats pike protein S1 of SARS Cov-2

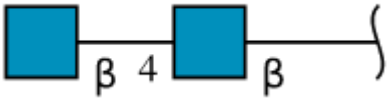

Figure 5: 2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4)-2-acetamido-2-deoxy-beta-D – glucopyranose

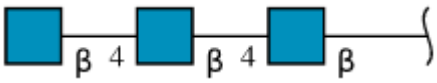

Figure 6: 2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4)-2-acetamido-2-deoxy-beta-D-glucopyranose-(1-4)-2-acetamido-2-deoxy-beta-D-glucopyranose

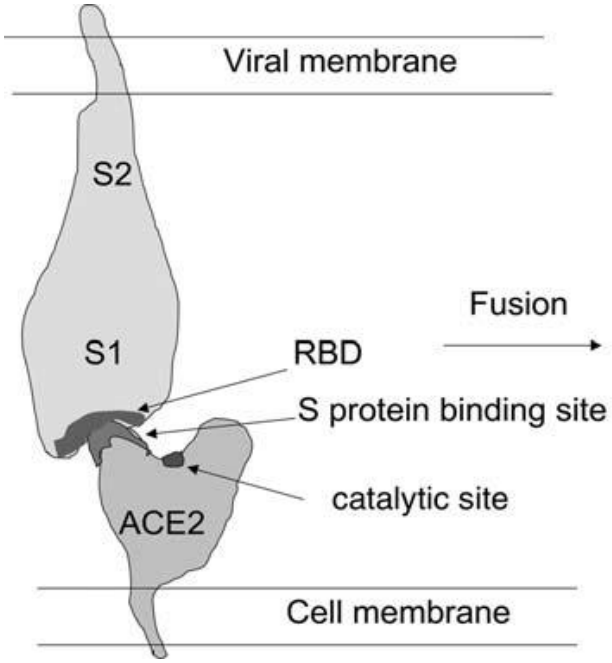

Figure 7: Schematic representation of the interaction between ACE2 and the SARS-CoV S-glycoprotein leading to binding and fusion
(Source-Biochemical and Biophysical Research Communications 314 (2004) 235–241)

Polymorphism and Susceptibility

As SARS-CoV-2 primarily depends on ACE2 for fusion and entry, some particular genetic variants of ACE2 could potentially alter the binding affinity and susceptibility to infection. Several Studies have shown the association between ACE2 variants and diseases such as cardiovascular disorders, hypertension and diabetes. by modifying the glycosylation site
(Asn90) in rats, ACE2 altered the ACE2 conformation which in turn improved S protein-mediated SARS-CoV infection. Thus, it might be obvious that genetic variation in ACE2 might have the power to affect the expression level, alongside protein conformation and stability. Thus, this could alter SARS-CoV-2 S protein affinity producing more susceptible or resistant individuals to infection. However, more work is needed to assert this possibility. Analysis of ACE2 expression records in normal lung cells showed that Asian males have a higher expression of ACE2 comparing white and African populations deducing, they could be more susceptible to a viral infection. The present studies also have shown an undeniable relationship between the susceptibility and the polymorphism of the ACE 2 receptor because it has deliberately been differing from one individual to another individual depending on several biochemical, Physiological factors. Cutting-edge research works are still going on to decode this.

In a study, it was reported that out of 31 ACE 2 receptor variants 13 were reported to bind more efficiently to SARS-CoV-2 whereas other 18 variants were found as interaction inhibitors. Among the 13 that helps in improving binding, Ser19Pro, Ile21Thr, Lys26Arg, Thr27Ala, Asn64Lys, and His378Arg were found abundantly in almost all population groups [96]. An Analysis involving 290, 000 genomic samples showing more than 400 population groups identified various ACE2 variants. The data portrayed that

ACE2 variants Ser19Pro, Ile21Val, Glu23Lys, Lys26Arg, Thr27Ala, Asn64Lys, Thr92Ile, Gln102Pro and His378Arg found in the binding region increased disease susceptibility whereas the variants Lys31Arg, Asn33Ile, His34Arg, Glu35Lys, Glu37Lys, Asp38Val, Tyr50Phe, Asn51Ser, Met62Val, Lys68Glu, Phe72Val, Tyr83His, Gly326Glu, Gly352Val, Asp355Asn, Gln388Leu and Asp509Tyr showed lower binding affinity to SARS-CoV-2 S protein.1

The effect of a Covid infection differs concerning countries, races, ethnic groups, habitats etc. From the aforementioned discussion, it can be deduced that An individual's ACE2 could significantly affect susceptibility or resistance to the virus. The variants being identified or the polymorphs that are being studied will come into help for developing preventive and controllable measures against COVID-19. However, a long and intensive research work must be done to define a strong relation between ACE2 variants and COVID-19.

ACE2 polymorphic variants can be divided into two categories concerning their predicted effect on ACE2-RBD-binding as enhancing or disrupting (Fig.8). These two sections of polymorphic variants mapped with the ACE2 structure segregate into two distinct important groups at the ACE2/CoV-2 RBD interface (Fig.8a). Probable enhancing variants gather around the ACE2 surface which is most proximal to the receptor-binding domain of CoV-2 RBD (Fig.8b) while the larger amount of the disrupting variants stays centrally on the two major ACE2 α-helices contributing to the buried surface area at the interface (Fig.8b).

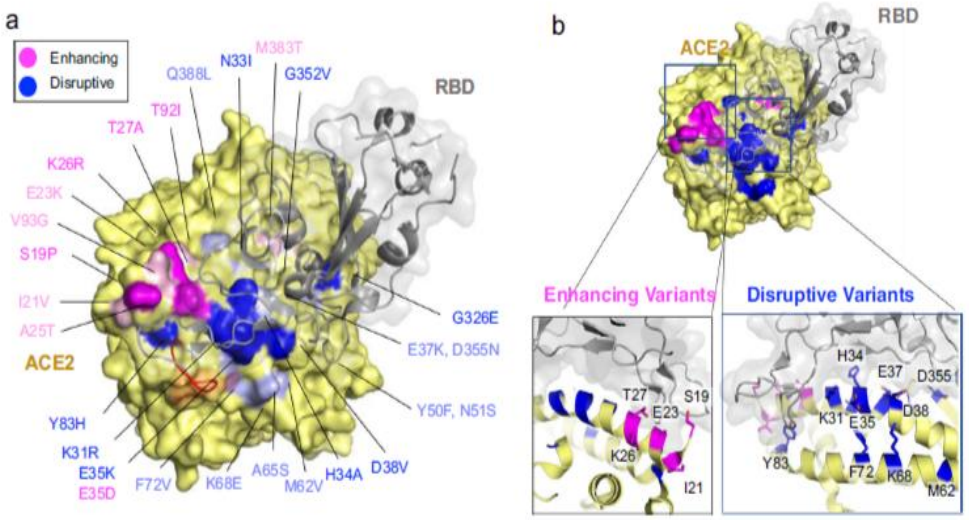

Figure 8: Human ACE2 polymorphisms mapped to the structure of human ACE2 in complex with the SARS-CoV-2 RBD. Residues in ACE2 showing polymorphic variation in human populations were mapped onto the ACE2/SARS-CoV-2 RBD (PDB: 6VW1) structure and coloured according to their effect on the predicted affinity to SARS-CoV-2 RBD. Polymorphisms that were predicted to enhance the binding between ACE2 and the S-protein are coloured in magenta. Polymorphisms that are predicted to disrupt the binding between ACE2 and the S-protein are coloured in dark blue. The variable loop in the ridge binding motif consisting of residues V483 and E484 is shown in red. This region in the structure (PDB: 6LZG) is zoomed in to show variants predicted to enhance or disrupt the ACE2

SARS-CoV-2 interaction. (Source-Communications Biology-Nature)

Influences of COVID-19 on multi-organs, cardiovascular comorbidities, and COVID-19 disease outcome ACE2 is the "entryway" for viral infection, it has quickly become the primary target for extensive therapeutic studies. ACE2 internalization by SARS-CoV-2 is responsible for the reduction of ACE2 levels on the airway epithelial surface. Symptomatic patients with SARS-CoV-2 infection Patients already infected with SARS-CoV-2 exhibit an overall downregulation in ACE2 due to internalization. Furthermore, ACE2 is fundamental to the regulation of the renin-angiotensin-aldosterone system (RAAS), which is a major regulator of blood pressure as well as fluid and electrolyte homeostasis. In addition to being part of the circulatory system, the RAAS regulates various functions at the local level in an organ-specific manner, and the genes involved in the RAAS could provide some explanation to the variation and localization in the expression of ACE2. To help our understanding of the biology of SARS-CoV-2 infection, the varied clinical outcomes of COVID-19, and its potential long-term pathophysiological effects, we provide a perspective review on the distribution and expression of ACE2 across multiple organs and the consequential effects from altered ACE2-mediated pathways.

It is important to note that ACE2 expression is not exclusive to the lungs but is present in most other tissues, including the nasal and oral mucosa, vasculature, kidney, heart, gastrointestinal (GI) tract, pancreas, and brain. (M. Ashraf et al.)

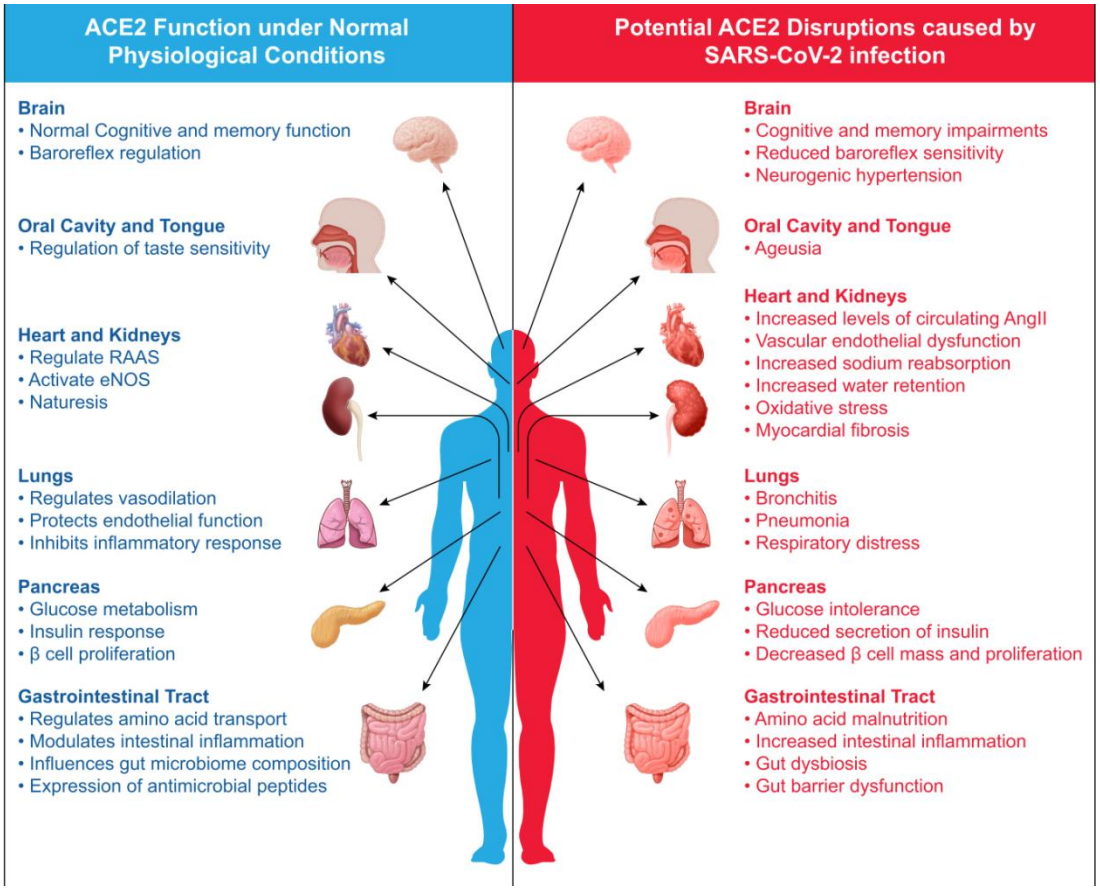

Figure 9: An organ review of normal ACE2 function versus potential pathophysiological consequences ofACE2 disruption caused by SARS-CoV-2 infection. ACE2 is present in various tissues, and its expression is vital to normal physiological functions. ACE2 disruption initiated through the binding of SARS-CoV-2 may have short-and long-term pathophysiological consequences to numerous organ systems that utilize ACE2 for proper function. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2 (Source www.physiolgenomics. org)

The action of ACE2 in the Cardiovascular System

Recent studies have found that some pre-existing conditions greatly increase the risk of severe symptoms and mortality in COVID-19 patients. These include pulmonary diseases, cardiovascular diseases, kidney disease, type 2 diabetes and hypertension. Sequential Organ Failure Assessment (SOFA) scores have been reported significantly greater in SARS-CoV-2 associated deaths [49, 69]. While COVID-19 primarily affects the respiratory system in the early stages of the disease, while it also affects the cardiovascular system of patients, greatly increasing their risk of fatality. Multiple studies reported elevated death rates in patients with SARS-CoV-2 infections and increased levels of markers of chronic heart failure. Similarly, studies found hypertension as comorbidity is associated with an increased risk of severe disease with SARS-CoV-2 infection. Huang et al. found 32% of COVID-19 patients with other health conditions, most commonly hypertension and cardiovascular disease were at risk. The most frequent comorbidities in patients with severe symptomatic (such as acute respiratory distress) COVID-19 are hypertension (27%) and cardiovascular disease (6%) [62]. Since patients with COVID-19 and pre-existing cardiovascular diseases and hypertension have an increased risk of severe disease and death, studies are needed to identify the interactions between these diseases and COVID-19.).

ACE2 was first discovered as a homologue of ACE1 in 2000, which converts angiotensin II to angiotensin 1-7. ACE2 is a type I transmembrane protein, which is mainly anchored at the cell's apical surface. Its catalytic domain is located at the extracellular side of the cell, which can be cleaved and released into the blood by ADAM17 (a disintegrin and metalloproteinase domain-containing protein 17).12 The recombinant human ACE2 (rhACE2), which is purified from the supernatant of ACE2 transfected cells, can generate angiotensin 1-7 from angiotensin II and shows the ability to prevent angiotensin II-induced myocardial hypertrophy, diastolic dysfunction, and myocardial fibrosis.12 But the role of cleaved ACE2 in circulation is still unclear.

ACE2/angiotensin 1-7 axis is another arm of RAS, which generally shows the opposite effect to the ACE1/angiotensin II axis.12 While angiotensin II can induce strong vasoconstriction, proinflammatory effects, and profibrotic effects, angiotensin 1-7 exhibits antiproliferative, antiapoptotic, and mild vasodilating abilities and presents various cardiovascular protective effects, including anti–heart failure, antithrombosis, anti–myocardial hypertrophy, anti fibrosis, antiarrhythmic, anti-atherogenesis, and attenuating vascular dysfunction related to metabolic syndrome.

The disruption of the subtle balance between ACE1 and ACE2 can lead to the dysregulation of blood pressure. ACE2 is widely expressed in cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells, which are also a regulator for heart function. Studies have found that over expression of ACE2 can prevent or even reverse the heart failure phenotype, whereas loss of ACE2 can accelerate the progression of heart failure. The activity of circulating ACE2 in patients with heart failure is also significantly higher than in normal people, which is associated with a poor prognosis. Shedding of the membrane-bound ACE2 may be responsible for the increased circulating ACE2 activity in patients with heart failure.

Heart Injury in COVID-19

As with SARS, patients with COVID-19 also showed potential cardiac injuries. Chen et al reported that among the 99 confirmed COVID-19 patients admitted to Wuhan Jinyintan

Hospital, 13 (13%) presented elevated creatine kinase and 75 (76%) showed the elevation of lactate dehydrogenase.3 Wang et al described the clinical characteristics of 138 hospitalized COVID-19 patients at Zhongnan Hospital of Wuhan University and found elevated hypersensitive troponin I in 10 (7.2%), whereas 23 (16.7%) had arrhythmia.4 Besides, Guan et al extracted the data on 1099 COVID-19 patients from 552 hospitals in 31 provinces/provincial municipalities and found that 90 of 675 (13.7%) were with an elevated creatinine kinase level and 277 of 675 (37.2%) showed an increased lactate dehydrogenase level.5 The myocardial dysfunction can be indirect, caused by reduced oxygen supply, severe lung failure, and the cytokine storm after the SARS-CoV-2 infection. However, there is also the possibility that it might be attributable to the decreased activity of ACE2 in the heart, just like SARS. Audit et al18 detected the presence of SARS-CoV and a marked decreased ACE2 expression in the heart of intranasal SARS-CoV–infected mice. They also reported that SARS-CoV was isolated from 7 of 20 of the human autopsy hearts, and the myocardial damage was accompanied by the decreased protein expression of myocardial ACE2 as well. Recently, an autopsy case of COVID-19 was reported in Chinese.19 Liu et al19 observed a moderate amount of transparent light-yellow liquid in the pericardial cavity and mild pericardial oedema in an 85-year-old man who died from COVID-19. They also reported that the myocardial section was grey-red fish-like. Considering that this old patient showed a history of coronary heart disease, whether the myocardial injury was associated with SARS-CoV-2 infection is still unclear. However, direct evidence demonstrating that SARS-CoV-2 infects the heart and decreases the ACE2 expression is currently lacking.

Symptomatic patients with SARS-CoV-2 infection are most often reported having fever, cough, nasal congestion, fatigue, and other signs of an upper respiratory tract infection, which can quickly develop into acute respiratory distress syndrome (ARDS) with a low survival rate. Although SARS-CoV-2 infection into host lung cells contributes largely to the severe symptoms in patients, it is noted by the Centers for Disease Control and Prevention that individuals with underlying medical conditions such as heart disease, diabetes, obesity, and asthma have a higher rate of infectivity and increased mortality from COVID-19. It is important to note that ACE2 expression is not exclusive to the lungs but is present in most other tissues, including the nasal and oral mucosa, vasculature, kidney, heart, gastrointestinal (GI) tract, pancreas, and brain.

As we know, ACE2 receptor expression is vital for maintaining tissue integrity and preventing injury. Restoring diminished ACE2 levels helps alleviate and reverse tissue damage. Recent studies examining the applicability of recombinant ACE2 have shown promising results for potential clinical application in the treatment of patients with COVID-19 suffering from ARDS (80, 81). However, it should be noted that restoration of ACE2 may increase the likelihood of SARS-CoV-2 reinfection for individuals who have not acquired immunity upon first exposure. For this reason, here we will review two novel prophylactic treatments and treatments, both targeting the interaction between SARS-CoV-2 and ACE2 for disease prevention. One method currently being investigated for treating (Guo et al.29)

SARS-CoV-2 is the use of fusion inhibitors. This treatment involves lipopeptide targeting of the heptad repeat 1 (HR1) domain of SARS-CoV-2 and disrupting viral membrane fusion that is critical for entry into the host cell. This approach has previously been designed and utilized in the prevention of fusion/entry of other HR1-HR2 domain-mediated viruses, including SARS-CoV. Recent studies have examined another potential therapeutic utilizing modified antibodies, with sequence homology similar to that of the ACE2 receptor, to target the S1 domain of the spike protein of SARS-CoV-2, effectively preventing viral interaction and attachment to host cells. Finally, four human-origin monoclonal antibodies have a neutralization effect on the cells infected with SARS-CoV-2. Moreover, these antibodies show a therapeutic effect in vivo through a transgenic mouse model, displaying inhibitory and neutralizing effects of the antibodies.

Drug-related heart damage during COVID-19 treatment is a concern. In particular, the use of antiviral drugs should be monitored. In a study of 138 patients with COVID-19, 89.9% were given antiviral drugs. However, many antiviral drugs can cause cardiac insufficiency, arrhythmia or other cardiovascular disorders. Therefore, during treatment of COVID-19, especially with the use of antivirals, the risk of cardiac toxicity must be closely monitored.

Collectively, the cross and counter effects by every organ system in the body must be taken into consideration when proposing new therapeutic strategies to combat this unprecedented and formidable viral threat.

2. Conclusion

Several studies encompassing major areas of virology have been conducted throughout countries. From the above overview, it can be concluded that the Accession Relevance of the ACE 2 receptor and its susceptibility has a lot to do with the host infection and variation in the spreading of

infestation of the disease in individuals. For reference, a study published in nature has said that several covid variants are responsible for causing life-threatening infections and affecting the immune system. It reveals that the TYK2 gene is supposed to hold the key to an answer to this. Thus, this proves the genetic variations have significant doings toward the binding to RBD. Also, the epsilon variant of the SARS-Cov-2 is currently an alarming concern which depicts three mutations in its spike protein that clamps down the efficacy of vaccines-A study suggests. So, it can be said that the polymorphism and susceptibility of the ACE-2 receptor and along with the ever-changing conformation of COVID 19, should be studied with more crucial efforts. The overview simply sheds light on a cumulative effort of combating the disease as ACE2 expression is not exclusive to the lungs only due to the diverse functions. It is present in most other tissues, which also provides a base to its related subjects that are relevant to the pathogenesis of cardiovascular disease.

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