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The Role of Angiotensin II in the Pathogenesis of SARS-CoV-2

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Abstract

Corona Virus induced disease Covid-19 is an infectious disease caused by SARS-CoV-2 virus. People infected are likely to develop mild, moderate or severe illness and people suffering from chronic diseases are more likely to develop life-threatening complications.

We reviewed the literature of the last six months on manuscripts on SARS-CoV-2 during the first two waves of the pandemic.

Our manuscript describes viral transmission among humans through droplets of infected individuals and attempts to clarify the main pathogenetic mechanisms of this novel coronavirus. As there is not yet an approved treatment, we also present potential therapeutic targets including drugs of the renin angiotensin system.

Introduction

Corona Virus Induced Disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. People infected with the new coronavirus are likely to developmild-to-moderate respiratory symptoms; however, people suffering from chronic illnesses (e.g. cardiovascular disease, diabetes) and the elderly are likely to develop complications leading to Intensive Care Unit (ICU). The mortality rate in the severe forms of the disease remains high [1].

SARS-CoV-2 spreads mainly through air droplets when an infected person sneezes or coughs [2]. As there is not yet an approved vaccine or treatment for the disease, it is necessary to follow the instructions of WHO (World Health Organization) and local health authorities to avoid infection, especially social distancing and general hygiene measures in daily activities.

The aim of this article is to present the structural features of SARS-CoV-2 and explain the mechanisms of viral binding to angiotensin converting enzyme 2 (ACE2) receptors and suggest potential therapeutic solutions. Moreover, we also aim to analyze the impact of SARS-CoV-2 pandemic to certain population and especially to the elderly.

Coronavirus Types

Coronaviruses is a large family of viruses known to cause disease in humans ranging from a common cold to the most serious forms of the disease such as Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). There are 7 different types of Coronaviruses to date [3]. Among them the most important is SARS Coronavirus (SARS-CoV) which appeared in southern China in late February 2002 and according to scientific research was found to be transmitted from civet cats to humans [4]. The SARS epidemic spread in South-East Asia but was confined without wide global transmission.

Another Coronavirus outbreak happened in mid-2012

in the Middle East and was named after this same region as MERS-CoV(Middle East syndrome). It was presented as a viral respiratory infection. Clusters of this viral infection still exist in that region of the Arab peninsula causing human infection [5].

The most recent Coronavirus is the SARS-CoV-2 that prevails and has caused one of the biggest pandemics in the history. It was first described in China in the city of Wuhan and then spread in almost all countries and territories around the world [6]. COVID-19 that is caused by SARS-CoV-2 is challenging health systems in all affected countries; thus, there has been an urge to study the pathogenetic mechanisms of the virus in order to develop effective treatments and vaccines against it [7].

SARS Emergence and Pathogenesis

Severe Acute Respiratory Syndrome (SARS) is a viral respiratory disease of zoonotic origin that appeared in the early 2000s caused by severe acute coronovirus respiratory syndrome (SARS-CoV). In 2003, an outbreak of SARS began in China and spread to other countries before ending in 2004. In factsince the 2004 epidemic there have been no reported cases of the first SARS-CoV worldwide.

In 2019, its successor, the Associated strain of severe acute respiratory syndrome virus now called SARS-CoV-2 was discovered. This new strain causes COVID-19, a disease that has caused the 2020 pandemic. The symptoms of SARS-CoV-2 are very similar to the previous SARS-CoV and are mostly flu-like including fever, muscle pain, lethargy, cough, sore throat, and other nonspecific symptoms [8]. SARS can eventually lead to shortness of breath and pneumonia. It is estimated that the average incubation period for SARS is 4-6 days, although it can rarely be as short as 1 day or up to 14 days [9].By the end of 2020, the first vaccines against SARS-CoV-2 have already been developed and proven to be both safe and effective in humans.

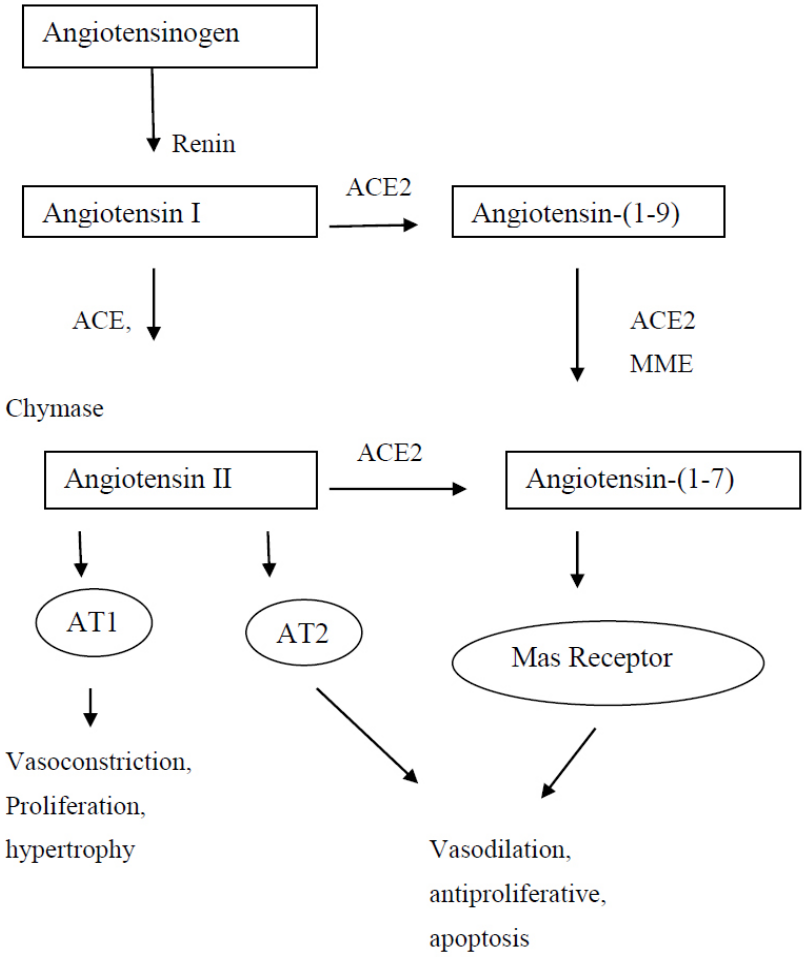
ACE 2 and its Correlation to SARS-CoV-2

Research conducted in 2003 by Michael Farzan and his colleagues showed that the S1 region of the SARS-CoV protein, which is permissible for virus replication, is directly related to the expression of ACE-2 [10]. Additional studies carried out by the scientific team of Xiao and Farzan demonstrated that inhibitor binding caused a large formative change in the enzyme that aligns critical residues for catalysis, but also that the inhibitor binds to the enzyme in an inverse orientation from that provided by ACE-1 binding in the active position of ACE. The ACE-2 inhibition plays a crucial role in heart function, specifically in hypertension and diabetes through its ability to convert angiotensin II to angiotensin - (1-7) [11].

The ACE-2 peptide inhibitor is a carboxypeptidase (consisting of 805 amino acids) of Type I zinc with a membrane that includes an aminotelic end and a peptide region, which is oriented extracellularly. ACE-2 is expressed in all tissues, with the greatest activity in the small intestine, namely in the ileum, kidneys, heart, brain stem, lungs, vascular system, stomach, liver and nasal and oral mucosa. As mentioned above, the main objective of the peptide inhibitor is to convert angiotensin II to angiotensin-(1-7) by removing the C-terminal phenylalanine residue; an important component of the anti-regulation axis of Renin Angiotensin System (RAS).

Similarly,thenovelSARS-CoV-2 uses the protein spike to integrate into the ACE-2 receptor. This protein is found on the surface of human cells and allows the virus to attach to the cell membrane. Researchers are trying to discover chemical compounds that could block protein spikes, preventing the virus from entering the human body [12]. An X-ray crystal structure of the receptor binding area of SARS-CoV-2 when it binds to ACE-2 was studied and 15 amino acids were found, which are directly linked to viral protein [13].

ACE-2 binds to cell membranesin the lungs, arteries, heart, kidneys and intestine. ACE2 lowers blood pressure by catalyzing the hydrolysis of angiotensin II to angiotensin (1-7) (vasodilator) [14]. ACE-2 is characterized as an opposite remainder of ACE, i.e. ACE breaks down the angiotensin I hormone into the vasoconstrictor angiotensin II and ACE2 in turn breaks down the carboxylic terminal amino acid phenylalanine from angiotensin II (Asp-Arg-Val-Tyr-Ile-his-Pro-Phe) by hydrolyzing it into the vasodilator angiotensin (1-7), (H-ASP-Arg-Val-Tyr-Ile-His-Pro-OH). ACE2 can also break down other peptides, such as bradykinin and ghrelin.



Viral Binding to the ACE-2 Receptor

Studies have shown that the Spike viral protein binding affinity to ACE-2 is correlated with higher transmission of the disease. Angiotensin receptor blockers have been tried as therapeutic agents against SARS-CoV-2. Interestingly, the activity of the peptide inhibitor can also have a protective effect against lung damage, by increasing the production of vasodilator angiotensin 1-7 [15].

The virion of SARS-CoV-2 has a diameter of 50-200 nm and contains four structural proteins: S (spike), E (envelope), M (membrane) and N (nucleocapsid). More specifically, the protein S is responsible for the attachment of the host and the compilation of the virus membranes and host cells. The S1 subunit of the S protein is the one responsible for connecting to a host cell. To make the binding with a host cell the S1 receptor undergoes modifications. This protein causes receptor binding and membrane fusion. Spike protein contains two subunits, S1 and S2. S1 contains a receptor binding domain (RBD), which is responsible for the recognition and binding to the receptor of the cell surface [16].

When identifying the RDB, the ACE2 protease area (PD) is mainly involved by the alpha-helix with a contribution from the A2 Helix and the ligand of the B3 and B4 sheets. Subunit S2 is the "stem" of the structure, which contains other basic elements necessary for the fusion of the membrane. Spike protein is a potential target for neutralizing antibodies and vaccines [17].

Nucleocapsid protein (N-protein) is the most abundant protein in the coronovirus. N-protein is a highly immunogenic phosphoprotein and is usually highly preserved and is often used as an indicator in diagnostic determinations [18].

Molecules against SARS-CoV-2 and Targeting the ACE-2

As previously described, SARS-CoV-2 is easily transmitted due to Spike proteins located on the

surface of the virus that allow effective bindingto ACE-2 receptors found on the surfaces of human cells. Current studies aim to target Spike proteins in order to prevent SARS-CoV-2 infection [19].

Remdesivir an effective drug against Ebola virus and it seems to have the ability to inhibit genome proliferation of RNA viruses. As a nucleotide analogue remdesivir proved effective in preventing replication of MERS-CoV in monkeys. Disease severity, virus replication and lung damage were reduced with the use of this drug. These results are the basis for considering remdesivir as a promising drug and against Covid-19 [20].

Other clinical studies support the use of Type I interferons including interferon A2B and interferon B known for their antiviral activity. Beneficial effects are expected at an early stage of infection; however, their administration at a later stage may worsen cytokine and therefore inflammation [21]. It is worth noting that some interferon antagonists and inflammatory coding activators from SARS-CoV are not retained in SARS-CoV-2.

Steroids have also been used in Covid-19 to stop cytokine actions and prevent pulmonary fibrosis [22]. The timing of steroids use is crucial, because an early administration is supposed to enhance the development of microbial infection. It is interesting to study whether the fungal infection in the lungs of some patients in Wuhan may be associated with the abuse of steroids.

There are also drugs initially used in Covid-19, but later proved ineffective. An example is the use of antimalarial drug hydroxychloroquine. In fact, a recent double-blind, multicenter study of 150 people with Covid-19 concluded that hydroxychloroquine has no therapeutic effects. These drugs cause serious side effects such as cardiotoxicity and deadly cardiac arrhythmias [23].In addition, hemolytic anemia may occur in people of Mediterranean origin lacking the enzyme G6PD.

An increasing number of studies is also targeting drugs involved in the renin angiotensin system and more specifically angiotensin converting enzyme (ACEIs) inhibitors or angiotensin receptor blockers (ARBs), which are mainly used in treating arterial hypertension. Reducing the activity of ACE2 in cell membranes could theoretically allow the virus to enter the cells [24]. But ACE inhibitors such as enalapril and ramipril currently used for hypertension and heart failure do not inhibit ACE-2. Inhibition of ACE1 leads to an increase in the concentration of angiotensin I which could be converted to angiotensin (1-9), but the conversion of angiotensin (1-9) to angiotensin (1-7) is done by ACE1 which would be limited by the presence of an ACE1 inhibitor [25]. Thus, the increased amount of angiotensin I may increase ACE2 as was the case in experimental animals using ACE1 and ARB inhibitors. It is still unclear whether this intervention is beneficial or not [26].

Experimental data show that the increased concentration of Angiotensin (1-7) via ACE2 may result in an anti-inflammatory effect to which inhibition of COX-2 synthesis contributes and some protection against lung damage caused by the virus has been observed [27].

A promising idea for the treatment of SARS-COV-2 involves targeting and understanding the mechanisms that lead to high virulence. The structure of COVID-19's glycoprotein S(spike) reveals that receptor binding domains (RBDs) tightly bind basic free fatty acid (FFA) linoleic acid (LA) into three complex binding follicles. The binding site also appears to be present in SARS-CoV and MERS-CoVcoronoviruses. LA binding stabilizes a locked configuration S causing decreasing interaction with ACE2 in vitro. In human cells, The Binding of LA in combination with the drug remdesivir against COVID-19, suppresses the replication of SARS-CoV-2. This structure that directly connects LA and S, proves that treatment methods need to focus on the LA bond with SARS-COV-2.

Upregulation of ACE2 with activators such as DIZE [4,4'-(1-Triazene-1,3-diyl)bis (benzenecarboximidamide)] is also a promising approach [28]. DIZE is enhancing ACE2 and subsequently A(1-7) of the AT2/MasR/A(1-7) axis which is beneficial for homeostasis and vasodilation. The potential actions of ACE2 activator diminazene aceturate (DIZE) in various diseases have been recently reported [29].

Conclusions

To sum up, SARS-CoV-2 is an RNA virus that is transmitted by human contact through the droplets of an infected individual. The disease is now called Covid-19 and the symptoms may vary in terms of severity from mild disease to lethal and the prognosis depends on the immune system status of the patients. Usually

people belonging to vulnerable groups (elderly, chronic illness) may have more severe disease and higher mortality rates.

A few clinical trials are underway to discover various possible therapeutic drugs, but until today the appropriate one has not been found and therefore the sufferers are given drugs against symptoms and consequences of Covid-19.

The way the virus enters human cells is related to the virus Spike protein binding affinity to the ACE-2 peptide inhibitor whose normal function in humans is to convert angiotensin II to angiotensin (1-7) [30]. One treatment being considered against coronovirus involves the use of RAS inhibitors, which has not been clarified whether it is fully beneficial, although there seems to be some protection to the lungs.

Additionally, patients belonging to vulnerable groups should immediately seek medical advice to receive the appropriate treatment. Finally, in addition to the ongoing research on the drug against the virus itself, scientists aim to develop vaccines which must have the full safety and efficacy required [31].

References

[1] Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, etal. A comprehensive review of COVID-19 characteristics. BiolProcedOnline. 2020;22:19

[2] Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281-286

[3] Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology. 2018;23(2):130-137

[4] Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. VirusRes. 2008;133(1):74-87

[5] Chafekar A, Fielding BC. MERS-CoV: Understanding the Latest Human Coronavirus Threat. Viruses. 2018;10(2):93

[6] Lai CC, Shih TP, Ko WC, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J AntimicrobAgents. 2020;55(3):105924

[7] Li H, Zhou Y, Zhang M, et al. Updated Approaches against SARS-CoV-2. AntimicrobAgentsChemother. 2020;64(6):e00483-20

[8] Pascarella G, Strumia A, Piliego C, et al. COVID-19 diagnosis and management: a comprehensive review. J InternMed. 2020;288(2):192-206

[9] Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. AnnInternMed. 2020;172(9):577-582

[10] Li W, Zhang C, Sui J, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. EMBO J. 2005;24(8):1634-43

[11] Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. CritCare. 2020;24(1):422

[12] Seyran M, Takayama K, Uversky VN, et al. The Structural Basis of Accelerated Host Cell Entry by SARS-CoV-2†. FEBS J. 2020

[13] Toelzer C, Gupta K, Yadav SKN, et al. Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein. Science. 2020;370(6517):725-730

[14] Hisatake S, Kiuchi S, Kabuki T, et al. Serum angiotensin-converting enzyme 2 concentration and angiotensin-(1-7) concentration in patients with acute heart failure patients requiring emergency hospitalization. HeartVessels. 2017;32(3):303-308

[15] Verdecchia P, Cavallini C, Spanevello A, et al. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J InternMed. 2020;76:14-20

[16] Mönkemüller K, Fry L, Rickes S. COVID-19, coronavirus, SARS-CoV-2 and the small bowel. RevEspEnfermDig. 2020;112(5):383-388

[17] Tai W, He L, Zhang X, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. CellMolImmunol. 2020;17(6):613-620

[18] Zeng W, Liu G, Ma H, et al. Biochemical characterization of SARS-CoV-2 nucleocapsid protein. Biochem Biophys Res Commun. 2020;527(3):618-623

[19] Robson B. COVID-19 Coronavirus spike protein analysis for synthetic vaccines, a peptidomimetic antagonist, and therapeutic drugs, and analysis of a proposed achilles' heel conserved region to minimize probability of escape mutations and drug resistance. ComputBiolMed. 2020;121:103749

[20] Pardo J, Shukla AM, Chamarthi G, et al. The journey of remdesivir: from Ebola to COVID-19. DrugsContext. 2020;9:2020-4-14

[21] Schreiber G. The Role of Type I Interferons in the Pathogenesis and Treatment of COVID-19. FrontImmunol. 2020;11:595739

[22] Richard SA, Kampo S, Sackey M, et al. Elucidating the Pivotal Role of Immune Players in the Management of COVID-19: Focus on Mesenchymal Stem Cells and Inflammation. CurrStemCellResTher. 2020

[23] Alanagreh L, Alzoughool F, Atoum M. Risk of using hydroxychloroquine as a treatment of COVID-19. Int J RiskSafMed. 2020;31(3):111-116

[24] Sriram K, Loomba R, Insel PA. Targeting the renin-angiotensin signaling pathway in COVID-19: Unanswered questions, opportunities, and challenges. ProcNatlAcadSci U S A. 2020;117(47):29274-29282

[25] Abuohashish HM, Ahmed MM, Sabry D, et al. The ACE-2/Ang1-7/Mas cascade enhances bone structure and metabolism following angiotensin-II type 1 receptor blockade. Eur J Pharmacol. 2017;807:44-55

[26] Hrenak J, Simko F. Renin-Angiotensin System: An Important Player in the Pathogenesis of Acute Respiratory Distress Syndrome. Int J Mol Sci. 2020;21(21):8038

[27] Ratajczak MZ, Bujko K, Ciechanowicz A, et al. SARS-CoV-2 Entry Receptor ACE2 Is Expressed on Very Small CD45- Precursors of Hematopoietic and Endothelial Cells and in Response to Virus Spike Protein Activates the Nlrp3 Inflammasome. StemCellRevRep. 2020:1–12

[28] Qaradakhi T, et al, Could DIZE be the answer to Covid 19? Maturitas. 2020;140, 83-84

[29] Qaradakhi T, Gadanek LK, McSweeney KR, et al. The potential actions of angiotensin-converting enzyme II (ACE2) activator diminazene aceturate (DIZE) in various diseases. Clinical and Experimental Pharmacology and Physiology. 2020;47,5,751-758

[30] Yang Q, Hughes TA, Kelkar A, et al. Inhibition of SARS-CoV-2 viral entry upon blocking N- and O-glycan elaboration. Elife. 2020;9:e61552

[31] Chen WH, Strych U, Hotez PJ, et al. The SARS-CoV-2 Vaccine Pipeline: an Overview. CurrTropMedRep. 2020:1-4

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