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Review Article

Pathophysiology of COVID-19 and its potential therapeutics

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ABSTRACT

A series of acute and atypical serious respiratory illnesses were reported in December 2019 from Wuhan, a city of China. It spread to other places and became a global pandemic involving more than 200 countries of the world. Soon, it was discovered that this atypical respiratory illness was caused by a novel corona virus. It was named as the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) and the disease caused by it as corona virus disease-19 (COVID-19). Since COVID-19 is a new viral disease, world is still struggling to find out a permanent remedy to control this serious health problem. It seems prudent to study or have a look on the pathophysiology of SARS CoV-2 in the light of available research. Further, a review on pathophysiology may give an insight on the potential therapeutic options. Being a new virus and having potential to cause significant morbidity and mortality in short span of time various approved drugs are being repurposed for the treatment of COVID-19.

Keywords: COVID-19, Pathophysiology, Therapeutics

INTRODUCTION

A series of acute and atypical serious respiratory illnesses were reported in December 2019 from Wuhan, a city of China. It spread to other places and became a global pandemic involving more than 200 countries of the world. Soon, it was discovered that this atypical respiratory illness was caused by a novel corona virus. It was named as the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) due to its high resemblance to SARS-CoV, which was responsible for severe acute respiratory syndrome during 2002-2003 pandemic.[1] Novel corona virus (SARS-CoV-2) is also called as 2019-nCoV and the disease caused by it is called as corona virus disease-19 or COVID-19.[2]

The coronaviruses readily evolve by mutations and have extensive animal reservoirs especially among bats. They are highly effective in host switching.[3,4] SARS-CoV-2 was considered to have originated from a seafood market in Wuhan via a zoonotic transmission. Later human to human transmission played key role in the spread of epidemic.[5]

Over the last two decades three novel corona viruses have crossed species barrier and caused significant morbidity and mortality in humans i.e. SARS-CoV, Middle East Respiratory Syndrome (MERS-CoV) and SARS-CoV-2. The last is the latest one and the cause of COVID-19 pandemic.[6-8]

Though SARS-CoV-2 primarily affects respiratory system, other organ system may also get affected. Respiratory symptoms include fever, dry cough and dyspnea. In addition, it may present as headache, dizziness, generalized weakness, vomiting and diarrhea.[9, 10]

Since COVID-19 is a new viral disease, world is still struggling to find out a permanent remedy to control this serious health problem. It seems prudent to study or have a look on the pathophysiology of SARS CoV-2 in the light of available research. Further, a review on

pathophysiology may give an insight on the potential therapeutic options.

BRIEF OF SARS COV-2

Type

There are thousands of species of coronaviruses known to exist in animals. At present seven Coronaviruses are identified as human pathogens. The family of coronaviridae is divided into two subfamilies i.e. coronavirinae and torovirinae. Coronavirinae has four genera alpha, beta, gamma and delta. Alpha and beta coronavirinae infect only mammals. Gamma and delta coronaviruses infect both mammals and birds. SARS CoV-2 is a beta coronavirinae.[11,12]

Structure

SARS CoV-2 is a single stranded, positive sense, enveloped RNA virus. It is spherical in shape and has prominent club like projections on the surface called as 'spikes'. The viral membrane has four protein structures, the spikes (S), envelop (E), membrane (M) and nucleocapscid (N). S protein is a primary determinant of host and plays key role in pathogenicity. The E and M proteins together form envelop and determine its shape. The hemagglutinin esterase (HE) protein may work as another cell entry mechanism for virus. The N protein is bound to the RNA genome and form nucleocapscid(Figure 1).[13]

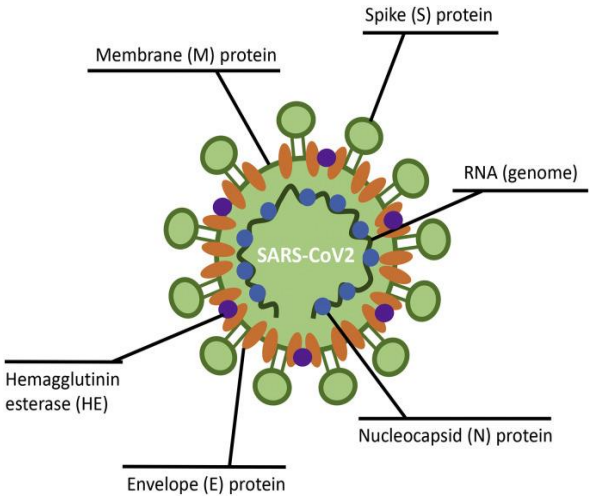

Figure 1: Structure of SARS-CoV-2.

PATHOPHYSIOLOGY OF COVID-19

Entry mechanism: Similar to SARS CoV, SARS CoV-2 use angiotensin converting enzyme receptor 2 (ACE 2) as a host cell receptor to establish infection. S protein consists of S1 and S2 subunits. S1 subunit binds to host cell through receptor binding domain (RBD), thereafter S2 subunit undergoes proteolytic activation and mediates fusion between viral and the cellular membranes.[14-16] ACE2 is highly expressed in alveolar cells, ciliated and goblet cells in the airway. These cells provide viruses' portal of entry in human.[17-19] It explains why pneumonia is a prominent manifestation of COVID-19. ACE 2 is also expressed in intestinal epithelium, cardiac cells and vascular endothelium, which may explain gastrointestinal and cardiovascular complications of COVID-19.[20,21] ACE2 is also expressed on monocytes and macrophages which may provide an entry mechanism for SARS CoV-2 into immune cells.[22]

Viral recognition and its evasion from immune system: At the very first step, immune cell detect viral infection through sensing virus derived pattern associated molecular pattern (PAMPs) such as viral RNA. PAMPs bind and activate pattern recognition receptors (PRRs) on immune cells resulting into immune cell activation. RNA viruses are detected by endosomal RNA PRRs including Toll-like receptors (TLR 3 and 7) and or cytoplasmic RNA sensors namely retinoic acid inducible gene I (RIG-I) and melanoma differentiation associated proteins 5 (MDA-5). Activation of these factors stimulate increased expression of type 1 interferon (TI IFN) through IFN regulatory factor (IRF 3) and other proinflammatory cytokines i.e. IL-1, IL-6, TNFα. SARS CoV-2 evade immune system recognition by inhibiting activation of mitochondrial antiviral signaling protein.

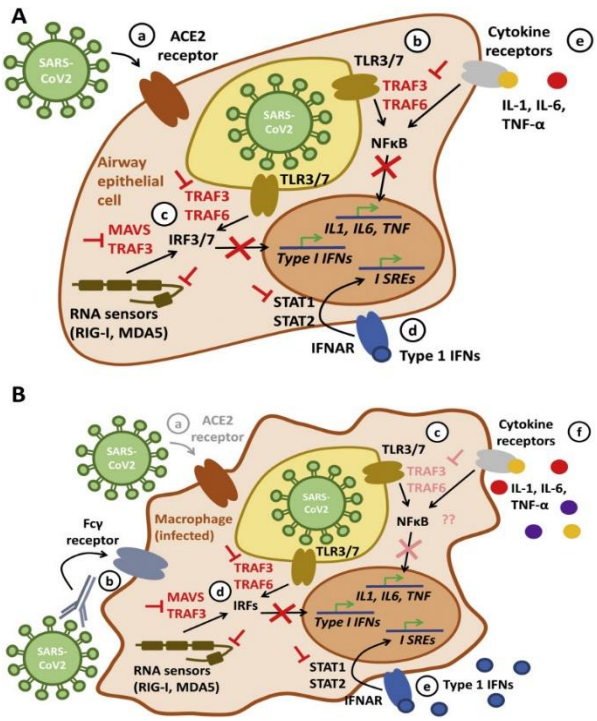

Figure 2: (A) Immune evasion strategies of SARS-CoV-2. (B) Antibody directed enhancement and cytokine storm syndrome.

It also inhibits TNF receptor associated factors (TRAF) 3 and 6, which are central for the induction of IRF 3/7 in response to TLR 3/7 and or RIG-I and MDA-5.[23, 24] Further, novel corona viruses can inhibit T1IFN signaling

through inhibition of STAT family transcription factor phosphorylation. In this way novel coronaviruses evade immune system and proliferate without triggering the innate antiviral responses of cells (Figure 2).

Later, infected cells die and release virus particles together with intracellular components that trigger innate inflammatory mechanism. As a result of it, adaptive immune response also get activated as a host's defense against virus. CD4+ T cell derived cytokines, CD8+ T cell mediated cytotoxicity and B cell mediated antibody production play important role in it.[25]

Humoral response: Kinetics of immune response was recently reported in a cohort study involving COVID-19 patients. The study reported median time for development of antiviral Ig G andIg M to be about 13 days after the start of symptoms, whereas all patients developed IgG within 19 days. However, a detailed quantifiable response in asymptomatic, mild and severe COVID-19 patients remains to be seen.[26]

While antibodies play important role in host defense against coronaviruses, there is a risk of antibodies triggering a harmful and exaggerated inflammatory response through a process called as antibody dependent enhancement (ADE).[27] Recently a preclinical study demonstrated that antibodies against S protein can activate FcϒR in M2 macrophages in the lung thereby triggering an exaggerated inflammatory response with release of large quantities of IL-6 and 8, recruitment of inflammatory cells to the lung leading to acute lung injury (ALI), diffuse alveolar damage and death.[28]

Cytokine storm: Recent studies from Wuhan demonstrated linkage between severity of disease and unfavourable outcome with cytopenia and or significantly elevated inflammatory parameters.[8,29] Enhanced innate immune activation including increase T1IFN, IL-1β, IL-6 and TNFα expression centrally contributes to morbidity and mortality in COVID-19 similar to MERS and SARS. In a process referred to ADE, virions inhibit type 1 IFN signaling in infected macrophages while allow pro-inflammatory IL-1, IL-6 and TNF α expression, which may contribute to hyper inflammation and cytokine storm syndrome. (Figure 2) Janus kinases (JAK) are involved in cytokine receptor signaling. They mediate phosphorylation of STAT family transcription factors which are involved in pro-inflammatory cytokine expression.[30]

Bradykinin storm: Recently the role of bradykinin has also been proposed in COVID-19 pathology. This idea was perpetuated by the increased expression of genes for the bradykinin receptors from the lung fluid of COVID-19 patients.[31] Fluid in the lung and inflammation, a key feature of COVID-19 patients, further strengthens this hypothesis. Kinin system gets activated in the back drop of blood clotting, being dysregulated in many COVID-19 patients. Bradykininand related peptides are produced through two distinct pathways: the plasma kallikrein pathway (activated by Hegeman factor, a clotting factor) and the tissue kallikrein pathway (activated by plasmin). Bradykinin is converted into des-Arg 9-bradykinin (DABK). When bradykininand DABK bind their corresponding receptors, B2R andB1R respectively, fluid starts leaking from blood vessels. The Renin angiotensin system (RAS) has control over kinin system. Angiotensin converting enzyme (ACE) breaks down bradykinin while ACE2 breaks down DABK. Both ACE and ACE2 act as regulatory break over kinin system. But since ACE2 gets internalized into cell during SARS CoV-2 infection, bradykinin cascade goes into over drive.[31,32]

Hypercoagulability in COVID-19: Coagulopathy is a commonly reported complication in COVID-19 patients.[33] The literature suggests links between RAS and coagulopathy. The Ang 1-9 peptide, that is increased in COVID-19 patients triggers thrombosis by inhibiting fibrinolysis.[34] ACE increases fibrinolysis and degrades antifibrotic peptide N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) which is produced from thymosin beta-4.[35]

POTENTIAL THERAPEUTIC TARGETS

Antiviral drugs

Nucleoside analogue like remdesivir, favipiravir, geldesivir are being evaluated for treating SARS CoV-2 in clinical trials. Remdesivir, a prodrug to adenosine, compete with ATP during RNA synthesis thereby inhibiting RNA dependent RNA polymerase. It was first approved for Ebola virus infection and is under phase 3 trial in hospitalized COVID -19 patients.[36,37] Favipiravir, an inhibitor of non-nucleoside RNA polymerase, was approved for treating influenza in Japan, is being under investigation for COVID-19.[38,39] Galidesivir is another adenosine analogue initially developed for hepatitis C virus is also under clinical evaluation for COVID-19.[40,41] Proteases are critical for viral replication as they cleave both structural and functional proteins from its precursor polypeptide.[42]

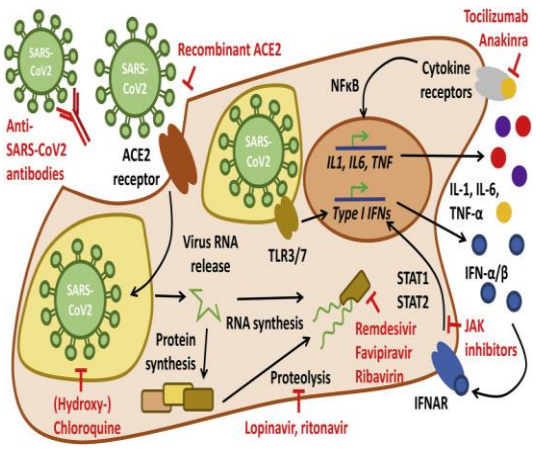

Figure 3: Potential therapeutic targets in COVID-19.

Protease inhibitors Lopinavir/ritonavir combination has shown improved outcome in a recent clinical trial for SARS CoV-2 infection (Figure 3).[43] Danoprevir, a hepatitis C virus protease inhibitor, is under clinicalevaluation for COVID-19.[44]

Antimicrobial and antibiotics

Ivermectin is a broad spectrum antiparasitic and anthelmintic agent, is being investigated for its efficacy in COVID-19 patients.[45,46] Suramin sodium, which has been used to treat trypanosomiasis and onchocerciasis, has also demonstrated activity as inhibitor of reverse transcriptase enzyme of various retroviruses and growth factors.[47] It is also being investigated in COVID-19 patients.[48] Azithromycin, a broad spectrum macrolide antibiotic effective against various respiratory pathogens is also being experimented as a prophylactic treatment in cancer patients undergoing chemotherapy.[49,50] Doxycycline, a second generation tetracycline, has been reported to act as a potent inhibitor of dengue viral replication and diminish serum IL-6 levels at the time of infection.[51] It is under phase 3 study to evaluate its efficacy in severe COVID-19 patients.[52]

Nonspecific anti-inflammatory and immunosuppresants

Corticosteroids are the powerful broad spectrum anti-inflammatory drugs. They have been used to treat acute respiratory distress syndrome (ARDS) because of their anti-inflammatory, antifibrotic activity and ability to prevent collagen deposition.[53] Corticosteroids have been evaluated for anti-ARDS effect in COVID-19 patients without significant efficacy.[54] Fingolimod is an immunomodulator of sphingosine-1-phosphate-a receptor. It has been reported to cause sequestration of lymphocytes in lymph nodes.[55] It is also under investigation for COVID-19 patients.[56] Thalidomide is a known immunomodulator. It has antiangiogenesis, antifibrotic and anti-inflammatory property and is being investigated for safety and efficacy in COVID-19.[57,58] Leflunomide is a FDA approved immunomodulator for treatment of rheumatoid arthritis. It inhibits dihydroorate dehydrogenase and tyrosine kinases and causes degradation of intracellular transcription factors.[59] It is being investigated in ambulatory and mild COVID-19 patients.[60] Nonspecific anti-inflammatory drugs like colchicine, ibuprofen and Naproxen are also being investigated for their efficacy in COVID-19 patients.[61-63]

Kinase inhibitors

Janus kinase inhibitors efficiently limit cytokine expression and may help in controlling cytokine storm. (Figure 3) JAK inhibitors like jakotinib, ruxolitinib, baricitinib and tofacitinib are under various phases of clinical trial to test their efficacy and safety in severe COVID-19.[64-67]

Monoclonal antibodies

The blockade of cytokines during cytokine storm appears to be a more targeted approach as compared to corticosteroids and is a promising therapeutic option. Tozumabis used for treatment of bilateral lung lesions as immunotherapy, while adamumab is used in rheumatoid arthritis.[68] Their combination is under evaluation for severe COVID-19 patients.[69] Ravulizumab is a humanized monoclonal antibody which was first approved for paroxysmal nocturnal hemoglobinuria. It is investigated for safety and efficacy in severe COVID-19 patients.[70,71] Leronlimab is a CCR5 antagonist and significantly prevents virus entry and inhibits infection of CD4 T-cells.Leronlimab safety and efficacy in severe COVID-19 patients is under clinical trial.[72] Tocilizumabis an IL-6 antagonist that selectively inhibits IL-6 mediated proinflammmatory signaling and interrupts the process of cytokine release syndrome.[73] It's efficacy and safety in secondary cytokine syndrome in COVID-19 patients is under investigation (Figure 3).[74]

The recombinant IL-1 receptor antagonist drug anakinra was originally developed to contain cytokine syndrome in sepsis patients. It has lower risk of neutropenia and hepatotoxicity as compared to tocilizumab.[75] A recent cohort study demonstrated significant efficacy of anakinra in severe COVID-19 patients.[76] Since, ACE 2 has been identified as a key molecule for cell invasion, its therapeutic blockade has been suggested to control SARS CoV 2 infection (Figure 3). A recombinant human ACE2 to neutralize virions prior to their attachment is being explored as a therapeutic option.[77] As mentioned earlier, SARS CoV-2 inhibits expression of type 1 interferons resulting in exaggerated inflammatory cytokine responses and tissue damages. Recombinant interferons have been found to be effective against novel coronaviruses in in vitro studies, However clinical benefits remains to be established.[78]

RAS and kinin Inhibitors

The dysfunction of the renin-angiotensin system (RAS) has been observed in coronavirus infection disease (COVID-19) patients. A recent cohort study showed improved clinical out come with RAS inhibitors in COVID-19 patients with hypertehnsion.[79] Two drugs that target kinin system; icatibant (B2R blocker) and monoclonal antibody lanadelumab, which inhibit plasma Kallikrein, are under clinical trials for COVID-19 patients.[32]

Anticoagulants

The scientific evidence suggests linkage between RAS and coagulopathy. The Ang 1-9 peptide that is increased in COVID-19 patients has been found to trigger thrombosis by inhibiting fibrinolysis.34 Increased fibrinolysis could therefore be achieved by increasing ACE or by

administering thymosin beta-4 (Timbetasin), which is under investigation for COVID-19.[31]

Convalescent plasma

Plasma from COVID-19 recovered patients, rich in antibodies directed against SARS Co-2 is being explored as a therapeutic option. Initial results are promising in neutralizing the viral particles in the host.[80]

Vitamins

Vitamin C also known as ascorbic acid is popular for its antioxidant properties. It also plays important role in reducing inflammatory process, deters common cold and inhibits neutrophil accumulation in the lung.[81,82] Vitamin C is also under clinical evaluation for its safety and efficacy in COVID-19 patients.[83] Vitamin D may provide the boosting and priming effects against viral infections. Several in vitro and in vivo studies have demonstrated activity of vitamin D against acute respiratory distress syndrome and COVID-19 associated coagulopathy.[84,85]

Limitations

This review has tried to focus on potential therapeutic with specific target on SARS CoV-2. It may not have included all the substances under investigation as new drugs are being included in the trial or study in search of remedy on urgent basis. Information on vaccines has not been included as it requires a separate review. The review did not include special category like children and pregnant population.

CONCLUSION

The SARS COV-2 has emerged as a pandemic of potential threat of enormous magnitude to health and society with very limited success so far in terms of treatment. Being a new virus and having potential to cause significant morbidity and mortality in short span of time various approved drugs are being repurposed for the treatment of COVID-19. Targeted therapy against SARS CoV-2 remains the corner stone of treatment strategy till an effective vaccine or herd immunity is developed. This review may give an insight to researchers and treating physicians in the management of COVID-19.

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