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Role of ACE2 in Infection by Corona Viruses

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Introduction

It is the beginning of 21st century when the species of SARS-CoV start spreading the deadly pneumonia into in humans (Drosten et al., 2003, Ksiazek et al., 2003), Middle-East respiratory syndrome corona virus (Zaki et al., 2012) (MERS-CoV), and SARS-CoV-2 (Huang et al., 2020, Zhu et al., 2020).

It was in China, Guangdong where SARS-CoV came to the fore in 2002, spreading via air, infecting 8,098 people and claiming 774 lives in five continents MERS-CoV followed shortly after in 2012 in Arabian Peninsula, expanding to 27 countries infecting 2494 individuals and causing 858 death To this date, it is a weighty health perturbation in the Middle-Eeast. Erstwhile unexplored corona virus, SARS-CoV-2 was ascertained in China, Wuhan (2019) and later sequenced in January 2020 (Zhou et al., 2020, Zhu et al., 2020). Right now SARS-CoV-2 is linked with an underway outbreak of an aberrant pneumonia (Covid-2019) which has affected 123,902,242 people including 2,727,837 deaths as of 9:07 am CET, 25 March 2021 according to WHO, which also proclaimed it as a public health emergency of international concern. Although dromedary camels acted as a reservoir host unfurling the infection to humans but MERS-CoV was propounded to have emanated from bats. (Haagmans et. al., 2014, Memish et al., 2013). SARS-CoV and SARS-CoV-2 are conveniently related to each other and originated in bats (Ge et al., 2013, Hu et al., 2017, Li et al., 2005b, Yang et al., 2015a, Zhou et al., 2020). Palm civets and racoon dogs on the other hand have been acknowledged as intermediary hosts for zoonotic conveyance of SARS-CoV between bats and humans (Guan et al., 2003, Kan et al., 2005, Wang et al., 2005), although recognition of multiple SARS-related corona viruses in bats put

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forward the possibility of continuation of zoonotic transmissions (Anthony et al., 2017, Ge et al., 2013, Hu et al., 2017, Li et al., 2005b, Menachery et al., 2015, Menachery et al., 2016, Yang et al., 2015a, Zhou et al., 2020).
Four unhackneyed low morbific corona viruses are aboriginal in humans: HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E besides highly infective SARS-CoV, MERS-CoV, and SARS-CoV-2, all members of β-corona virus genus.

Transmissibility

Reproductive numbers of SARS-CoV-2, SARS-CoV and MERS-CoV are 2–3.58, 1.7–1.9 and < 1, respectively (Wu P, Hao X, EHY L, Wong JY, KSM L, Wu JT, Cowling BJ, Leung GM, 2020) show the level of transmissibility, which increased for SARS-CoV-2 to 5.7 later due to upswing of cases ubiquitously around the world (Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R., 2020). Transference by proximate contact between people via air droplets or contaminated veneers of devices (Olsen SJ, Chang HL, Cheung TY, Tang AF, Fisk TL, Ooi SP, Kuo HW, Jiang DD, Chen KT, Lando J, et al., 2003;Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ., 2016).
Spate of SARS-CoV in Hong Kong suggested transmission through airborne (Yu IT, Qiu H, Tse LA, Wong TW., 2014). Another outbreak proposed fecal contamination & feco-oral transmission (Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, et al., 2003). Person to person transmission is the main event for MERS-CoV but conceptually MERS-CoV can be spreading through stool, vomitus, urine, serum and cerebrospinal fluid of infected individuals (Memish ZA, Perlman S, Van Kerkhove MD, Zumla A., 2020). In uttermost cases, a few rare pieces of evidence show maternal-fetal transmission of SARS-CoV-2 (Egloff C, Vauloup-Fellous C, Picone O, Mandelbrot L, Roques P., 2020). Recently enough, SARS-CoV-2 was found in gastrointestinal tissues alongside sputum, urine, blood/serum, ocular surface, saliva and aerosol as well (Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W.,2020; Pan Y, Zhang D, Yang P, Poon LLM, Wang Q., 2020; Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H.,2020; Lu CW, Liu XF, Jia ZF.,2020;To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, Yip CC, Cai JP, Chan JM, Chik TS, et al.,2020; Zhang R, Li Y, Zhang AL, Wang Y, Molina MJ.,2020). Of course we should be very careful while handling the samples in order to avoid any mishappening.

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Structure & Genome

Showing a particular structure of a fringe like a spike onto the surface under electron microscope, the corona virus name was derived as this fringe take after solar corona (Masters, 2006). With an average diameter of about 80-120 nm, these viral organisms are curvilinear, having spikes projecting out to 17-20 nm with a swollen base of nigh 10 nm (Masters, 2006).

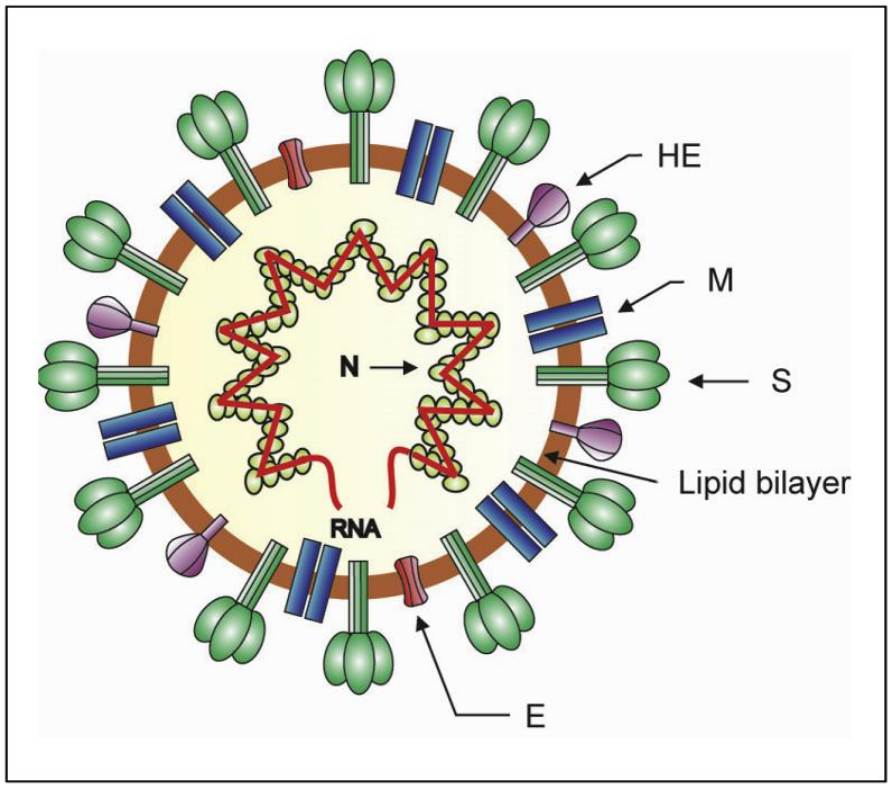

Figure 1: Diagrammatic view of corona virus (Source: **Molecular biology of corona viruses: current knowledge** I. Made Artika,a,b,⋆ Aghnianditya Kresno Dewantari,c and Ageng Wiyatnoc)

There are about 4 major constructional proteins which are coded by Corona virus genome: the nucleocapsid (N) protein, the spike (S) protein, the membrane (M) protein & the envelope (E) protein, every single one is crucial to structure & reproductive cycle of the virus in discussion. In other cases of a few corona viruses, not all the proteins are required to make a complete vicious viral structure. This stipulates how a few constructional proteins are inessential or code for indemnifiable functions (Schoeman and Fielding, 2019). As suggested by the figure shown, 3-4 main proteins are contained by viral envelope out of which important ones are S and

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M. Hemagglutinin esterase (HE) is a third substantial envelope protein found in a few corona viruses. Nevertheless , E protein makes up a significant part of the viral envelope despite being minor (de Haan et al., 1999). Talking about post translational changes endured by Viral structural proteins help in playing title roles in regulating folding, stability, enzymatic activity, subcellular localization and interaction of the viral protein with other proteins (Fung and Liu, 2018). These changes go by change in protein anatomy by making disulfide bonds and cleaving with the help of proteases or increasing the chemical stockpile of amino acids by ushering in new functional groups via phosphorylation, glycosylation and lipidation (such as palmitoylation and myristoylation).

Coming to N protein,although it is responsible for establishing nucleoprotein by binding viral genome, it might not be needed for envelope formation but in a few corona viruses, it forms a fleeting expression of N protein helps in packaging and stabilizing and hence production of virus like particles by tempering of host cellular response to viral infection such as regulating the host cell cycle, affecting cell stress response, influencing the immune system, etc (Schoeman and Fielding, 2019). Even so, contemporary research shows the ability of N proteins being able to semble oligomers without binding to genomic RNA somehow. Thus, hypotheses about constitutive N protein oligomerization allowing the optimal loading of the genomic viral RNA into a ribonucleoprotein complex through the presentation of multiple viral RNA binding motifs came into existence (Cong et al., 2017)". Into the bargain, Virus is able to fold its genome just like eukaryotic cells as it has a smaller structure & less space for uncondensed ribonucleoproteins as compared to other RNA viruses (Gui et al., 2017).

Concluding, SARS-CoV goes about for 3 functions: first, bringing the viral genome into the host cell crossing the plasma membrane; second, it sets out newly constructed genome orientation; third, guarding the genome unification during its passage between cells (Neuman and Buchmeier, 2016).

Spike Protein

A transmembrane spike (S) glycoprotein makes homotrimers obtruding out of the viral surface and facilitates the ingressing of the corona virus into the host cell (Tortorici and Veesler, 2019). Two in service proteins which bind to the host cell receptor (S1 subunit) & cause the fusion of viral and cellular membranes (S2 subunit) are possessed by S protein .S1 & S2 subunits continue to be in perfusion conformation non - covalently after being cleaved for multiple CoVs (Belouzard et

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al., 2009, Bosch et al., 2003, Burkard et al., 2014, Kirchdoerfer et al., 2016, Millet and Whittaker, 2014, Millet and Whittaker, 2015, Park et al., 2016, Walls et al., 2016a). S2 subunit contains the fusion machinery which is preserved by S1 subunit containing receptor binding domain(s) (Gui et al., 2017, Kirchdoerfer et al., 2016, Pallesen et al., 2017, Song et al., 2018, Walls et al., 2016a, Walls et al., 2017b, Yuan et al., 2017). Additionally S is severed by host proteases at upstreamed S2 site situated next to fusion peptide (Madu et al., 2009, Millet and Whittaker, 2015). This chasm has been thought to actuate the protein through irrevocable configuration changes for membrane fusion (Belouzard et al., 2009, Heald-Sargent and Gallagher, 2012, Millet and Whittaker, 2014, Millet and Whittaker, 2015, Park et al., 2016, Walls et al., 2017b). Hence, as stated, infection and entry of corona virus into animal cells is a stepwise process which occurs only due to proper action of receptor binding and processing of S protein.

Furthermore, corona viruses use well defined domains accordingly within the S1 subunit to apprehend the entry receptores. There are several instances such as endemic human corona viruses OC43 and HKU1 fasten with the host cell surface by their S domain A (SA) to 5-N-acetyl-9-O-acetyl-sialosides present on glycoproteins (Hulswit et al., 2019, Tortorici et al., 2019, Vlasak et al., 1988). On the other hand, using domain A, MERS-CoV S recognizes non acetylated sialoside attachment receptors (Li et al., 2017, Park et al., 2019) that encourage domain B latching to entry receptor, dipeptidyl-peptidase 4 (Lu et al., 2013, Raj et al., 2013) whereas SARS-CoV use angiotensin-converting enzyme 2 (ACE2) and SB interrelation to infect the cells (Ge et al., 2013, Kirchdoerfer et al., 2018, Li et al., 2005a, Li et al., 2003, Song et al., 2018, Yang et al., 2015a).

Receptors

Moreover, ACE2 is a presiding receptor for SARS-CoV (Li, Wenhui, et al., 2003) along side DC-SIGN (CD209) and L-SIGN (CD209L) being employed as co-receptors for SARS-CoV (Gu J, Korteweg C.,2007). Furthermore, cellular receptor for MERS-CoV is dipeptidyl peptidase 4 (DPP4, also termed CD26), (Lu G, Hu Y, Wang Q, Qi J, Gao F, Li Y, Zhang Y, Zhang W, Yuan Y, Bao J, et al.,2013). However ACE2 has natural higher accord for SARS-CoV-2 than to SARS-CoV (Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS.,2020) but Christian et al. (Sigrist CJ, Bridge A, Le Mercier P.,2020) proposed SARS-CoV-2 could be substituting integrins as cell receptors which is deficient when it comes to legit experimental evidence. Although aiding corroboration

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was put forward that CD147-SP could be an additional ingressing pathway for SARS-CoV-2 (Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, Gong L, Zhang Y, Cui H-Y, Geng J-J, et al.,2020).

SARS-CoV, MERS-CoV and SARS-CoV-2 use serine protease TMPRSS2 & endosomal cysteine proteases cathepsin B/L for spike protein priming, that is important for paving their way in host cells (Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, et al., 2020; Hoffmann M, Kleine-Weber H, Pöhlmann S.,2020).

Besides ACE2 has extensive assortment from respiratory tract, gastrointestinal tract, heart, kidney and olfactory neuroepithelium (Imai Y, Kuba K, Ohto-Nakanishi T, Penninger JM.,2010; Fodoulian L, Tuberosa J, Rossier D, Landis BN, Carleton A, Rodriguez I.,2020), aside from these DPP4 affects liver, thymus, prostate and bone marrow (Memish ZA, Perlman S, Van Kerkhove MD, Zumla A, 2020), repercussions in wide ranging cellular & tissue movement of SARS-CoV, MERS-CoV, and SARS-CoV-2 (Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z, et al., 2004; Widagdo W, Raj VS, Schipper D, Kolijn K, van Leenders G, Bosch BJ, Bensaid A, Segales J, Baumgartner W, Osterhaus A, et al.,2016; Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W,2020). Summarising, these hCoVs are more than accoutered for producing an outspread range of symptoms.

Effect of SARS-CoV-2 Infection on Renin/Angiotensin System

It's of utmost crucial understanding that ACE2 receptor is the point of entry of virus in the body, so studying it will give us the outline of the pathophysiological changes because of the SARS-CoV-2. Getting a hold of molecular downstream effects of Angiotensin can lead to the mapping of "multiple respiratory distress", "myocardial injury", "renal failure", and "increased mortality" due to SARS-CoV-2 (Zhou et al., 2020; Zhu et al., 2020).

ACE Genes

ACE & ACE2 have 42% resemblance of amino acids as maintained by the study of sequences depicting ACE2 materialize because of gene duplication (Donoghue et al., 2000). Being present on chromosome Xp22, ACE2 possess 18 exons & 20 introns (Turner et al., 2002), also, type 1 membrane glycoprotein made up of 805 amino acids is coded by ACE2 itself (Marian, 2013). Domains on N-terminal & C-terminal which are functional carry out signaling task for peptide present on side of HEXXH zinc binding metalloprotease motif (catalytic domain) (Li et al., 2003; Cerdà-Costa and

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Xavier Gomis-Rüth, 2014). While manifesting almost all tissues, ACE2 is mostly found in epithelial cells of alveoli along endothelial cells of blood capillaries, additionally, it is present in blood vessel rich organs like kidneys & lungs (Hamming et al., 2004; Tikellis and Thomas, 2012; Roca-Ho et al., 2017). Although variegated, ACE and ACE2 are related to the diseases such as diabetes , hypertension & stroke (Crackower et al., 2002; Ramachandran et al., 2008; Jang and Kim, 2012; Fehr and Perlman, 2015). Apart from this, both receptors have different functions despite being kindred in constitution, as in ACE2 is responsible for tackling with perilous consequences of ACE/RAS pathway through ACE2/Angiotensin (1-7)/MAS axis and ACE looks out for RAS system (Renin Angiotensin Aldosterone system). In the development of metabolic disorders, RAS plays an important role (de Kloet et al., 2010). ACE & renin bring out angiotensin II where Prorenin is the dronish herald of renin. After Prorenin is converted to renin by special proteins due to actuation of afferent arteriole's Juxtaglomerular apparatus, it is released into blood breaking angiotensinogen in angiotensin (Ang) I, which is torpid physically & acts as a progenitor for Ang II due to catalytic activity of ACE. Ang II connects to arterioles, adrenal cortex, kidney, and the brain's type II & type I (AT) receptors (Figure 1A). While being detected in the upper respiratory system & lungs' epithelium, ACE is majorly found in kidneys & lungs (Wakahara et al., 2007). There's a complete body water, sodium hike along with soaring vascular tone due to RAS activation. Endothelial injury (Watanabe et al., 2005), vasoconstriction (Gustafsson and Holstein-Rathlou, 1999), endovascular thrombosis (Tay and Lip, 2008) & increment in volume of blood are the results of Ang II self indulgence to AT receptors. Multiple signaling reactions are initiated at cellular level by Angiotensin II which encompass JNK/MAPK & PKC, serine/threonine kinase, ERK (Malhotra et al., 2001). Several different researchers claimed that IL-6 is prompted by Ang II & maybe "serine tyrosine kinases",G protein coupled receptor activation", ERK/JNK MAPK activation or interaction with mineralocorticoid receptors starting off TNF- α (Funakoshi et al., 1999; Han et al., 1999; Ruiz-Ortega et al., 2002; Luther et al., 2006). Activator of NADPH oxidase is Ang II as it is a catalyst of reactive oxygen species production (ROS) (Garrido and Griendling, 2009). Furthermore, macrophage & neutrophil fluidity to target cells is commenced by Ang II leading to vascular injuries (Kato et al., 1996; Nabah et al., 2004). Studies of Ang II as an efficient multipotent agent to increase endothelial injury, oxidative injury, cytokines etc have been done for it to not be impede with target tissues, although trials at a clinical level for swotting the

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effect MABs against IL-6 receptor are going on (ClinicalTrials.gov Identifier: NCT04317092).

A few definite number of tissues such as myocardium, lungs, brain, kidney and arterioles have proteases which are insensitive to ACE inhibitors which leads to the shortlisting of a few inhibitors in order to decrease Ang II levels for a less amount of time (Mento and Wilkes, 1987).

Besides the proteases mentioned are "neutral endopeptidase", "tonin", "tryptensin", "cathepsin G", "kallikrein", and "chymase: (Figure1A), these can cleave Ang I to Ang II (Kramkowski et al., 2006; Lorenz, 2010; Becari et al., 2011; Uehara et al., 2013). Model animals had ACE2 articulation administered by Ang II receptor blocker (ARB) inhibitors and ACE (Ishiyama et al., 2004).

Safeguarding component of ARB & ACE is because of increment in number of ACE2 giving poor prognosis with higher viral load due to more receptors for entry of virus (Chu et al., 2004) connecting it with substitute pathways might play a part in structuring ANG II (Diaz, 2020).

Meanwhile, there have been clinical trials to study the upshots of ACE/ARB inhibitors related to SARS-CoV-2 (ClinicalTrials.gov Identifier: NCT04330300). If by chance there's a different route to the making of Ang II, it is implausible that ACE/ARB inhibitors take part in clinical trail of SARS-CoV-2 infection. Ang II was minced into 1-7 a heptapeptide & Ang I into Ang 1-9 a nonapeptide by ACE2 (Santos et al., 2003; Marian, 2013). Multiple uses such as antiproliferative, vasodilatory, and protective by prompting MAS receptor (a G protein coupled receptor) are illustrated by heptapeptides & nonapeptides discussed previously (Donoghue et al., 2000; Santos et al., 2003). Neutralization of the RAS system mechanism balancing ACE/Ang II/AT1 receptor axis's derogatory outcomes is done by the axis of ACE2 / Ang / MAS1 (Santos et al., 2003). MAS1 or ACE2 receptor scarce mice depicted several cardiac & metabolic anomalies (Yamamoto et al., 2006; Tikellis and Thomas, 2012). Thus ACE2 is major in warding off the deleterious effects of Ang II (Fraga-Silva et al., 2010; Tikellis and Thomas, 2012).

Necropsy of people died due to SARS-CoV-2 infection showed severely impaired alveoli with capillary clogging alongside clotting in vessels (Menter et al., 2020). In association with MAS, ACE 2 produces Ang 1-7 which sets off multiple advantageous actions such as inhibition of cell growth, vasodilation,anti-thrombotic, anti arrhythmogenic and antifibrotic effects (le Tran and Forster, 1997; Schindler et al., 2007; Li et al., 2008) and as stated by other researchers, it also shows guardian effect on brain and protecting against ischemic stroke (Jiang et al., 2013).

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Vaccine & Drug Development

Being surface exposed, S glycoprotein is counterpoised by antibodies(Abs) which is now th+e main focus of drug and vaccine development. S trimers are equipped with N-linked glycans which are crucial for folding (Rossen et al., 1998) and providing convenience to host proteases alongside neutralizing antibodies (Walls et al., 2016b, Walls et al., 2019, Xiong et al., 2018, Yang et al., 2015b). Earlier cogent human-neutralizing Abs were distinguished from scarce memory B cells of SARS-CoV (Traggiai et al., 2004) or MERS-CoV (Corti et al., 2015) patients to communicate molecular level understanding of competitive inhibition of SB attachment to the host receptor (Walls et al., 2019). However, ACE2 has a natural accord to SARS-CoV-2 than to SARS-CoV (Wrapp, Daniel, et al., 2020).

Manipulation of ACE2/Ang(1-7) and Protease Activity as Novel Therapeutic Targets

In view of the significant SARS-CoV-2 related periling factors for hospitalization and deaths among patients with metabolic diseases, including obesity, cardiovascular diseases, arterial hypertension, and diabetes that could depict overall activation of the RAS system, tweaking of RAS activation through the ACE2/(Ang1-7)/MAS pathway should be reviewed for treatment of this disease. Moreover, the clinical observation and published clinical data paint a unique clinical presentation of SARS-CoV-2 patients: many patients with relatively preserved hemodynamics and lack of lactic acidosis. Albeit they have respiratory distress, are in a hypercoagulable state “(Liu et al., 2020; Menter et al., 2020)”, show progressivekidney failure “(Cheng et al., 2020)”, have stroke-like characteristics and myocardial injury “(Zhou et al., 2020)”. Clinical experimental studies pertain that in most cases the respiratory distress happen many days (in general about 14 days) after the infection, indicating that this may not be a direct effect of the initial viral infection albeit the hosts reaction to the forfeiture of function of ACE2 and misregulation of Ang II/ACE2 pathways as well prompting of host proteases. Our main hypothesis is that the binding of the corona virus spike protein to ACE2 results in shedding of ACE2 receptors vis various proteases, which in result in leads to the loss of preserving function of the ACE2/MAS axis in the lungs and other organs (Figure 1B). Furthermore to the loss of protective function of ACE2/MAS, prompting of classical pathway (ACE/RAS/Ang II) and different pathways through tissue specific proteases, including cathepsins, chymase-like proteases, leads to an excessive production of Ang II at the tissue level. These actions may further tilt the balance of protective Ang (1-7)/MAS and ACE2 function to the

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harmful effects of increased Ang II contributing to lung epithelial and endovascular injury. Thus, installment of the downstream pathway of ACE2, by triggering the ACE2/Ang1-7/MAS axis could prove a meaningful strategy in averting lung and cardiovascular damage associated with SARS-CoV-2 infections. As less ACE2/MAS activity augments the Ang II/AT1R activity and its deleterious outcomes on increased pulmonary vascular endothelial/epithelial injury and lung pathology. Baring the activity of proteases important for splintering of viral spike proteins: for example hindrance of enzymatic activity of ADAM17 and TMPRSS2 could serve as other novel therapeutic targets. This could potently block viral interaction with the receptor and its entry into the cells. Recognising specific proteases and advancement of inhibitors targeting proteases important for cleavage of spike proteins could prove to be viable. In addition,using the protective effect of Ang1-7 or its analogs, such as AVE0991 AVE0991 "(Pinheiro et al., 2004)" against harmful effect of increased Ang II is feasible and could be effective for the symptomatic treatment of these patients.

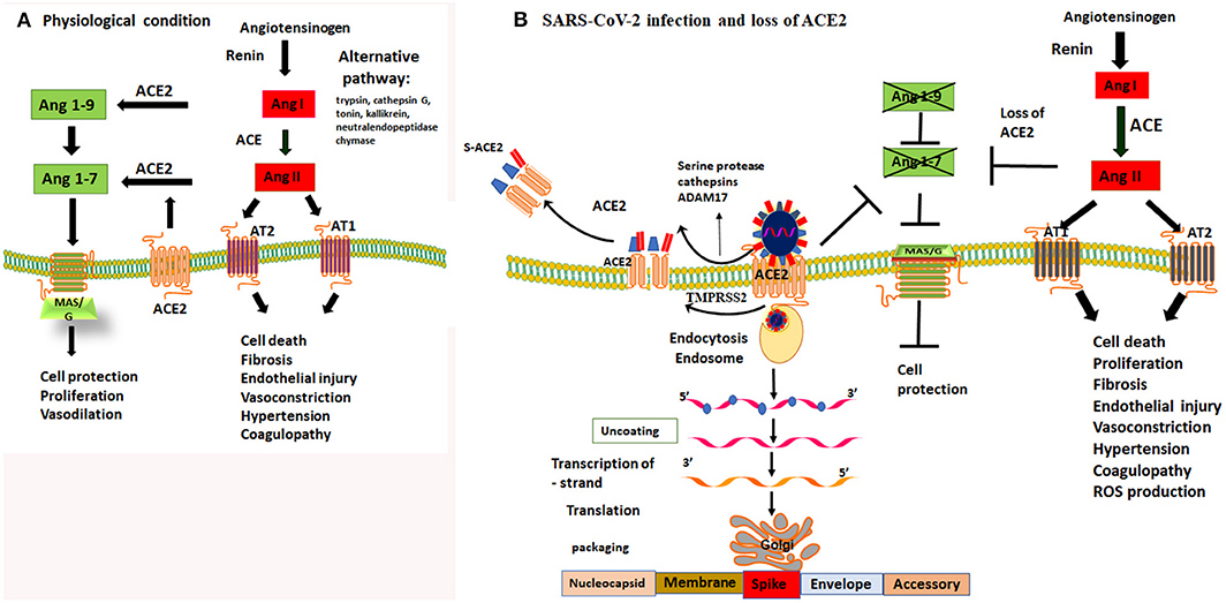

Figure 1. Dysregulation of Ang II and Ang (1-7) by loss of protective function of ACE2 receptor. (A) under physiological condition there is a balance in ACE and ACE2 receptor activity. ACE regulates the Renin Angiotensin Aldosterone system (RAS) and cleaves Ang I to produce Ang II. Ang II is a potent vasoconstrictor and detrimental for endothelial and epithelial function through activating AT1 and AT2 receptors. The counterbalance of the RAS/Ang II output is regulated by ACE2 and

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Mas/G protein coupled receptor activity. ACE2 cleaves Ang I and Ang II into Ang-1-9 and Ang1-7, respectively, thereby it activates MAS/G protein coupled receptor that protect cell death. (B) SARS-CoV-2 binds to ACE2 to gain entry to epithelial cells of the lungs. Cleavage of spike proteins by a protease such as trypsin/cathepsin G and or ADAM17 on ectodomain and TMPRSS2 of endodomain sites facilitate viral entry into the cells. This process leads to shedding of host ACE2 receptors and loss of its protective function. Loss of function of ACE2 activity prevents production of Ang 1-9 and Ang1-7. Lack of Ang1-7 diminishes the activity of MAS/G receptor, leading to the loss of its protective functions including vasodilatation, cell protection both at the epithelial and endothelial sites. Loss of ACE2 function leads to an imbalance and unchecked effects of Ang II and upregulation of RAS/Ang II pathway. Upregulation of Ang II leads to vasoconstriction, thrombophilia, microthrombosis, alveolar epithelial injury and respiratory failure. Therefore, inhibiting the proteolytic function of trypsin/cathepsin and ADAM17 or TMPRSS2 and or direct activation of MAS/G receptor by enhancing Ang-(1-7) can overcome the loss of function ACE2 and are viable targets to prevent tissue damage to the host.
Source "(http://www.frontiersin.org/articles/10.3389/fcimb.2020.00317full)"
Another suggestion from the studies is that if mutations occur at the site of attachment of SARS-CoV-2 with ACE2 receptor, the vaccine will be doubtful.
So all the sites of attachment of SARS-CoV-2 in all the available strains should be studied.

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