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Evaluation of Angiotensin-converting Enzyme 2 (ACE2) in COVID-19: A Systematic Review on All Types of Studies for Epidemiologic, Diagnostic, and Therapeutic Purposes

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses the angiotensin-converting enzyme 2 (ACE2) receptor of SARS-CoV for cell entry. We aimed to check the association between ACE2 and COVID-19 (coronavirus disease 2019) in a systematic review. Two databases (PubMed/Medline and Scopus) and bioRxiv were checked for retrieving all types of studies in relation to ACE2 and COVID-19 until March 18, 2020. Forty-one studies were entered to the systematic review. These studies included nineteen original, eight reviews, four letters to the editor, three research papers, one correspondence, one commentary, one mini review, two reports, one opinion, and one perspective. In summary, the results showed that the ACE2 receptor for COVID-19 is similar to that of SARS-CoV. However, its expression was different in various populations as well as in the two genders. ACE2 may be used as a therapeutic target. Patients who take ACE inhibitors may have benefit in severe disease outcomes. Finally, pangolins and snakes and turtles may act as the potential intermediate hosts transmitting disease to humans.

Introduction

COVID-19 or 2019 novel coronavirus epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was emerged in late December 2019 in Wuhan, China [1]. This disease has been rapidly expanded in the world with a short time [2] and it is named a COVID-19 pandemic. The COVID-19 strains are genetically correlated to SARS-CoV and Middle-East respiratory syndrome coronavirus (MERS-CoV) [3]. A hypothesis reported that angiotensin II type I receptor (AT1R) inhibitors might be helpful for COVID-19 patients who experience pneumonia and suggested the treatment of COVID-19 patients with AT1R blockers [4]. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor-binding domain for its spike (S) protein glycoproteins [4], [5], [6]. ACE2 is a negative regulator of the renin-angiotensin system and reduces angiotensin II [5]. Mutant S proteins are capable of detecting host receptors within species [6], [7]. Almost all the coronaviruses detect their host cells through S proteins [8], [9]. Each S protein consists of two subunits that the S1 subunit contains a region called the receptor-binding domain (RBD) (targeting receptors in host cells) and the S2 subunit regulates membrane fusion between the virus and the host cells [10]. The single-cell transcriptomes showed that ACE2 and TMPRSS (transmembrane protease and serine) are highly expressed in AT2 (type II alveolar) cells of lung, esophageal upper epithelial cells, and absorptive enterocytes [11]. It was also reported an identity of more than 70% between the S protein sequences of SARS-CoV and SARS-CoV-2 [12]. Different methods of nucleic acid testing, protein testing, and point-of-care testing are on the way along with imaging techniques for better diagnosis [13]. Herein, we aimed to summary the results of all types of studies checking association between ACE2 and COVID-19 in a systematic review for the 1st time.

Search strategy

Two databases, namely, PubMed/Medline and Scopus were comprehensively searched by an author (M.S) to retrieve all relevant references published until March 18, 2020, without restrictions. The searched queries were “2019 novel coronavirus” or “2019-nCoV” or “COVID-19” or “SARS-CoV-2” and “angiotensin” or “angiotensin-converting enzyme 2” or “ACE2”. We manually searched the citations (original and review articles and meta-analyses) related to our topics as well as bioRxiv (https://www.biorxiv.org/). We know that we cannot rely solely on bioRxiv preprints and papers due to the absence of peer review. However, we did not omit these articles, not to lose sources of data in a new emerging entity.

Eligibility criteria

Inclusion criteria were as follows: (1) Studies evaluating the correlation ACE2 and COVID-19 and (2) all types of studies.

Study selection and data extraction

Two authors (H.N and M.S) read independently the titles and abstracts of the retrieved studies. Then, the two authors selected the relevant studies, while another author (M.R) retrieved the full texts of the articles. Two authors (M.R and M.S) independently extracted the data from each study for being included in the systematic review. If there was a disagreement between the two authors, the third author (H.N) helped to find a final decision. The data extracted for the systematic review included basic information including the first author, publication year, type of study, and main result(s)/conclusion(s). Other authors (F.N, B.S, and M.N) rechecked independently the extracted data. At last, the disagreement resolved by a discussion between all authors.

Study selection

Out of 52 records retrieved from two databases and 10 studies from bioRxiv, after removing duplicates, 47 records were screened (Figure 1). After that, 6 other

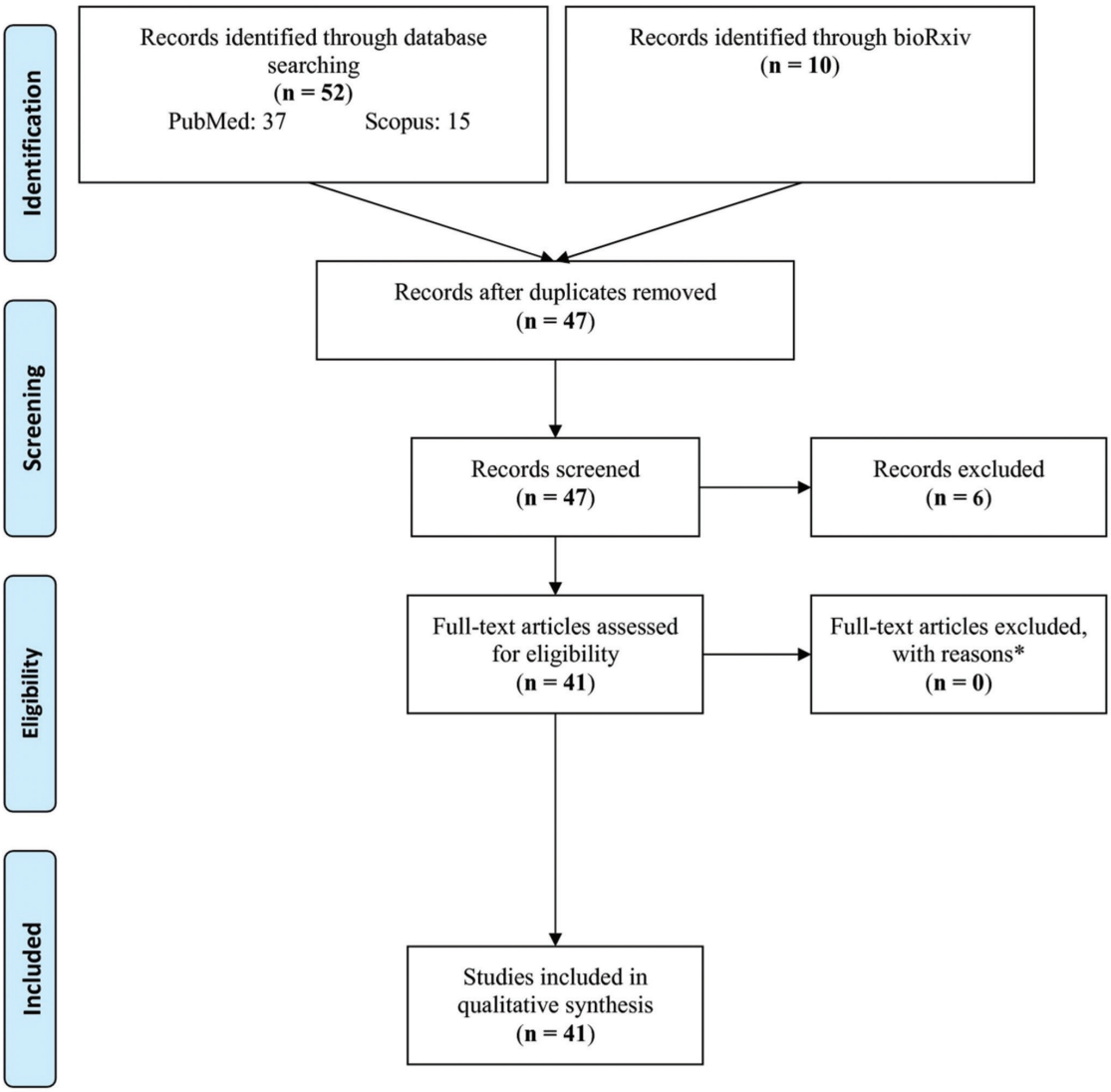

Figure 1: Flowchart of the study selection

studies were removed with further evaluation because they were irrelevant records. At last, 41 full texts met eligibility criteria and all of them were entered to the systematic review.

Characteristics

Table 1 shows the characteristics of 41 studies included in the systematic review [4], [11], [12], [14], [15], [16], [17],[18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29] [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51]. The studies included nineteen original articles [11], [12], [15], [17], [20], [22], [25], [28], [33], [35], [36], [40], [43], [44], [45], [48], [49], [50], [51], eight reviews [14], [19], [23], [29], [34], [37], [38], [47], four letters to the editor [4], [18], [30], [39], three research papers [31], [32], [46], one correspondence [16], one commentary [24], one mini review [26], two reports [21], [41], one opinion [27], and one perspective [42].

Blockers and inhibitors

Host cell entry from SARS-CoV-2 is dependent on the ACE2 receptor of SARS-CoV and may be clinically prevented by a proven inhibitor of TMPRSS2, a cellular serine proteinase used by SARS-CoV-2 for S protein priming. The antibody responses increased against SARS-CoV can at least partially protect

Table 1: Characteristics of studies included in systematic review

First author, publication year	Type of study	Journal	Main result(s)/conclusion(s)
Diaz, 2020 [4]	Letter to the editor	J Travel Med	Patients who take angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be at elevated risk of severe disease outcomes because of SARS-CoV-2.
Zou, 2020 [51]	Original	Front Med	Indicating the vulnerability of different organs to SARS-CoV-2.
Guo, 2020 [23]	Review	Mil Med Res	The ACE2 receptor of SARS-CoV is similar to SARS-CoV and mainly spreads through the respiratory tract.
Baig, 2020 [14]	Review	ACS Chem Neurosci	There was the ACE2 expression in the CNS.
Batlle, 2020 [16]	Correspondence	Clin Sci (Lond)	The association between SARS-CoV, SARS-CoV-2, and ACE2 suggests a rational reason for soluble ACE2 as a potential treatment.
Hoffmann, 2020 [25]	Original	Cell	SARS-CoV-2 uses the ACE2 receptor of SARS-CoV for cell entry.
Kannan, 2020 [26]	Mini review	Eur Rev Med Pharmacol Sci	The ACE2 receptor of SARS-CoV is similar to SARS-CoV.
Sun, 2020 [38]	Review	Int J Environ Res Public Health	SARS-CoV-2 uses the ACE2 receptor of SARS-CoV for cell entry.
Cao, 2020 [18]	Letter to the editor	Cell Discov	High expression of ACE2 in Asian males compared to others.
Yan, 2020 [46]	Research paper	Science	The RBD is identified by the extracellular peptidase domain of ACE2 chiefly through polar residues.
Gurwitz, 2020 [24]	Commentary	Drug Dev Res	Angiotensin II type I receptor (AT1R) blockers are as treatments for decreasing the aggressiveness and mortality from SARS-CoV-2.
Deng, 2020 [21]	Report	Chin Med J (Engl)	ACE2 expression in the human kidney indicated the kidney is a potential target organ of SARS-CoV-2.
Kruse, 2020 [27]	Opinion	F1000 Research	The ACE2-Fc therapy will decrease ACE2 levels in the lungs during infection.
Liu, 2020 [32]	Research paper	J Med Virol	SARS-CoV-2 might also use ACE2 receptor.
Letko, 2020 [28]	Original	Nat Microbiol	The hACE2 is the receptor for the SARS-CoV-2.
Xu, 2020 [45]	Original	Int J Oral Sci	There was ACE2 expression in the mucosa of oral cavity.
Li, 2020 [30]	Letter to the editor	J Infect	Structural studies of human and other ACE2 species in the SARS-CoV-2 S protein complex will help understand the use of cross-receptors for SARS-CoV-2.
Li, 2020 [29]	Review	Microbes Infect	SARS-CoV-2 may have wide host ranges.
Chen, 2020 [20]	Original	Biochem Biophys Res Commun	SARS-CoV-2 RBD has a stronger interaction with ACE2.
Guan, 2020 [22]	Original	Zhonghua Gan Zang Bing Za Zhi	ACE2 expression was in bile duct epithelial cells of normal liver tissues, and very low in hepatocytes in COVID-19 patients.
Wrapp, 2020 [41]	Report	Science	It has reported that the binding capacity of SARS-CoV-2 S protein to ACE2 is much stronger than that of SARS-CoV, which indicts that there are more intermediate hosts for SARS-CoV-2.
Tian, 2020 [39]	Letter to the editor	Emerg Microbes Infect	CR3022 has the potential to be expanded as candidate therapeutics for the SARS-CoV-2 prevention and treatment.
Sun, 2020 [37]	Review	Zhonghua Jie He He Hu Xi Za Zhi	The COVID-19/ACE2 binding resulted in the ACE2 exhaustion, and then, ACE2/Ang/Mas receptor pathway was inhibited.
Liu, 2020 [31]	Research paper	Sci China Life Sci	The angiotensin II plasma level in SARS-CoV-2 patients was significantly increased and linearly associated to viral load and lung injury.
Wu, 2020 [42]	Perspective	Virol Sin	SARS-CoV-2 uses the same cell entry ACE2 receptor similar to SARS-CoV.
Chen, 2020 [19]	Review	Microbes Infect	CoV-NL63 uses the same receptor ACE2 as SARS-CoV-2, but with very different severity of disease.
Morse, 2020 [34]	Review	Chembiochem	Potential drug candidates (an ACE2-based peptide, remdesivir, CLpro-1, and a novel vinylsulfone protease inhibitor) could be used to treat COVID-19 patients.
Zhou, 2020 [50]	Original	Nature	SARS-CoV-2 uses the same cell entry receptor – ACE2 – as SARS-CoV.
Walls, 2020 [40]	Original	Cell	The receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2.
Zhang, 2020 [47]	Review	Intensive Care Med	ACE2 is rationally and scientifically valid therapeutic target for the current COVID-19 epidemic.
Lu, 2020 [12]	Original	Lancet	SARS-CoV-2 might be able to bind to the ACE2 receptor in humans.
Wu, 2020 [43]	Original	bioRxiv	Bat SARS-like CoVs have an evolutionary convergent RBD sequence with SARS-CoV-2 and SARS-CoV may be pre-adapted to hACE2 receptor.
Brielle, 2020 [17]	Original	bioRxiv	Evolution of S protein binding to the ACE2 receptor is similar to the rapid evolution along the antibody-antigen affinity maturation process.
Lukassen, 2020 [33]	Original	bioRxiv	The high rate of human-to-human transmission of SARS-CoV-2 and severe cases of COVID-19 may be caused by additional sites, resulting in a higher binding affinity of ACE2 and/or membrane fusion.
Othman, 2020 [35]	Original	bioRxiv	The S protein RBD might be obtained by SARS-CoV-2 through a complex evolutionary process rather than the accumulation of mutations.
Su, 2020 [36]	Original	bioRxiv	The SARS-CoV-2 S protein mediates its recognition with the human receptor ACE2.
Bao, 2020 [15]	Original	bioRxiv	The mouse model may simplify the therapeutic and vaccine development against SARS-CoV-2.
Zhang, 2020 [48]	Original	bioRxiv	Pangolin-CoV will be useful for tracing the origin and potential host of SARS-CoV-2.
Xie, 2020 [44]	Original	bioRxiv	SARS-CoV-2 and SARS-CoV bind to hACE2 with same affinities and consequently may have same transmissibility.
Meng, 2020 [11]	Original	bioRxiv	The single-cell RNA sequencing showed that high expression of ACE2 in type II alveolar cells (AT2) cells of lung, esophageal upper epithelial cells, and absorptive enterocytes.
Zhao, 2020 [49]	Original	bioRxiv	ACE2 receptor is necessary for the SARS-CoV-2 viral entry.

ACE2: Angiotensin-converting enzyme 2, ACE2-immunoglobulin Fc domain ACE2-Fc, hACE2: Human ACE2, RBD: Receptor-binding domain, S: Spike.

against SARS-CoV-2 [25]. Patients under treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increase the number of ACE2 receptors in their lungs to bind to coronavirus S proteins, thus may be at elevated risk for severe disease outcomes due to SARS-CoV-2 virus. Many patients with cardiovascular disease are treated with ACEIs and ARBs, so their ACE2 receptors are increased. In fact, the patients for cardiovascular diseases should refrain from congestion, mass accidents, ocean cruises, prolonged air travel, and all cases with respiratory illnesses during COVID-19 outbreaks to reduce the risks of infection of SARS-CoV-2 virus [4]. ACE2 is likely to act as the SARS-CoV-2 virus junction [24], [25] and the strain involved in the current COVID-19 epidemic is similar to the SARS-CoV strain in the 2002–2003 SARS epidemic [24]. However paradoxically, AT1R blockers, such as losartan, can be as tentative treatment to decrease the aggressive forms and mortality caused by SARS-CoV-2 virus. Higher expression of ACE2 with losartan protects against lung injury by complementary mechanisms: (1) Blocking the excessive angiotensin-mediated AT1R activation caused by viral infection and (2) upregulating ACE2 culminating in reducing angiotensin production by ACE and increasing angiotensin 1–7 (vasodilator) [24]. Broking the balance of the RAS (renin-angiotensin system) leads to aggravation of severe acute pneumonia. However, it is speculated that ACEI and AT1R inhibitors can be used in COVID-19 pneumonia patients under controlling hypertension and may decrease the pulmonary inflammatory response and mortality [37]. Further research is needed for approving this treatment modality in COVID and side effect of hypotension must be kept in mind [24].

Cell expression

Among 536 COVID-19 patients, 6.7% presented acute kidney injury (AKI) in spite of normal plasma levels of creatinine at the first clinical manifestation, and these patients experienced exceedingly great mortality of up to 91.7% [52]. A report showed ACE2 expression in the human kidney and that the kidney is a possible target organ of SARS-CoV-2 virus [21]. ACE2 expression was established in several other human organs such as the intestines (glandular cells), gallbladder (glandular cells), adrenal gland, lungs, and lung macrophages and the expression was highly in the urogenital, digestive systems, and the proximal tubules. In addition, the single-cell RNA sequencing (scRNA-seq) showed that ACE2 is highly coexpressed in type II alveolar cells of lung, along with esophageal upper epithelial cells and absorptive enterocytes [11]. These results may propose that antibodies or biological inhibitors may target virus proteins such as S protein showing that the ACE2 receptor can be a part of therapeutic guidelines of SARS-CoV-2 virus [21]. Interestingly, this receptor is highly enriched in tongue epithelial cells, and the findings have explained the underlying mechanism that the oral cavity is another potential risk for the SARS-CoV-2 virus [45]. The scRNA-seq data of fetal and adult kidney samples appeared that ACE2 expression was significantly in tubule cells [21] and also in myocardial cells (> 7.5%), ileal epithelial cells (~30%), esophagus epithelial cells (> 1%), kidney proximal tubule (< 1%), and bladder urothelial cells (2.4%) [51]. Therefore, the pattern of ACE2 expression shows other modes of SARS-CoV transmission that may involve the intestine, testis, kidney, and other tissue functions [19].

One study reported the ACE2 expression in neurological tissue that this illustrates a connection between the tissue damage and the morbidity and mortality by SARS-CoV-2 [14]. A mouse model checking acute liver injury with partial hepatectomy showed that ACE2 expression changed after treatment (day 1: Downregulated, day 3: Increased up to twice of the normal level, and day 7 or liver recovering: Returned to the normal level). Based on scRNA-seq data, 77 transcription factors were positively related to the ACE2 expression, which were mainly enriched in the development, differentiation, morphogenesis, and cell proliferation of glandular epithelial cells. This ACE2 expression upregulation in liver tissue induced by compensatory hepatocyte proliferation obtained from bile duct epithelial cells may also be the possible mechanism of liver tissue injury caused by COVID-19 [32]. The ACE2 expression in several cells, such as to lung type II alveolar cells, upper part of esophagus, epithelial cells, and ileum- and colon-absorbing enterocytes, may play to a role of the multitissue infection of SARS-CoV-2 [49]. Around 40% of ACE2-positive transient secretory cells are coexpressing TMPRSS2 proteinase, including FURIN as another proteinase in SARS-CoV-2 entry of the host cell, the percentage of transient secretory cells expressing the ACE2 receptor, both or one of the TMPRSS2 and FURIN proteinases increased by up to 50%. Thus, these cells can be highly vulnerable to SARS-CoV-2 infection [33].

Receptor-binding domain (RBD) and proteins

Human ACE2 (hACE2) is a receptor for different lineage B viruses such as SARS-CoV-2 to gain entry into human cells [28]. The CoV S glycoprotein plays a significant target for therapeutic antibodies, vaccines, and diagnostics [41] that affinity of SARS-CoV-2 S protein bind to ACE2 is more than SARS-CoV S protein. Antibody cross-reactivity is limited between the two RBDs [40]. Glycosylation may impact on interaction of the RBD with ACE2, and therefore, the aim is to test the drugs for their ability to block the RBD/ACE2 interaction. Antibodies and small molecular inhibitors blocking the RBD/ACE2 interaction should be developed to combat the SARS-CoV-2 virus [19]. Checking m396 and CR3014 (SARS-CoV-specific neutralizing antibodies)

that target the ACE2 binding site of SARS-CoV, there was no bind to SARS-CoV-2 S protein [38]. RdRp and 3CLpro regions of RBD binding to ACE2 are significantly different between the SARS-CoV and SARS-CoV-2 [11], [34]. This difference effectively rules out the use of previously developed antibodies and therapeutic peptides for the SARS-CoV S RBD [11]. Therefore, the difference in the RBD of between two viruses (SARS-CoV and SARS-CoV-2) shows a critical impact for the antibodies and that it should develop novel monoclonal antibodies that could bind specifically to SARS-CoV-2 RBD. To prevent SARS-CoV-2 and COVID-19 treatment, CR3022 does not overlap with the ACE2 binding site of SARS-CoV-2 RBD, and therefore, CR3022 may be as a candidate treatment, alone or in connection to other neutralizing antibodies [38]. One perspective study [32] checked Asn501 in RBD with the sites 41 and 353 of ACE2 receptor and the result showed that turtles and pangolins as potential expanded hosts of SARS-CoV-2 are closer to humans than bat [32]. Furthermore, the Q493 and P499 amino acid residues of SARS-CoV-2 RBD bind to hACE2 and maintain interface stability, neither of which is likely to interact with SARS-CoV-2 RBD [34]. SARS-CoV-2 and SARS-CoV interfaces include long flexible loops and nine aromatic residues in the interface with ACE2 [16].

Bat SARS-like CoVs have a RBD sequence with high similarity to SARS-CoV-2 [43]. ACE2 is widely expressed with conserved primary structures throughout the animal kingdom from fish, amphibians, reptiles, birds, to mammals. Therefore, it suggests that ACE2 from these animals (possible natural hosts for the virus) can potentially bind SARS-CoV-2 RBD [20]. Antibodies targeting the receptor-binding motif (RBM) regions may have more potential because of their ACE2 blocking activities but cross-protecting antibodies [43]. Another study [48] checking interactions of hACE2 between pangolin-CoV and SARS-CoV-2 showed that the S1 protein of pangolin-CoV was very closely related to SARS-CoV-2 than RaTG13 and this result shows a similar pathogenic potential of pangolin-CoV to SARS-CoV-2, showing pangolin as probable intermediate host of SARS-CoV-2 [29]. The nucleocapsid (N) protein of SARS-CoV-2 has approximately 90% amino acid sequence similar to SARS-CoV that therefore the N protein antibodies of SARS-CoV may cross-react with SARS-CoV-2 but may not provide cross-immunity. The N protein of SARS-CoV-2 may have a significant role in suppressing the RNA interference (RNAi) to overcome the host defense, similar to SARS-CoV [25]. One study [39] reported the striking structural similarity and sequence conservation among the SARS-CoV-2 S and SARS-CoV S glycoproteins emphasize the close correlation between these two viruses that recognize hACE2 to enter target cells [45]. The interaction between the key amino acids of S protein RBD and ACE2 indicated that except for pangolins and snakes, turtles may be as other potential intermediate hosts transmitting SARS-CoV-2 to humans [31].

Mutation

ACE2 sequence and structure from different species alert to potential intermediate translocation of SARS-CoV-2 and provide further monitoring in other animals [30]. Genotype distribution and allele frequencies (AFs) may be involved in further ACE2 research, including its role in lung function and acute lung injury. The AFs in the Eastern Asian people were much higher and associated with higher ACE2 expression in tissues that may propose different susceptibility or response to SARS-CoV-2 among different populations under the same conditions [17]. The distribution of ACE2-expressing cell population in different cohorts showed potentially identifies the susceptible population: Asian donor (male): 2.50% of all cells and African-American donors: 0.47% of all cells [49]. Furthermore, the ACE2 distribution is also more prevalent in male donors than females [49].

Treatment

The less correlation between SARS-CoV-2 and ACE2 can lead to longer incubation time, while still having a relatively higher level of viral concentration in human body [36]. CoV-NL63 uses the same ACE2 receptor as SARS-CoV-2, whereas it creates very different severity of disease [19]. Several studies [16], [23], [26], [38], [42], [50] demonstrate that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and to explain the connection between the SARS-CoV, SARS-CoV-2, ACE2, and the rationale for soluble ACE2 as a potential therapy [16]. Furthermore, checking the sites of interaction between ACE2 and SARS-CoV at the atomic level showed the interaction between ACE2 and SARS-CoV-2 [46]. The ACE2-immunoglobulin Fc domain (ACE2-Fc) protein sequence was investigated and the result showed that the ACE2-Fc therapy would also supplement reduced ACE2 levels in the lungs during infection, thereby directly treating acute respiratory distress pathophysiology as a third mechanism of action before a protective vaccine is administrated and widely available in the coming months to year(s) in the COVID-19 patients [27]. Results have shown that angiotensin II levels in plasma samples from 2019-nCoV-infected patients are significantly correlated linearly with viral load and lung injury, suggesting a number of diagnostic potential biomarkers and ARB drugs for the treatment of 2019-nCoV [31]. Weight loss and virus replication in the lungs were noticed in hACE2 mice infected with SARS-CoV-2 and this event was not established in wild-type mice with SARS-CoV-2. Therefore, the mouse model may make easier the treatment and vaccine development against SARS-CoV-2 [15].

Limitations

COVID-19 is a new emerging disease so the researches for systematic review are limited. Some studies may have lower levels of validity with fast peer

review. More time is needed for evaluating the results of clinical trials.

Conclusion

Whatever there were some different residues for ACE2 receptor between SARS-CoV-2 and SARS-CoV, but most studies showed that the ACE2 receptor for SARS-CoV-2 is similar to that of SARS-CoV, and therefore, ACE2 is rationally and scientifically valid therapeutic target for the current COVID-19 pandemic. Therefore, four potential drug candidates (an ACE2-based peptide, remdesivir, CLpro-1, and a novel vinylsulfone protease inhibitor) may use to treat COVID-19 patients. ACE2 expression was found in several human organs introducing new organs such as brain tissue and oral cavity and the expression in various populations was different as well as in the two genders. These data may be used for epidemiologic, diagnostic, and therapeutic purposes. Patients who take ACEIs and ARBs may have benefit in severe disease outcomes due to SARS-CoV-2, but further investigation is necessary. The RBD/ACE2 interaction suggested pangolins and snakes, and turtles may act as the potential intermediate hosts transmitting SARS-CoV-2 to humans.

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