International Journal of Biochemistry Research & Review

29(5): 1-8, 2020; Article no.IJBCRR.57230
ISSN: 2231-086X, NLM ID: 101654445

Pathogenesis and Possible Drug Targets for Covid-19

N. Ramesh Kumar[1] and S. Chitra[2*]

[1]Department of Pharmaceutical Chemistry, C. L. Baid Metha College of Pharmacy, Thorapakkam, Chennai-600097, India.
[2]Department of Biochemistry, Captain Srinivasa Murti Regional Ayurveda Drug Development Institute, Central Council for Research in Ayurvedic Sciences, M/o of AYUSH, Government of India, Anna Hospital Campus, Arumbakkam, Chennai-600106, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author NRK Designed the study and managed the literature searches. Author SC Managed the analysis of the study and drafted the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJBCRR/2020/v29i530186
Editor(s):
(1) Dr. Enrico Sanjust, University of Cagliari, Italy.
Reviewers:
(1) Manju Nagpal Chitkara, Chitkara University, India.
(2) Falusi Bamidele Ayodeji, Federal College of Education (Special), Nigeria.
(3) Navaneethakrishnan Suganthan, University of Jaffna, Sri Lanka.
Complete Peer review History: http://www.sdiarticle4.com/review-history/57230

Mini-review Article

Received 02 May 2020
Accepted 27 May 2020
Published 03 June 2020

ABSTRACT

Coronavirus (CoVs) is a large family of enveloped, single-stranded, positive-sense RNA viruses that infect a wide range of vertebrates. They are extensively found in bats and also in many other birds and mammals including humans. SARS-CoV-2 is a global pandemic and originated from Wuhan States of China. The SARS-CoV-2 is more genetically similar to zoonotic SARS-CoV and less similar to MERS-CoV. The viral surface spike protein of SARS-CoV-2 binds to the human angiotensin-converting enzyme-2 (ACE-2) receptor of Type II alveolar cells of the lungs and it appears to be the major portal of entry by this virus. The subsequent activation of the spike protein by transmembrane protease-2 and in addition to lung, ACE-2 is highly expressed in heart followed by kidney and intestinal epithelium. SARS-CoV-2 infects more men than women due to ACE-2 receptor on the cells increased with age and generally it was higher in men than in women. The incubation period for this virus varies from place to place and asystematic symptoms are also commonly seen in infected patients. There are a number of pharmaceuticals already being tried and

**Corresponding author: E-mail: chiresh2006@gmail.com;*

are in different phase levels of testing, but a better understanding of the underlying pathobiology is required. In this circumstance, this article will briefly review the underlying principle for ACE-2 receptor as a specific target. Despite ACE-2 serving as the portal for infection, the role of ACE inhibitors or angiotensin receptor blockers requires further investigation.

Keywords: COVID-19; drug target; SARS-CoV-2; ACE-2; TMPRSS-2.

1. INTRODUCTION

Coronavirus (CoV) can cause a range of diseases such as upper respiratory ailment in chickens and enteritis in cows and pigs. In humans, it is likely to cause mild to moderate respiratory tract infections such as common cold, cough and fever. It unsurprisingly produced mild symptoms in certain individuals and responses were more severe. In acute cases, due to gradual respiratory failure results in alveolar damage and this virus strain exhibited stronger virulence and quickly passed from human to human. Epidemiologic investigation in Wuhan, Hubei Province, China identified an initial association with a seafood and live-animal market where most of them worked or visited [1]. A novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) initially named it as 2019-nCoV (beta coronavirus) on 9th January 2020, formally identified as the cause of an outbreak of viral pneumonia which was declared by World Health Organization (WHO) as a public health emergency of international concern [2]. SARS-CoV-2 is a single-stranded positive sense enveloped RNA virus and the seventh known human CoV. Covid-19 is caused by SARS-CoV-2 and is a global pandemic; the infected patients were from 215 countries/regions around the globe. As per the registry of WHO as on 01, May 2020, there were about 32,59,978 confirmed cases and nearly 2,30,575 deaths globally and in India around 37,036 active cases and 1,220 deaths due to COVID-19. While the outbreak began in China, the number of cases outside of China exceeded more and is currently rising at an exponential rate. Furthermore, the number of infected cases was found to be higher in America, Spain, Italy, France and Germany. This SARS-CoV-2 is different from the other CoV recognized to cause the common cold (229E, NL63, OC43 and HKU1), but similar to the zoonotic SARS-CoV (beta coronavirus) originated in 2002 [3] and less similar to MERS-CoV (beta coronavirus from Middle East respiratory syndrome) in 2012 [4]. SARS-CoV-2 is believed to have originated in bats, similar to many other CoV, as it shares 89-96% nucleotide identity with bat CoV [5]. SARS-CoV-2 originated from bats and to humans and possibly the intermediate host is Malayan Pangolin, which shares 91% nucleotide identity [6]. The homologous recombination might have occurred in the intermediate host and the infection severity and aggressiveness varies from S and L type of SARS-CoV-2. It is less genetically similar to MERS-CoV and it shares around 50% nucleotide identity. The CoV genome encodes four major structural proteins called the spike protein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein (E). The S protein is responsible to make possible entry into the target cell using the cell surface receptor, ACE-2. It is composed of a short intracellular tail, a transmembrane attachment, and a large ectodomain that consists of a receptor binding S_1 subunit and a membrane-fusing S_2 subunit. Spike protein genome of SARS-CoV-2 is 75% identical with SARS-CoV S protein [7]. The receptor binding motif of S protein of SARS-CoV and SARS-CoV-2 showed most of amino acid residues essential for receptor binding share the common characteristics suggesting that both viruses use the same host receptor for cell entry [8]. Human-to-human transmission has been confirmed and transmission from asymptomatic individuals during the incubation period may occur. The viral incubation period is estimated at approximately 5 days. The Chinese authorities reported that the incubation period may be upto 14 days [9]. Signs and symptoms at all illness onset include fever (83-98%), cough (76-82%) and myalgia or fatigue (11-44%) [9]. It is difficult to predict the mortality rate of COVID-19 as it has been changeable. WHO estimated mortality rate of some selected viral diseases include pH1N1 (0.02-0.4%), COVID-19 (2-3%), SARS (10%), MERS (37%) and Ebola (63%) [10]. ACE-2 was highly expressed on lung epithelial cells. After entry into the host cell, by cough, sneeze or droplets, the SARS-CoV-2 attaches the ACE-2 receptor in upper airway and alveoli of lungs in turn causes possible sequential pathogenic changes (Fig. 1). COVID-19 is caused by SARS-CoV-2, which invades cells through the ACE-2 receptor. After entry into airway the spike protein of virus attaches to ACE-2 receptor with the help of transmembrane protease serine-2 (TMPRSS2)

present on the membranes. The positive single strand RNA makes its own copy and releases the polyproteins also it utilizes the RNA-dependent RNA polymerase of the host cell and produce more number of copies of viral protein. Viral assembly is takes place after post translational modifications in golgi apparatus, ultimately SARS-CoV-2 is released from the cell.

2. MECHANISM OF PATHOGENESIS OF COVID-19

The viral S protein of SARS-CoV-2 binds to the human angiotensin-converting enzyme-2 (ACE-2) receptor and subsequent activation of the S protein by TMPRSS-2 which is located on the cell membrane. TMPRSS-2 helps the virus to make entrance into the cell by endocytosis followed by viral replication and cell-to-cell transmission [11-13]. The ACE-2 is expressed predominantly in Type 2 alveolar cells of the lungs and it appears to be the major portal of entry by this virus. ACE-1 could act as a potential risk factor for fatal SARS-CoV-2 by up-regulating ACE-2 (Fig. 3). After entry by endocytosis the positive single strand RNA (+ssRNA) of SARS-CoV-2 utilizes freely available ribosomes of cytoplasm and translated into polyproteins, which in turn facilitates the formation of functional components of SARS-CoV-2. This polyproteins subsequently cleaved to yield core and envelop proteins, which assemble into new virus particles and enzymes necessary for viral replication. The generation of viral replicate components from a single large polyprotein is a mechanism conserved in many +ssRNA viruses and the role of polyprotein precursors in viral replication have been studied [14]. RNA dependent RNA polymerase in the host cell assists to create a multiple copies of +ssRNA, and localization of viral components in golgi complex which further create an ultimate product of viral copies.

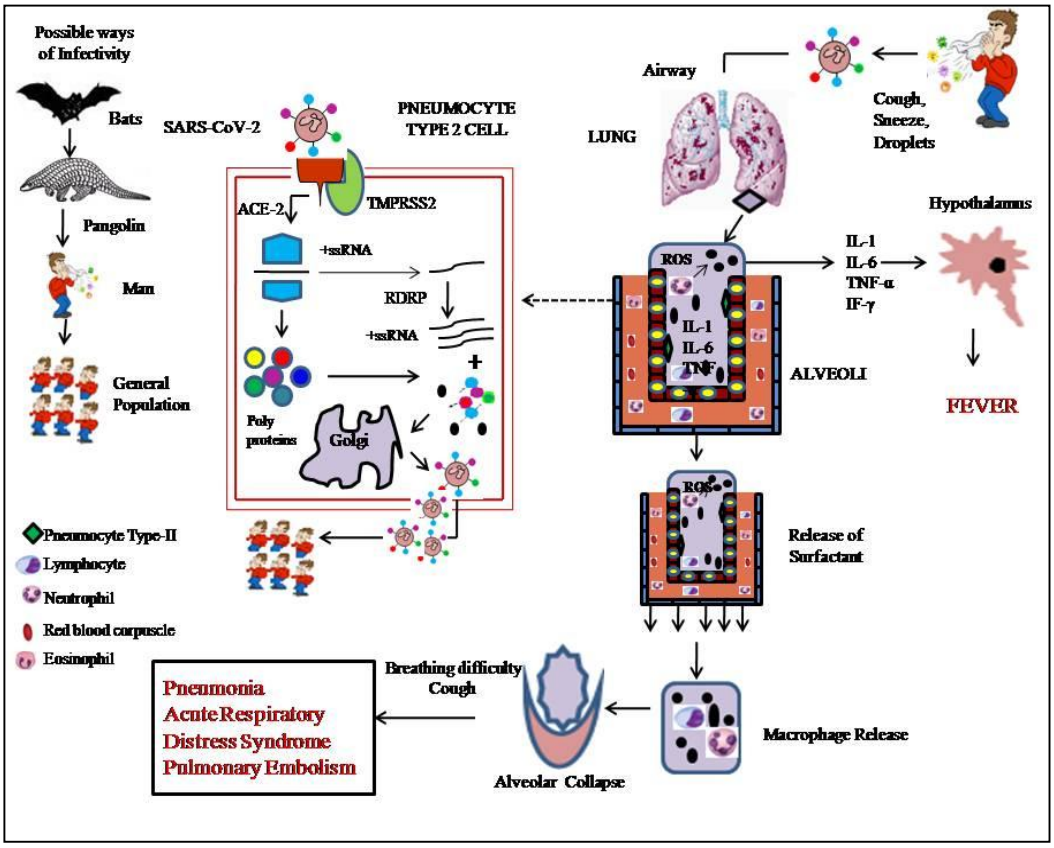

Fig. 1. Pathogenic mechanism of SARS-CoV-2 after entry into cell

ACE-2- Angiotensin converting enzyme-2; ssRNA-Single stranded RNA; RDRP- RNA- dependant RNA polymerase; IL- Interleukin; TNF-α-Tumor necrosis factor alpha; IF-γ- Interferon gamma; SARS-CoV-2- Severe acute respiratory syndrome-coronavirus-2; ROS-Reactive oxygen species

This SARS-CoV-2 is ready to infect neighboring cells which move forward from the alveolar cells by exocytosis. The other functions of polyproteins are that, it enhances the macrophage activation in the type 2 pneumocyte cell which in turn releases interleukins (IL) and cytokines. During the incubation and non-severe stages, a specific adaptive immune response is required to eliminate the virus and to prevent disease progression to severe stages. The cytokine release syndrome seems to affect patients with severe conditions. SARS-CoV-2 infected patients have IL-1, IL-6, Tumor necrosis factor (TNF) alpha, TNF-β, and interferon-γ. These cytokines produce deleterious effects by generating reactive oxygen species (ROS) and reactive nitrogen species (NOS). These free radicals further affect type 1 alveolar cells of the lung causing hypoxemia by central nervous system reflex through prostaglandin E2 and leukotriens. Hypoxemia results O_2/CO_2 imbalance in lungs that leads to difficulty in breathing, which in turn might leads to pneumonia, acute respiratory distress syndrome (ARDS) and pulmonary embolism. Hypoxia due to extensive clogging of pulmonary microcirculation and autopsy findings from COVID-19 patients showed microthrombi in the pulmonary microvasculature [15-17] suggesting that ventilation-perfusion mismatch due to capillary obstacle could be a essential feature in the refractory hypoxemia presented by these patients. The effects of ACE-1/ARBs (Ang II receptor blocker) on ACE-2 mRNA levels and protein activity in human lung tissues are still unclear. The use of ACE-1/ARBs might be a double-edged sword in SARS-CoV-2 patients. On one hand, it might lead to an increased risk of SARS-CoV-2 infection and on the other hand, it might reduce the severity of lung damage caused by the infection.

3. SARS-COV-2 AND HEART INJURY

Adverse outcomes of COVID-19 were associated with comorbidities, including hypertension, cardiovascular disease, and lung disease. ACE-2 is highly expressed in heart and counteracting the effects of angiotensin II (Ang II). Apart from heart and lungs, it is expressed in the vascular endothelium, kidney and intestine providing a mechanism for the multi-organ dysfunction which could be seen in SARS-CoV-2 infected patients [18,19]. SARS-CoV-2 interacts with cardiovascular system on multiple levels, increasing morbidity and mortality in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction. ACE-2 is a membrane-bound aminopeptidase, has a vital role in the cardiovascular and immune systems [20]. In addition, ACE-2 has been identified as a functional receptor for CoV including SARS-CoV and SARS-CoV-2 [20]. ACE-2 is a type I trans-membrane metallo-carboxypeptidase with homology to ACE, it play a key role in the renin-angiotensin system (RAS) and target for the treatment of hypertension [21]. ACE-2 is highly expressed in the heart and lungs when binding of the viral spike protein of SARS-CoV-2 to the host cell and it also expressed in vascular endothelial cells, leydig cells of testes and the renal tubular epithelium. The anti-hypertension therapy with ACE inhibitors or angiotensin receptor blockers (ARB) in patients with SARS-CoV-2 should be cautiously considered for their safety and its possible effects. It mainly invades alveolar epithelial cells, resulting in respiratory symptoms and these are more severe in patients with cardio vascular diseases that might be associated with increased secretion of ACE-2 in these patients compared with healthy individuals [22]. COVID-19, there is a higher prevalence of cardiovascular disease and more than 7% of patients suffer myocardial injury from the infection (22% of the critically ill) [23]. Common laboratory findings among hospitalized patients with COVID-19 include lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, and elevated inflammatory markers such as ferritin, C-reactive protein, and erythrocyte sedimentation rate [24,25]. Patients with SARS-CoV-2 also showed potential cardiac injuries like SARS-CoV. Among 99 confirmed SARS-CoV-2 patients admitted to Wuhan Jinyintan Hospital, showed 13% elevated creatine kinase and 76% lactate dehydrogenase levels [26]. Also 7.2% elevated hypersensitive troponin I and 16.7% had arrhythmia among 138 patients reported [25]. An autopsy case of SARS-CoV-2 was reported with moderate quantity of transparent light-yellow liquid in the pericardial cavity and mild pericardial edema in 85-year-old man who died from SARS-CoV-2 [27]. However, SARS-CoV-2 infects the heart and reduces the ACE-2 expression is presently lacking. ACE-2 expression is up regulated by ACE-1/ARBs and also it blocks the Ang II, type 1 receptor. Patients with SARS-CoV-2 also showed potential cardiac injuries and the RAS activation. The SARS-CoV-2 infection possibly influences the balance between Ang II and Ang (1-7), while ACE-1/ARBs can block the rennin-angiotensin system (RAS) and protect the heart and other

organs which are susceptible to injury caused by the RAS activation. ACE-2 converts Ang II to Ang-(1–7), which acts on the Mas receptor (MasR) and expressed on a variety of cell lineages in many tissues relevant to cardiovascular disease including type 2 alveolar epithelial cells (Fig.3). It also moderately lowers blood pressure through vasodilation by promoting kidney sodium and water excretion; however it also attenuates inflammation through the production of reactive oxygen species, nitric oxide [28].

4. SARS-COV-2 AND OTHER ORGANS

SARS-CoV-2 virus primarily affects the respiratory system, although other organ systems are also involved. ACE-2 expression was high in lung, heart, ileum, kidney and bladder. Autopsy studies have noted detectable SARS-CoV-2 RNA in the kidneys, liver, heart, brain, and blood in addition to respiratory tract specimens, suggesting that the virus disseminates systemically in some cases; whether direct viral cytopathic effects at these sites contribute to the complications observed is uncertain [29,30]. Studies published in the beginning of SARS-CoV-2 outbreak suggested that patients infected with severe SARS-CoV-2 were more likely to have a history of hypertension, cardiovascular disease, chronic kidney disease and diabetes mellitus than those with milder disease [31]. The affinity of SARS-CoV-2 for ACE-2 is 10-20 folds higher than that of SARS-CoV and also it has high thrombotic tendency. In severe COVID-19 cases cause excessive blood clotting occurs due to disseminated intravascular coagulation (DIC) further it leads to shortness of breath and multi organ failures. ACE-1 disrupts the renin-angiotensin-aldosterone system (RAAS) and conversion of angiotensin-I (Ang I) to angiotensin-II (Ang II) fails which results in vasodilation. ACE-1 can cause acute kidney injury due to inadequate renal perfusion might be due to hypovolemia. Ang II is a potent vasoconstrictor and produced from RAAS pathway which helps in activation of aldosterone. It is a mineralocorticoid helps kidneys to reabsorb more sodium at the expense of potassium excretion [18]. An increased vasoconstriction and sodium reabsorption results in higher blood pressure and retention of volume. ACE-1 has been shown to be beneficial for the treatment of acute myocardial infarction, hypertension, systolic heart failure, chronic kidney disease and preventing progression of diabetic nephropathy and retinopathy. ACE-2 receptor is present in liver and intestine which finally cause metabolic disarrangement and diarrhea in patients affected with COVID-19 (Fig. 2).

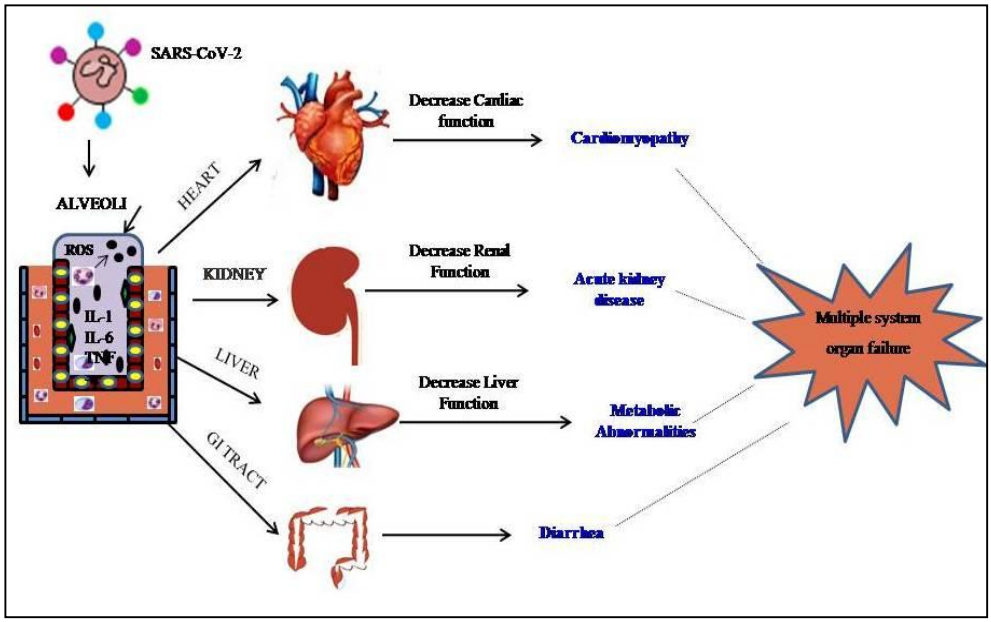

Fig. 2. Possible changes in organs after entry of SARS-CoV-2

IL- Interleukin; TNF-α-Tumor necrosis factor alpha; SARS-CoV-2- Severe acute respiratory syndrome-coronavirus-2; ROS-Reactive oxygen species

5. THERAPEUTIC APPROACH

Effective SARS-CoV-2 vaccines are essential for reducing disease severity, viral shedding and transmission, thus helping to control the coronavirus outbreaks. The first and foremost therapeutic drug target would be the inhibition of spike protein of SARS-CoV-2 binding to ACE-2 receptor on the cell membrane [15,18]. This will be the potential drug candidate to prevent initial binding of this virus. The other important drug target could be the inhibition of TMPRSS2 activity. Without this transmembrane protein, ACE-2 could not allow the virus to enter into the cell. The other site would be blocking ACE-2 receptor of the membrane (Fig. 3). Another target for SARS-CoV-2, if any, can help the virus to directly infect dendritic cells and alveolar macrophages. This needs future research. These antigen presenting cells move to the draining lymph nodes to present viral antigens to T cells. $CD4^+$ and $CD8^+$ T cells play a significant role. $CD4^+$ T cells activate B cells to promote the production of virus-specific antibody, while $CD8^+$ T cells can kill viral infected cells. Patients with severe diseases were reported to have increased plasma concentrations of proinflammatory cytokines, including interleukin IL-6, IL-10, granulocyte-colony stimulating factor, macrophage inflammatory protein-1α, and tumor necrosis factor-α [24]. $CD4^+$ and $CD8^+$ T cells were activated in those patients as suggested by higher expression of CD69, CD38 and CD44.

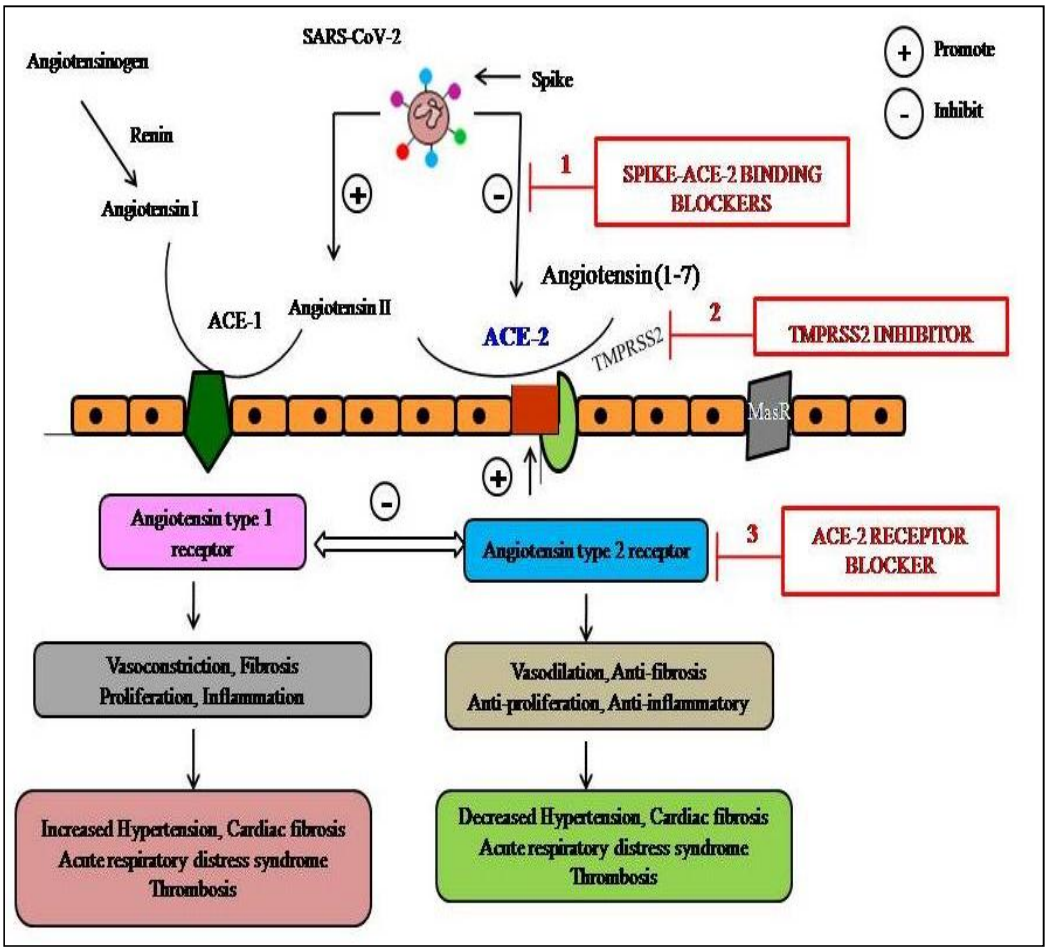

Fig. 3. Biochemical role of ACE-2 and its possible drug target

ACE-1-Angiotensin converting enzyme-1; ACE-2- Angiotensin converting enzyme-2; TMPRSS2-Transmembrane protease serine-2;; MasR-Mas receptor; SARS-CoV-2- Severe acute respiratory syndrome-coronavirus-2

6. CONCLUSION

Based on the available data at present scenario, it is a crucial time for the researchers and clinicians to come forward and access the preventive and curative efficacy of the drug targets or vaccine candidates in possible aspects of controlling SARS-CoV-2 globally. Reported that this virus affects men predominantly than women and also it enters via respiratory airways ultimately leads to end organ failures of heart, gastrointestinal tract, liver and kidney of COVID-19 infected patients. In addition to those cardiovascular diseases, asthma, chronic kidney disease patients are more probably affected by this virus. Therefore, particular attention should be given to patients with above ailments during treatment for COVID-19. Need more research on the inhibition of spike protein of SARS-CoV-2 binding to ACE-2 receptor may provide a potential drug target to control this virus without any loss of human life.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Report of clustering pneumonia of unknown etiology in Wuhan City. Wuhan Municipal Health Commission; 2019. Available:http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989
2. Wu P, Xinxin Hao X, Lau EHY, Wong JY, Leung KSM, Wu JT, Cowling BJ, Leung GM. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China. Euro Surveill. 2020;25(3):2000044. DOI:10.2807/1560-7917.ES.2020.25.3.2000044
3. Chan JWM, Ng CK, Chan YH, Mok TYW, Lee S, Chu SYY, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). Thorax. 2003;58:686-9.
4. Badawi A, Ryoo SG. Prevalence of co-morbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): A systematic review and meta-analysis. Int J Infect Dis. 2016;49:129-33.
5. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26:450–2.
6. Zhang TWQ, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr Biol. 2020;30: 1346-51.
7. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;180: 281-92.
8. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Sci. 2005;309:1864-8.
9. World Health Organization. WHO MERS global summary and assessment of risk; 2018. Available:https://www.who.int/csr/disease/coronavirus_infections/riskassessment-august-2018.pdf
10. Suganthan N. Covid-19. Jaffna Med J. 2019;31:1-6.
11. Shulla A, Taylor HS, Subramanya G, Jincun Z, Perlman S, Gallagher T. A trans-membrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J Virol. 2011;85:873-82.
12. Heurich A, Winkler HH, Gierer S, Liepold T, Jahn O, Pöhlmann S. TMPRSS2 and ADAM17 cleave ACE-2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J Virol. 2014;88:1293-307.
13. Hoffmann M, Kleine-Weber H, Simon Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE-2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181:271–80.
14. Cameron CE, Oh HS, Moustafa IM. Expanding knowledge of P3 proteins in the poliovirus lifecycle. Future Microbiol. 2010; 5: 867–81.
15. Tian S, Hu W, Niu L, et al. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in

Two Patients With Lung Cancer. J Thorac Oncol; 2020.
DOI: 10.1016/j.jtho.2020.02.010
[Published Online First: 2020/03/03]

16. Yao XH, Li TY, He ZC, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. 2020;49: E009.
DOI:10.3760/cma.j.cn112151-20200312-00193
Published Online First: 2020/03/17
17. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemostasis. 2020;1538-7933.
18. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE-2) is a key modulator of the renin angiotensin system in health and disease. Int J Pept. 2012; 2012:1-8.
19. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE-2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46:586-90.
20. Turner AJ, Hiscox JA, Hooper NM. ACE-2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25: 291-4.
21. South AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin–angiotensin system inhibition during the COVID-19 pandemic. Nat Rev Nephrol; 2020.
Available:https://doi.org/10.1038/ s41581-020-0279-4
22. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol; 2020.
Available:https://doi.org/10.1038/s41569-020-0360-5
23. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and Cardiovascular Disease. Circulation. 2020;141:1648–1655.
24. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China Lancet. 2020;395(10223): 497.
25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-9.
26. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
27. Liu X, Wang R, Qu G, Wang Y, Liu P, Zhu G, *et al.* Histological findings of COVID-19 based on autopsy: A case report. J Forensic Med. 2020;36:1-3.
28. South AM, Shaltout HA, Washburn LK, Hendricks AS, Diz DI, Chappell MC. Fetal programming and the angiotensin-(1–7) axis: A review of the experimental and clinical data. Clin Sci. 2019;133:55–74.
29. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and Renal Tropism of SARS-CoV-2. N Engl J Med; 2020.
30. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med; 2020.
31. Madjid, M, Naeini PS, Solomon SD, Vardeny O. Potential effects of corona viruses on the cardiovascular system- A Review. JAMA Cardiol; 2020.
DOI: 10.1001/jama cardio.2020.1286

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/57230