From SARS-CoV to SARS-CoV2: a potential guide to better understanding of pathophysiology of the disease and potential therapeutic modality

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Abstract. – Currently, the outbreak and spread of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), are increasing worldwide. Furthermore, it has been considered as a major challenge, which threatens human beings and affects all aspects of their life. Understanding the cellular and molecular pathophysiology of the disease is currently under the focus of investigations. Accordingly, this turns the human scientific community attention to find a solution for addressing the challenge. The development of vaccines and efficient therapeutic modality is critical. So, both primary and clinical scientists are not only trying to decipher the structure of SARS-CoV-2, but also attempting to understand the underlying molecular mechanisms that cause tissues and cell injuries. SARS-CoV and SARS-CoV2 are highly homologous and share a highly similar function and behavior patterns. Therefore, this might guide us toward decoding the molecular mechanisms that are behind the SARS-CoV2 pathologic effects. It is noteworthy to mention that, the undesired host immune reactions play important roles in the pathophysiology of the disease, and it also seems that, renin-angiotensin signaling (RAS) is a key contributor in this regard. In this review, we provided a vision, highlight as well as discussing on potential therapeutic targets that might be considered to address the COVID-19 challenge.

Key Words: SARS-CoV, SARS-CoV2, COVID-19, ACE2.

Abbreviations
ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; COX-2: Cyclooxygenase-2; CTnI: Cardiac troponin I; GCSF: Granulocyte colony-stimulating factor; ICU: Intensive Care Unit; IFN-I: Interferon type I; MERS: Middle East Respiratory Syndrome; NCP: Nucleocapsid protein; RAS: Renin-angiotensin signaling; SARS: Severe acute respiratory syndrome; TACE: TNF-alpha converting enzyme.

Introduction

In December 2019, a cluster of severe respiratory infections was reported in Wuhan, Hubei Province, China. At the first sight, it appeared that, some patients had a history of working or are working in the wholesale market for fish and seafood. A few days later, on January 9, after rejecting the diagnosis of seasonal influenza, avian influenza, adenovirus, SARS, MERS, and other pathogens, a new virus with 70% genetic homology with SARS was declared as a causative agent. On January 11, the first deaths from the virus were reported in China, and consequently, positive cases from other countries, such as Thailand, Japan, South Korea, and the United States were reported by January 20. In this situation, the person-to-person transmission to health-care staff additionally complicated the situation. There are seven Coronaviruses in the potential of human infection, namely 229E, OC43, NL63, and HUK1. These sets of viruses can rarely make severe respiratory infections. Accordingly, three other viruses, however, can make much more emergency and could lead to deadly pneumonia so far including, SARS-COV, MERS-CoV, and SARS-CoV2. The latter group is called zoonotic pathogen, which means they stemmed from animals, and make themselves adjust to the human body as well by transmitting2-4. SARS-CoV outbreak was a tragedy in 2002, which infects
the respiratory system, initiated from Guangdong, China, and covered more than 29 countries with 8000 infected cases and more than 916 death based on the official reports. MERS was also an acute respiratory illness that emerged in the Arabian Peninsula in 2012, and lead to more than 850 deaths after a few months. There are similar features, such as the age of victims, males to females’ susceptibility ratio, transmission route, and the origin, wherein all three of viruses were bats. Also, there is no information on how viruses are transmitted from intermediate hosts, particularly cats (SARS), camels (MERS), and pangolin (SARS-CoV2) to human being. SARS-CoV2 shares 88% amino acid identity with two other bats’ Coronavirus and 79% with SARS-CoV and 50% with MERS coronavirus. SARS-CoV2 was a surprising event in late 2019; same as other Coronaviruses which use spikes to attach the receptors, this process carries on by cellular proteases (which cleavages the spike into two subunits), then, it is ready to enter host cells. It is recently revealed that, angiotensin-converting enzyme 2 (ACE2) is the main receptor in SARS-CoV and SARS-CoV2. To fulfil infection, spikes must be processed, a serine proteases TMPRSS2, is in charge of spike priming, and for the cells without it, endosome cysteine proteases CatB/L offers the same operation. In this regard, in SARS-CoV, two sorts of proteanse can cleavage spike as TMPRSS2 and trypsin that cleavage different sites of the spike. Therefore, targeting these proteins is conceived as a rational approach. Camostat Mesylate, which is an inhibitor for TMPRSS2, affects MERS, SARS, and SARS 2 spikes, as well as decreasing viral entry with no side effects in lung cells, and it also needs in vitro test to measure its veracity. ACE2 expresses in kidneys, lungs, heart, and intestine; furthermore, a declined level of ACE2 is associated with cardiovascular disease. In addition, males tend to have a substantial level of ACE2, and several studies have proven that, 70% of SARS-CoV2 patients are male. High levels of ACE2 will weaken lung tissue facing SARS-CoV. ACE2 offers leading roles in lung healing and protection, and research on SARS-CoV has revealed that (Figure 1), ACE2 level dwindles as the virus infects cells. Accordingly, injecting spike to mice model showed lung injury and the injury was interrupted by ACE2 inhibition.

**Figure 1.** The renin-angiotensin-aldosterone system (RAAS), is a hormonal regulating system for blood pressure and electrolyte balance. Its regulation effect starts from the liver by releasing Angiotensinogen in the plasma. Renin then cleaves angiotensinogen into angiotensin I. This product is inactive and it has to convert into the active form, angiotensin-converting enzyme (ACE) is in charge of conversion. ACE is available, particularly in kidneys, lungs, heart, and intestine. Studies show ACE2 as a priming receptor for entry/infection. SARS-CoV binds to ACE2 and its downregulation is the first ramification, therefore, signaling flow switches back to the accumulation of Angiotensin I/II tissue and I injury. Aside from ACE2 main duty, it has a significant role in inflammatory, fibrotic and vasodilation regulation.
Receptor Diversity

Even though there is no sequence homology between HIV gp41 and s2 in SARS-CoV, both of them have aromatic-rich regions. HIV and SARS-CoV viruses have a common mechanism of fusion to host members and share the same hairpin\(^6\). There are two types of receptor as entry receptor (ER) and hanging receptor (HR). CD209L and DC-SIGN are expressed in human lung type II alveolar cells, as well as endothelial cells; and generally, viruses, e.g., Ebola and Sindbis, can use CD209L to enter. HIV and Hepatitis C use CD209L to attach to the cells, so it can be merely used due to efficiency in comparison with ACE2. Notably, ACE, as the homolog of ACE2, cannot mediate the procedure\(^17\). However, for SARS-CoV, it can also be used as a portal to entry\(^18\), as well as TNF-alpha converting enzyme (TACE), which is actively involved in SARS-CoV entry (Table I)\(^19\). Also, vimentin, as an intermediate filament (IF) protein, directly interact with SARS-CoV spike. It translocates from cytoplasm to the cell surface and with spike-ACE2 fabricates an entry complex pathway for SARS-CoV\(^20\). Cell attaching is in a calcium-dependent manner\(^21\), and DC-SIGN could also mediate SARS-CoV infection\(^22\). The victim’s body dissection indicated that SARS-CoV can be detected in several tissues and mostly cause cytopathogenic effects (Table II). The collected sample from Singapore SARS-CoV2 cases demonstrated that, nasopharynx-shedding virus prolongs for a limited time around seven days that means the virus change the infected scope\(^23\).

Despite the high level of ACE2 receptors in the heart, no SARS-CoV virus was detected\(^26\). Conversely, heart is a comfortable house for SARS-CoV2 to be infected, and causes myocardial injury and heart necrosis\(^27\) with the elevated cardiac troponin I (cTnI) above the reference range (>28 pg/mL) that has been reported; therefore, for the people who suffer from SARS-CoV2, cTnI should be constantly evaluated\(^12,28\). Cytokines analysis demonstrated that, IFN-β and IFN-α treatments in SARS-CoV have a slim efficacy on the virus replication, while IFN-γ was ineffective on SARS-CoV\(^29\). Rather SARS-CoV can induce the expression of IFNγ-α either, both types hit the peak within 24-48 hours and remain for days, the simultaneous presence of IFN makes the significant viral inhibition, and this will deteriorate pathogenesis as well as tissue-damaging\(^30,31\). SARS-CoV infection vastly corrupt the lung tissue, the infection can include endothelial cells, pneumocytes, fibroblasts, T lymphocytes, and macrophages, inflammatory cytokines that accelerating distraction (Figure 2)\(^32\). Nevertheless, early IFN induction can offer priming protection against SARS-CoV\(^32\). Further analysis demonstrated that, IFN-γ is a dominant cytokine in SARS-CoV infection, and can be circulating in the body for at least one year, T- helper1 produce IFN-γ, IL-2, and T helper2

### Table I. Different receptor and their interaction with different viruses. Entry Receptor (ER), Hanging Receptor (HR).

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ebola</th>
<th>SARS-CoV</th>
<th>SARS-CoV2</th>
<th>MERS-CoV</th>
<th>Sindbis</th>
<th>HIV</th>
<th>Hepatitis C</th>
<th>NL63</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD209L</td>
<td>ER</td>
<td>HR</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>HR</td>
</tr>
<tr>
<td>DC-SIGN</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>HR</td>
</tr>
<tr>
<td>ACE2</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>HR</td>
</tr>
<tr>
<td>DPP4</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>HR</td>
</tr>
<tr>
<td>Integrin</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>HR</td>
</tr>
<tr>
<td>CD147</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>ER</td>
<td>HR</td>
</tr>
</tbody>
</table>

### Table II. ACE2 receptor detection in different tissues.

<table>
<thead>
<tr>
<th>SARS-CoV</th>
<th>Detectable</th>
<th>Undetectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detectable</td>
<td>Stomach</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Undetectable</td>
<td>Spleen</td>
<td>Esophagus</td>
</tr>
</tbody>
</table>
produce IL-4, IL-5 cytokines and cause intense neutrophils, eosinophils, and lymphocytes recruitment into lung area, meanwhile T-cytotoxic secretes IFN-γ. The immune reaction was observed to be different between young and old mice, and a Nucleocapsid protein (NCP) vaccine study found that, the old group was predictable with the IFN-γ increase; however, the young one had the same reaction at the beginning, then tune down over time; therefore, lung damage was not significant in the second group. Notably, NCP can induce IL-6 production by NF-κB pathway; NCP directly binds to NF-κB binding element promoter, high IL-6 expression is considered as the leading cause of mortality among SARS-CoV animal models. NCP vaccination profile illustrated IFN-γ and IL-10 as considerably elevated, while IL-2, as an immunoadjuvant interleukin, and IL-4 were normal. Primate reaction to SARS-CoV follows the same result regarding the age item. Adult macaques’ response is substantially higher than young with an increased level of NF-κB. SARS-CoV-infected the old macaques with type I and IFN treatment lead to an decrease in pro-inflammatory level and overall acute lung injury (ALI) has improved, probably innate host immune system was the cause of remedy. Indeed, NK cells and adaptive cellular immunity cannot be used in viral infection and the only thing lift after their rousing is lung damage. As the virus robustly replicate, type I interferon (IFN-I) functionality suspended, although IFN-I compensates, its early function is a crucial moment in body defense, as the intense body response has already fired, and IFN-I compensation becomes useless. Legitimately, the immune reaction can be relegated into two waves as follows: when the virus replicates into lung cells in the first invade, this time cells tend to produce a set of inflammatory cytokines leading to recruit the innate immune cells such as macrophage, natural killer cells, and dendritic cells. In following days, the second wave occurs as T Cells walkthrough battlefield and significantly prompts higher amounts of cytokines, and all this tragedy causes lung damage. Glucocorticoids can effectively tackle inflammatory reactions and keep T-cell out of call. However, in vivo studies show that, these drugs can escalate mortality. It is noteworthy that, alveolar type II cells are the primary supports in SARS-CoV replication. However, alveolar macrophages cells cannot be infected and be the hosts of SARS-CoV virus. SARS-CoV2 cytokine profile (Table III) represented the elevation in IL-1beta, IFN-γ, and MCP-1 at the early time along with granulocyte colony-stimulating factor (GCSF), IP-10, MCP-1, macrophage inflammatory protein (MIP)-1A.
and TNF-α high concentration. Further evaluation showed that, IL-6 elevation is an alarm of cardiac damage, in practice, cardiac injury has already occurred.\textsuperscript{28,51}

**SARS-CoV/CoV2 Fellow Signaling**

To have an acute infection, need to be persistent in viral replication. SARS-CoV virus induces apoptosis; however, a variety of pathways implement oppose apoptosis. SARS viruses affect several pathways, such as activation of the p38 mitogen-activated protein kinase (MAPK) and p38 MAPK inhibitor inhibited. At first, they activate phosphatidylinositol 3-kinase (PI3K)/Akt pathway, and then, it diminished within 24 hours, Akt signaling rescue cell from apoptosis, and glycogen synthase kinase 3beta (GSK-3beta) is also activated.\textsuperscript{52} These interventions make cells cease proliferation.\textsuperscript{53} In fact, apoptosis is a sort of potent cell sieving approach, SARS-CoV does not achieve much from apoptosis, and also apoptosis prevention cannot be useful to get rid of SARS-CoV.\textsuperscript{54} In this respect, some cells have excellent potential in producing infectious virus. Thus, it makes a low level of Akt to work in this tragedy, also rare cells can be alive, and these cells are the best candidates for constant virus production. Later, they make colonies with high virus production capacity, and barely proliferate because the virus modulates CCNE2 and CDKN 1A and makes cell cycle arrest in the G1/S phase.\textsuperscript{56} *In vivo* study showed that, survival cells tend more to produce cytokines. Hence, both Akt and p38 MAPK can be crucial targets for anti-SARS-CoV drugs.\textsuperscript{57} Also, commercial anti-cancer drugs can be the answer to SARS-CoV2 outbreak; moreover, the probable drug is the apoptosis inducers, like Doxorubicin hydrochloride. Cyclooxygenase-2 (COX-2) activation is another SARS-COV facility to enhance the inflammatory reaction in lung tissue by NF-κB and C/EBP elements pathway.\textsuperscript{58} The NF-κB function is a Ca\textsuperscript{2+} dependent pathway with PKC alpha Companionship.\textsuperscript{60} Ca\textsuperscript{2+} requires beyond COX2 activation, SARS-CoV infection is deeply dependent on the Ca\textsuperscript{2+} concentration of the cell milieu.\textsuperscript{60,61} SARS-CoV also implicates into alveolar fluid clearance by modulation of amiloride-sensitive epithelial sodium (Na\textsuperscript{+}/H\textsuperscript{+}) channels. Channels function works with making an osmotic gradient, and transferring sodium (Na\textsuperscript{+}/H\textsuperscript{+}) ions across the alveolar epithelium, and consequently Ph manipulates around the epithelial cells.\textsuperscript{62} Chloroquine and hydroxychloroquine can change pH at the surface of the cell membrane and exert immunomodulatory effect,\textsuperscript{64,65} and they show a useful effect on the SARS patients. SARS-CoV also reduces pyruvate kinase (PK) activity and causes anemia and hepatocytes death.\textsuperscript{66} Infants from the SARS-CoV infected mothers did not acquire the infection; however, the infants were in a great danger of mother fluid contraction and several other sources of infection.\textsuperscript{67} Concerning the reports and exciting media, SARS-CoV2 vertically transmit is still controversial. Accordingly, in a study on 13 labor women, all the infants’ SARS-CoV2 tests were negative, and one infant died before birth.\textsuperscript{68} In another study on 38 pregnant women, no neonatal fatality or infection was reported.\textsuperscript{69} Indeed, the risk of infection in intrauterine is low; however, it can make adverse pregnancy effects such as early birth and jeopardize mother life.\textsuperscript{70}

**Potential Therapeutic Approach**

Virus infection consists two steps as follows: integration and replication. In this process, there are moments that the virus is in the weakest condition, such as the time of packaging (Figure 3).

I. SARS-CoV is genetically the closest virus and patients who suffer from both viruses can trigger the ground for viruses particle transition between these two viruses, so if SARS-CoV genetic manipulates, we can hope for implicating in SARS-CoV2 packaging and changing the problem from SARS-CoV2 to SARS-CoV, which is less fatal anyway.

COVID 19 is swiftly spread across the world and suffering people need time until their body get rid of the virus meanwhile, lung problem is the predominant matter.

### Table III. Plasma level of cytokines. Of note, ICU patients show elevated cytokines than non-ICU.

<table>
<thead>
<tr>
<th>Non-ICU patients SARS-CoV2</th>
<th>IL-1β, IL-1Ra, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and VEGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU patients SARS-CoV2</td>
<td>IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α</td>
</tr>
<tr>
<td>Non-ICU patients SARS-CoV</td>
<td>IL-1, IL-6, IL-12, IFN-γ, TGF-Beta, CCL2, CXCL9, CXCL10, and IL-8</td>
</tr>
<tr>
<td>ICU patient SARS-CoV</td>
<td>IL-6, IFN-α, IFN-γ, lack of IL-10</td>
</tr>
</tbody>
</table>

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2. The virus naked RNA or DNA shall be translated into protein and package with RNA. Decoy technology can be considered as a game-changer in the SARS-CoV2 outbreak. It has enjoyed several studies so far to repress miRNA, RNA, and DNA. Impair virus packaging is the main point. Beyond the classical method of vaccine, we can make Decoys and package it in viral particles, and then use it directly for lung, as a nasal spray, because breathlessness is the common symptom and the leading cause of death toll. The aim is merely to impose a lack of some SARS-CoV2 particles and get overall imperfect SARS-CoV2.

Conclusions

SARS-CoV2 is a member of the coronavirus family, which already contains SARS-CoV. These viruses are phylogenetically relative, and either of them primarily infects lung tissue with respiratory droplets. Also, accommodation studies show incubation in people who died of SARS-CoV hit two weeks. However, the patients who pass this timeline had no SARS-CoV in the lung, within the time the virus is detectable. Therefore, it is conceivable that, early damages on the lung are extremely significant and body immune defense eliminates SARS-CoV on time and also anti-virus drugs merely work at the early time. In parallel, SARS-CoV2-infected the patient’s bears around 28 days of incubation/mortality resulted from SARS-CoV2 takes 28 days after ICU admission. SARS-CoV2 takes advantage of ACE2 more efficient and the wave of cytokine is intolerable for the body, adult people’s immune system, despite, overreact, young people’s immune system manipulates more effectively.
Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate
Not applicable

Consent for Publication
Not applicable.

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Authors’ Contribution
P.A.P.; co-wrote the paper. M.H.R.; co-wrote the paper. F.R.; co-wrote the paper. A.E.; co-wrote the paper.

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