European Review for Medical and Pharmacological Sciences 2020; 24: 7816-7825

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

P. ABBASI PASHAKI[1], M. HABIBI ROUDKENAR[1], F. RAHIM[2], A. EBRAHIMI[1]

[1]Department of Medical Biotechnology, School of Paramedicine, Guilan University of Medical Sciences, Rasht, Iran
[2]Thalassemia and Hemoglobinopathy Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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[1]. The latter group is called zoonotic pathogen, which means they stemmed from animals, and make themselves adjust to the human body as well by transmitting[2-4]. SARS-CoV outbreak was a tragedy in 2002, which infects

Corresponding Author: Ammar Ebrahimi, Ph.D; e-mail: Ebrahimi.am@outlook.com

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[5]. SARS-CoV2 shares 88% amino acid identity with two other bats' Coronavirus and 79% with SARS-CoV and 50% with MERS coronavirus[6]. 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[7]. In this regard, in SARS-CoV, two sorts of protease can cleavage spike as TMPRSS2 and trypsin that cleavage different sites of the spike[8]. 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[9], 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[10]. In addition, males tend to have a substantial level of ACE2[11], and several studies have proven that, 70% of SARS-CoV2 patients are male[12]. 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[13,14]. Accordingly, injecting spike to mice model showed lung injury and the injury was interrupted by ACE2 inhibition[14,15].

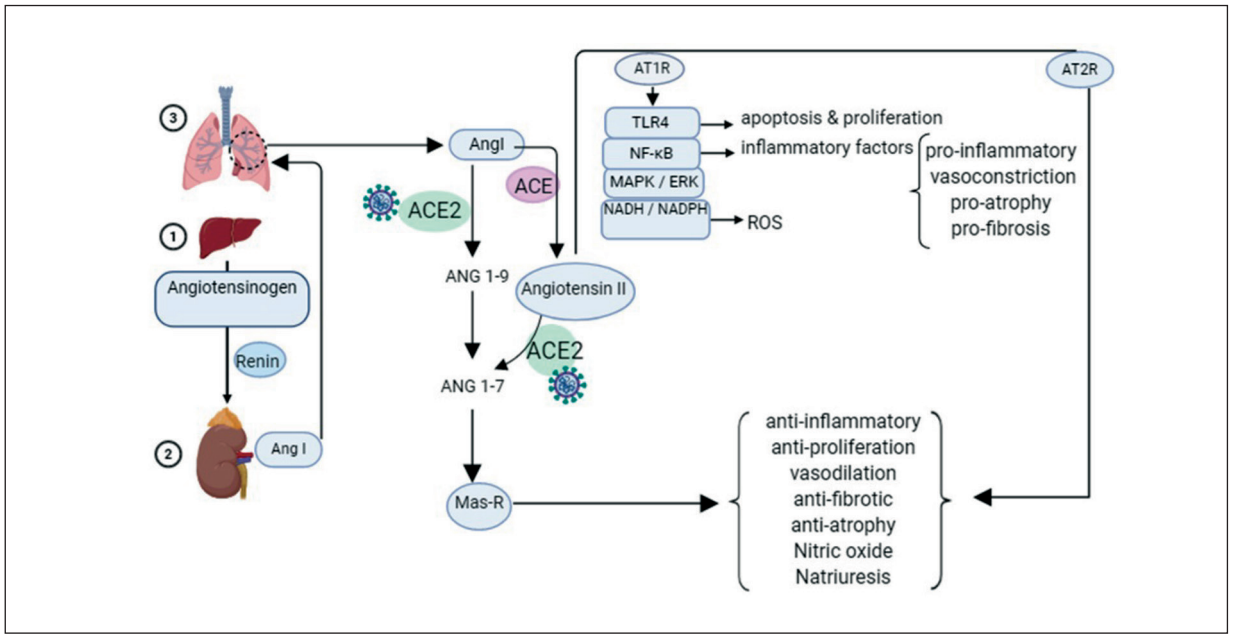

Figure 1. The renin-angiotensin-aldosterone system (RAAS), is a hormonal regulating system for blood pressure and electrolyte balance. Its regulation effect starts from the liver by releasing Angiotensinogen in the plasma. Renin then cleaves angiotensinogen into angiotensin I. This product is inactive 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.

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

Receptor	Ebola	SARS-CoV	SARS-CoV2	MERS-CoV	Sindbis	HIV	Hepatitis C	NL63
CD209L	ER	HR	ER		ER	HR	HR	
DC-SIGN	ER	ER			ER			
ACE2		ER	ER					
DPP4				ER				
Integrin			ER[24]					
CD147			ER[25]					

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[16]. 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 CD2019L to enter. HIV and Hepatitis C use CD2019L 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[33]. 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 II. ACE2 receptor detection in different tissues.

SARS-CoV									
Detectable	Stomach	Pancreas	Small intestine	Lung	Renal tubule	Liver	Parathyroid	Adrenal gland	Sweat gland
Undetectable	Spleen	Esophagus	Lymph node	Ovary	Thyroid	Testis	Bone marrow	Uterus	Aorta and muscle

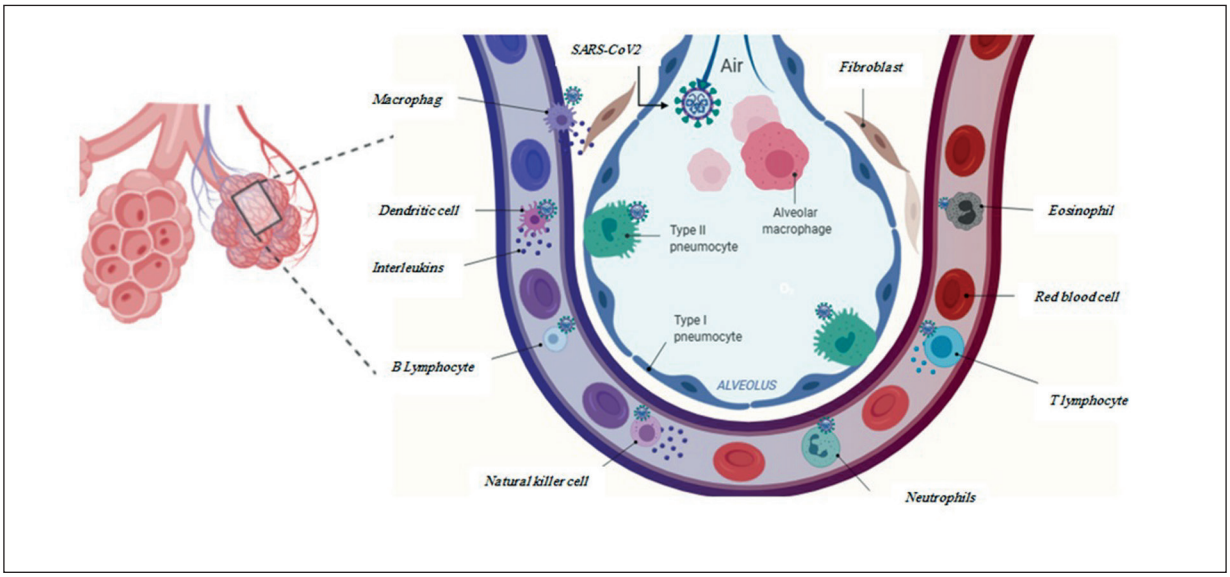

Figure 2. Once SARS-CoV2 virus reaches alveolar sac, it can infect type II pneumocytes, Macrophage, Dendritic cells, B lymphocyte, neutrophils, eosinophils, and Natural killer cells and their response makes first interleukin wave; further, the second wave of interleukins lunch as T lymphocyte cells reach the lungs alveolus and escalate lung damage. Of note, alveolar macrophage and type I pneumocytes cannot be infected by SARS-CoV2.

produce IL-4, IL-5 cytokines and cause intense neutrophils, eosinophils, and lymphocytes recruitment into lung area[34-36], meanwhile T-cytotoxic secretes IFN-γ[37]. 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[38]. Notably, NCP can induce IL-6 production by NF-κB pathway; NCP directly binds to NF-κB binding element promoter[39], high IL-6 expression is considered as the leading cause of mortality among SARS-CoV animal models[40]. NCP vaccination profile illustrated IFN-γ and IL-10 as considerably elevated, while IL-2, as an immunoadjuvant interleukin[41], and IL-4 were normal[42]. 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[43,44]. Indeed, NK cells and adaptive cellular immunity cannot be used in viral infection and the only thing lift after their rousing is lung damage[45]. 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[46]. 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[47]. Glucocorticoids can effectively tackle inflammatory reactions and keep T-cell out of call[48]. However, *in vivo* studies show that, these drugs can escalate mortality[49]. It is noteworthy that, alveolar type II cells are the primary supports in SARS-CoV replication. However, alveolar type I-like and alveolar macrophages cells cannot be infected and be the hosts of SARS-CoV virus[50]. 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,

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

Non-ICU patients SARS-CoV2	IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and VEGF
ICU patients SARS-CoV2	IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α
Non-ICU patients SARS-CoV	IL-1, IL-6, IL-12, IFN-γ, TGF-Beta, CCL2, CXCL9, CXCL10, and IL-8
ICU patient SARS-CoV	IL-6, IFN-α, IFN-γ, lack of IL-10

and TNF-α high concentration. Further evaluation showed that, IL-6 elevation is an alarm of cardiac damage, in practice, cardiac injure has already occurred[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[52]. These interventions make cells cease proliferation[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[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[55], and barely proliferate because the virus modulates CCNE2 and CDKN 1A and makes cell cycle arrest in the G1/S phase[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[57]. Also, commercial anti-cancer drugs can be the answer to the 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[58]. The NF-κB function is a Ca2+ dependent pathway with PKC alpha Companionship[59]. Ca2+ requires beyond COX2 activation, SARS-CoV infection is deeply dependent on the Ca^{2+} concentration of the cell milieu[60,61]. SARS-CoV also implicates into alveolar fluid clearance by modulation of amiloride-sensitive epithelial sodium (Na+/H+) channels[62]. Channels function works with making an osmotic gradient, and transferring sodium (Na+/H+) ions across the alveolar epithelium, and consequently Ph manipulates around the epithelial cells[63]. Chloroquine and hydroxychloroquine can change pH at the surface of the cell membrane and exert immunomodulatory effect[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[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[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[68]. In another study on 38 pregnant women, no neonatal fatality or infection was reported[69]. Indeed, the risk of infection in intrauterine is low[70]; however, It can make adverse pregnancy effects such as early birth and jeopardize mother life[71].

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).

1. 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.

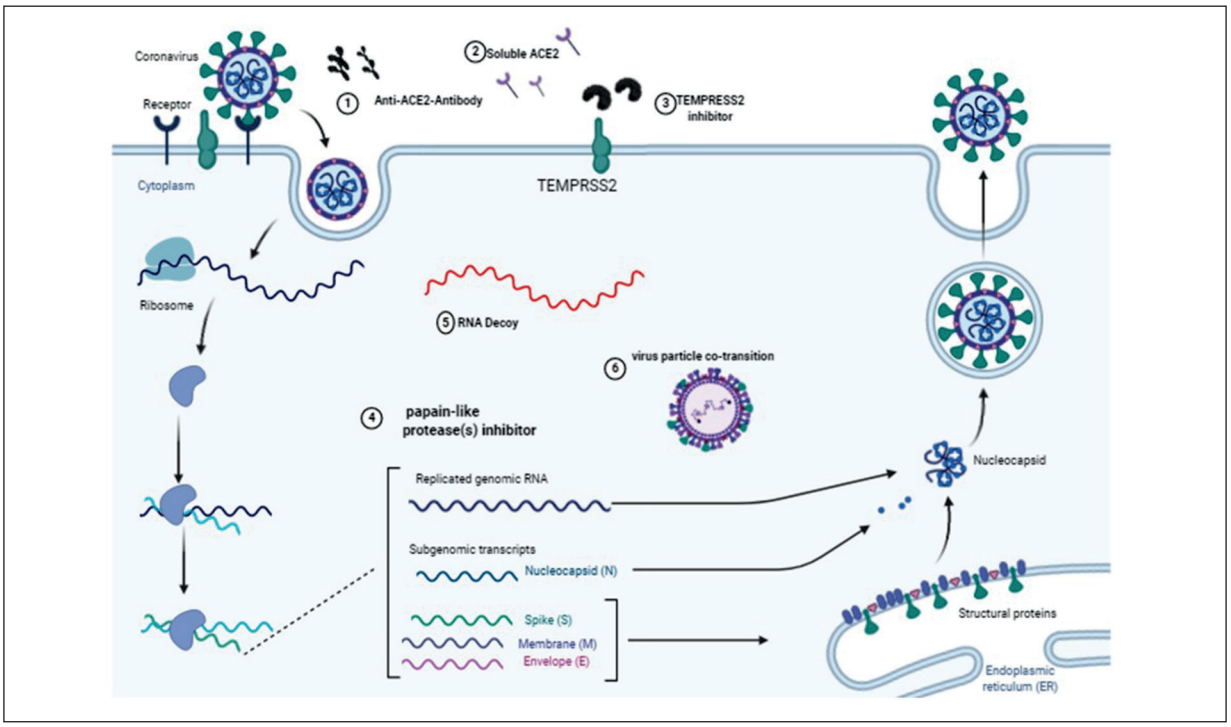

Figure 3. The SARS-CoV 2 infection-trajectory pass steps to occupy the cells, accordingly, a variety of strategies have been exercised. (1) Anti-ACE2 antibody is a synthetic peptide corresponding to human ACE2. It can block the SARS-CoV 2 entry portal, however, further research showed significant side effects, as such immune tidal and protective capacity. (2) This is a pilot trial using soluble human recombinant ACE2 (APN01) in patients with SARS-CoV2 (Clinicaltrials.gov #NCT04287686). they aimed to reduce viral load. (3) SARS-CoV2 required priming before entry, without this step the virus is not able to cross the cell membrane, therefore, TEMPRSS inhibition is a promising approach in virus fight ground, however, it seems there are other proteases, which is less effective, can reciprocate virus entry[9]. (4) Mpro (also called 3CLpro) along with a protease, the papain-like protease(s), makes substantial processing on the virus main polyprotein by different site cleavage. Synthesized peptidomimetic α-ketoamides can inhibit the board of proteases in beta-coronaviruses and alpha-coronaviruses. This strategy was able to tackle SARS-CoV *in vivo*.

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[72], RNA, and DNA[73-75]. 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[76,77] 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[78,79]. 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[12]. SARS-CoV 2 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.

Availability of Data and Materials
Not applicable.

Funding
This research was supported by the deputy of research, Guilan University of Medical Sciences, Iran (grant number: IR-96123).

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.

Acknowledgments
We would like to thank the European Review for Medical and Pharmacological Sciences for allowing the publication of this article without a fee.

References

1) Chakraborty C, Sharma A, Sharma G, Bhattacharya M, Lee S. SARS-CoV-2 causing pneumonia-associated respiratory disorder (COVID-19): diagnostic and proposed therapeutic options. Eur Rev Med Pharmacol 2020; 24: 4016-4026.
2) Al-Tawfiq JA. Asymptomatic coronavirus infection: MERS-CoV and SARS-CoV-2 (COVID-19). Travel Med Infect Dis 2020; 35:101608.
3) Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, Baghbanzadeh M, Aghamohammadi N, Zhang W, Haque U. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? Int J Epidemiol 2020 Feb 22: dyaa033.
4) Ceccarelli M, Berretta M, Rullo E V, Nunnari G, Cacopardo B. Editorial-differences and similarities between Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet. Eur Rev Med Pharmacol Sci 2020; 24: 2781-2783.
5) Park M, Thwaites RS, Openshaw PJM. COVID-19: lessons from SARS and MERS. Eur J Immunol 2020; 50: 308-311.
6) Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270-273.
7) Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci U S A 2005; 102: 11876-11881.
8) Reinke L M, Spiegel M, Plegge T, Hartleib A, Nehlmeier I, Gierer S, Hoffmann M, Hofmann-Winkler H, Winkler M, Pohlmann S. Different residues in the SARS-CoV spike protein determine cleavage and activation by the host cell protease TMPRSS2. PLoS One 2017; 12: 102-117.
9) Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-280.
10) Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart R E, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000; 87: 1-9.
11) Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 2020; 6: 1-4.
12) Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-481.
13) Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky A S, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11: 875-879.
14) Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower M A, Fukamizu A, Hui C C, Hein L, Uhlig S, Slutsky A S, Jiang C, Penninger J M. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005; 436: 112-116.
15) Yang XH, Deng W, Tong Z, Liu YX, Zhang LF, Zhu H, Gao H, Huang L, Liu YL, Ma CM, Xu YF, Ding MX, Deng HK, Qin C. Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. Comp Med 2007; 57: 450-459.
16) Kliger Y, Levanon E Y. Cloaked similarity between HIV-1 and SARS-CoV suggests an anti-SARS strategy. BMC Microbiol 2003; 3: 20-24.
17) Nie Y, Wang P, Shi X, Wang G, Chen J, Zheng A, Wang W, Wang Z, Qu X, Luo M, Tan L, Song X, Yin X, Chen J, Ding M, Deng H. Highly infectious SARS-CoV pseudotyped virus reveals the cell tropism and its correlation with receptor expres-

sion. Biochem Biophys Res Commun 2004; 321: 994-1000.

18) Jeffers SA, Tusell S M, Gillim-Ross L, Hemmila EM, Achenbach JE, Babcock GJ, Thomas W D, Jr., Thackray LB, Young MD, Mason RJ, Ambrosino DM, Wentworth DE, Demartini J C, Holmes KV. CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus. Proc Natl Acad Sci U S A 2004; 101: 15748-15753.

19) Haga S, Nagata N, Okamura T, Yamamoto N, Sata T, Yamamoto N, Sasazuki T, Ishizaka Y. TACE antagonists blocking ACE2 shedding caused by the spike protein of SARS-CoV are candidate antiviral compounds. Antiviral Res 2010; 85: 551-555.

20) Yu Y T, Chien S C, Chen I Y, Lai C T, Tsay Y G, Chang S C, Chang M F. Surface vimentin is critical for the cell entry of SARS-CoV. J Biomed Sci 2016; 23: 14-18.

21) Simmons G, Reeves JD, Grogan CC, Vandenberghe LH, Baribaud F, Whitbeck JC, Burke E, Buchmeier MJ, Soilleux EJ, Riley JL, Doms RW, Bates P, Pohlmann S. DC-SIGN and DC-SIGNR bind ebola glycoproteins and enhance infection of macrophages and endothelial cells. Virology 2003; 305: 115-123.

22) Yap YL, Zhang XW, Danchin A. Relationship of SARS-CoV to other pathogenic RNA viruses explored by tetranucleotide usage profiling. BMC Bioinformatics 2003; 4: 43-50.

23) Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC, Singapore Novel Coronavirus Outbreak Research Team. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020; 323: 1488-1494.

24) Sigrist CJ, Bridge A, Le Mercier P. A potential role for integrins in host cell entry by SARS-CoV-2. Antiviral Res 2020; 177: 104-109.

25) Wang K, Chen W, Zhou YS, Lian JQ, Zhang Z, Du P, Gong L, Zhang Y, Cui HY, Geng JJ, Wang B, Sun XX, Wang CF, Yang X, Lin P, Deng YQ, Wei D, Yang XM, Zhu YM, Zhang K, Zheng ZH, Miao JL, Guo T, Shi Y, Zhang J, Fu L, Wang QY, Bian H, Zhu P, Chen ZN. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. bioRxiv 2020;

26) Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, Wang H, Shen H, Qiu L, Li Z, Geng J, Cai J, Han H, Li X, Kang W, Weng D, Liang P, Jiang S. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathol 2004; 203: 622-630

27) Biondi Zoccai G, Landoni G, Carnevale R, Cavarretta E, Sciarretta S, Frati G. SARS-CoV-2 and COVID-19: facing the pandemic together as citizens and cardiovascular practitioners. Minerva Cardioangiol 2020; 68: 61-64.

28) Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz 2020; 45: 230-232.

29) Sainz B, Jr., Mossel E C, Peters C J, Garry R F. Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV). Virology 2004; 329: 11-17.

30) Castilletti C, Bordi L, Lalle E, Rozera G, Poccia F, Agrati C, Abbate I, Capobianchi M R. Coordinate induction of IFN-alpha and -gamma by SARS-CoV also in the absence of virus replication. Virology 2005; 341: 163-169

31) Barnard D L, Day C W, Bailey K, Heiner M, Montgomery R, Lauridsen L, Chan P K, Sidwell R W. Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. Antivir Chem Chemother 2006; 17: 275-284

32) Lu Y, Gong E C, Zhang Q Y, Gu J, Li X W, Zhang B, Hou L, Shao H Q, Gao Z F, Zheng J, Fang W G, Zhong Y F. [Expression of SARS-CoV in various types of cells in lung tissues]. Beijing Da Xue Xue Bao Yi Xue Ban 2005; 37: 453-457

33) de Lang A, Baas T, Teal T, Leijten L M, Rain B, Osterhaus A D, Haagmans B L, Katze M G. Functional genomics highlights differential induction of antiviral pathways in the lungs of SARS-CoV-infected macaques. PLoS Pathog 2007; 3: 112-118

34) Yasui F, Kai C, Kitabatake M, Inoue S, Yoneda M, Yokochi S, Kase R, Sekiguchi S, Morita K, Hishima T, Suzuki H, Karamatsu K, Yasutomi Y, Shida H, Kidokoro M, Mizuno K, Matsushima K, Kohara M. Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV. J Immunol 2008; 181: 6337-6348

35) Rahim F, Ebrahimi A. Gene therapy modalities in lung transplantation. Transpl Immunol 2014; 31: 165-172.

36) Ebrahimi A, Abbasi P, Cucchiarini M. Exploring the Role of Stem Cells in Cancer Development and Progression. Ann Cancer Res Ther 2020; 28: 3-8

37) Fan YY, Huang ZT, Li L, Wu MH, Yu T, Koup RA, Bailer RT, Wu CY. Characterization of SARS-CoV-specific memory T cells from recovered individuals 4 years after infection. Arch Virol 2009; 154: 1093-1099.

38) Zhu Y G, Qu J M. Differential characteristics of the early stage of lung inflammation induced by SARS-CoV Nucleocapsid protein related to age in the mouse. Inflamm Res 2009; 58: 312-320.

39) Zhang X, Wu K, Wang D, Yue X, Song D, Zhu Y, Wu J. Nucleocapsid protein of SARS-CoV activates interleukin-6 expression through cellular transcription factor NF-kappaB. Virology 2007; 365: 324-335.

40) Day C W, Baric R, Cai S X, Frieman M, Kumaki Y, Morrey J D, Smee D F, Barnard D L. A new mouse-adapted strain of SARS-CoV as a lethal

model for evaluating antiviral agents in vitro and in vivo. Virology 2009; 395: 210-222.

41) Hu H, Tao L, Wang Y, Chen L, Yang J, Wang H. Enhancing immune responses against SARS-CoV nucleocapsid DNA vaccine by co-inoculating interleukin-2 expressing vector in mice. Biotechnol Lett 2009; 31: 1685-1693.

42) Zheng N, Xia R, Yang C, Yin B, Li Y, Duan C, Liang L, Guo H, Xie Q. Boosted expression of the SARS-CoV nucleocapsid protein in tobacco and its immunogenicity in mice. Vaccine 2009; 27: 5001-5007.

43) Smits S L, de Lang A, van den Brand J M, Leijten L M, van I W F, Eijkemans M J, van Amerongen G, Kuiken T, Andeweg A C, Osterhaus A D, Haagmans B L. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog 2010; 6: 11-19.

44) He L, Ding Y, Zhang Q, Che X, He Y, Shen H, Wang H, Li Z, Zhao L, Geng J, Deng Y, Yang L, Li J, Cai J, Qiu L, Wen K, Xu X, Jiang S. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. J Pathol 2006; 210: 288-297.

45) Glass W G, Subbarao K, Murphy B, Murphy P M. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. J Immunol 2004; 173: 4030-4039.

46) Channappanavar R, Fehr A R, Vijay R, Mack M, Zhao J, Meyerholz D K, Perlman S. Dysregulated Type I Interferon and Inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016; 19: 181-193.

47) Chen J, Lau Y F, Lamirande E W, Paddock C D, Bartlett J H, Zaki S R, Subbarao K. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. J Virol 2010; 84: 1289-1301.

48) Hao D, He L X, Qu J M, Pan J, Hu B J, Zhang J, Li Z Z. [A study of pulmonary inflammatory reaction induced by N-protein of SARS-CoV in rat models and effects of glucocorticoids on it]. Zhonghua Nei Ke Za Zhi 2005; 44: 890-893.

49) Arabi Y M, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, Jose J, Alraddadi B, Almotairi A, Al Khatib K, Abdulmomen A, Qushmaq I, Sindi A A, Mady A, Solaiman O, Al-Raddadi R, Maghrabi K, Ragab A, Al Mekhlafi G A, Balkhy H H, Al Harthy A, Kharaba A, Gramish J A, Al-Aithan A M, Al-Dawood A, Merson L, Hayden F G, Fowler R. Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study. Clin Infect Dis 2019; 70: 1837-1844.

50) Mossel E C, Wang J, Jeffers S, Edeen K E, Wang S, Cosgrove G P, Funk C J, Manzer R, Miura T A, Pearson L D, Holmes K V, Mason R J. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. Virology 2008; 372: 127-135.

51) Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, Trilling M, Lu M, Dittmer U, Yang D. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020; 92: 491-494.

52) Mizutani T, Fukushi S, Saijo M, Kurane I, Morikawa S. Importance of Akt signaling pathway for apoptosis in SARS-CoV-infected Vero E6 cells. Virology 2004; 327: 169-174.

53) Mizutani T, Fukushi S, Iizuka D, Inanami O, Kuwabara M, Takashima H, Yanagawa H, Saijo M, Kurane I, Morikawa S. Inhibition of cell proliferation by SARS-CoV infection in Vero E6 cells. FEMS Immunol Med Microbiol 2006; 46: 236-243.

54) Bordi L, Castilletti C, Falasca L, Ciccosanti F, Calcaterra S, Rozera G, Di Caro A, Zaniratti S, Rinaldi A, Ippolito G, Piacentini M, Capobianchi M R. Bcl-2 inhibits the caspase-dependent apoptosis induced by SARS-CoV without affecting virus replication kinetics. Arch Virol 2006; 151: 369-377.

55) Mizutani T, Fukushi S, Saijo M, Kurane I, Morikawa S. JNK and PI3k/Akt signaling pathways are required for establishing persistent SARS-CoV infection in Vero E6 cells. Biochim Biophys Acta 2005; 1741: 4-10.

56) Yeung Y S, Yip C W, Hon C C, Chow K Y, Ma IC, Zeng F, Leung FC. Transcriptional profiling of Vero E6 cells over-expressing SARS-CoV S2 subunit: insights on viral regulation of apoptosis and proliferation. Virology 2008; 371: 32-43.

57) Mizutani T. Signal transduction in SARS-CoV-infected cells. Ann N Y Acad Sci 2007; 1102: 86-95.

58) Yan X, Hao Q, Mu Y, Timani K A, Ye L, Zhu Y, Wu J. Nucleocapsid protein of SARS-CoV activates the expression of cyclooxygenase-2 by binding directly to regulatory elements for nuclear factor-kappa B and CCAAT/enhancer binding protein. Int J Biochem Cell Biol 2006; 38: 1417-1428.

59) Liu M, Yang Y, Gu C, Yue Y, Wu K K, Wu J, Zhu Y. Spike protein of SARS-CoV stimulates cyclooxygenase-2 expression via both calcium-dependent and calcium-independent protein kinase C pathways. FASEB J 2007; 21: 1586-1596.

60) Millet J K, Whittaker GR. Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. Virology 2018; 517: 3-8.

61) Dube M, Etienne L, Fels M, Kielian M. Calcium-dependent Rubella virus fusion occurs in early endosomes. J Virol 2016; 90: 6303-6313.

62) Ji H L, Song W, Gao Z, Su X F, Nie HG, Jiang Y, Peng J B, He Y X, Liao Y, Zhou YJ, Tousson A, Matalon S. SARS-CoV proteins decrease levels and activity of human ENaC via activation of distinct PKC isoforms. Am J Physiol Lung Cell Mol Physiol 2009; 296: 372-383.

63) Matalon S, Lazrak A, Jain L, Eaton DC. Invited review: biophysical properties of sodium channels

in lung alveolar epithelial cells. J Appl Physiol (1985) 2002; 93: 1852-1859.

64) Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9:ciaa237. doi: 10.1093/cid/ciaa237. Epub ahead of print.

65) Meo S, Klonoff D, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci 2020; 24: 4539-4547.

66) Wei W Y, Li HC, Chen CY, Yang CH, Lee SK, Wang CW, Ma HC, Juang YL, Lo SY. SARS-CoV nucleocapsid protein interacts with cellular pyruvate kinase protein and inhibits its activity. Arch Virol 2012; 157: 635-645.

67) Ksiezakowska K, Laszczyk M, Wilczynski J, Nowakowska D. SARS-CoV infection and pregnancy. Ginekol Pol 2008; 79: 47-50.

68) Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect. 2020 Mar 4. doi: 10.1016/j.jinf.2020.02.028. Epub ahead of print.

69) Schwartz DA. An analysis of 38 pregnant women with COVID-19, Their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med. 2020 Mar 17. doi: 10.5858/arpa.2020-0901-SA. Epub ahead of print.

70) Fan C, Lei D, Fang C, Li C, Wang M, Liu Y, Bao Y, Sun Y, Huang J, Guo Y, Yu Y, Wang S. Perinatal Transmission of COVID-19 associated SARS-CoV-2: should we worry? Clin Infect Dis 2020 Mar 17:ciaa226.

71) Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. J Microbiol Immunol Infect 2019; 52: 501-503.

72) Abbasi Pashaki P, Rahim F, Habibi Roudkenar M, Razavi-Toosi S, Ebrahimi A. MicroRNA tough decoy knockdowns miR-195 and represses hypertrophy in chondrocytes. Appl Biochem Biotechnol 2020; 190: 214-221.

73) Nakaya T, Iwai S, Fujinaga K, Sato Y, Otsuka E, Ikuta K. Decoy approach using RNA-DNA chimera oligonucleotides to inhibit the regulatory function of human immunodeficiency virus type 1 Rev protein. Antimicrob Agents Chemother 1997; 41: 319-325.

74) Koppikar P, Bromberg J. STATe-of-the-art approach: using oligonucleotide decoys to target the "undruggable". Cancer Discov 2012; 2: 670-672.

75) Crinelli R, Bianchi M, Gentilini L, Palma L, Sorensen M D, Bryld T, Babu R B, Arar K, Wengel J, Magnani M. Transcription factor decoy oligonucleotides modified with locked nucleic acids: an in vitro study to reconcile biostability with binding affinity. Nucleic Acids Res 2004; 32: 1874-1885.

76) Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.

77) Ahmad A, Rehman M, Alkharfy K. An alternative approach to minimize the risk of coronavirus (Covid-19) and similar infections. Eur Rev Med Pharmacol Sci 2020; 24: 4030-4034.

78) Nicholls JM, Butany J, Poon LL, Chan KH, Beh SL, Poutanen S, Peiris JS, Wong M. Time course and cellular localization of SARS-CoV nucleoprotein and RNA in lungs from fatal cases of SARS. PLoS Med 2006; 3: 27-32.

79) Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Lancet Gastroenterol Hepatol 2020; 5: 335-337.