A Review on Emerging Therapeutic Interventions for Corona Virus
Running Title: Therapeutic Interventions for COVID-19

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Abstract

The Coronavirus (SARS-CoV-2) is one of the deadliest viruses of current era and is etiological agent of novel coronavirus disease-2019 (COVID-19). This disease stances a severe risk to mankind due to its unexplored pathologies. It was declared as a COVID-19 pandemic by the world health organization. This outbreak has challenged the public health concerns at large, killing the most vulnerable person, causing generalized panic and become a top debate among scientists, clinicians, physicians, pathologists, economists, athletes and politicians. Anti-viral vaccines and target drugs to treat this virus are unavailable due to its diverse genetic instability. Currently, its prevention, control and treatment are questionable as no proven remedies have been effective for its cure so far. From a research assessment, many number of drugs or medicines are being manufactured and tested at fast pace, goals and objectives are being celebrated on daily basis, and also many drugs are be subjected to clinical tests. Scientists are interested about how to provide the better care to everyone before a vaccine can be made available to common community. To stop COVID-19, effective solutions (i.e., personal protection elements, vaccines, drugs, etc.) are needed urgently. Red bells are ringing but there is no way out. Current review focuses on the ongoing regimes and therapeutic interventions for better combat with COVID-19.

Keywords: coronavirus, genetic instability, interventions, pandemic, therapeutic, vaccine

Introduction

The global challenge of COVID-19 started in late December, particular with rapid increase of critically ill patients having symptoms of pneumonia (Cascella, Rajnik, Cuomo, Dulebohn, & Di Napoli, 2020). Our global health system unfortunately has often seen an array of novel emerging diseases such as Ebola, Dengue, SARS and MERS (Favalli et al., 2020). The list of emerging pathogens updated again with the addition of novel coronavirus (2019-nCoV) (Hui et al., 2020). This virus strain was reported to infect humans for the first time (El Zowalaty & Järhult, 2020) . In early reports the mortality rate was appears to be around 2% but with the passage of time virus became more contagious, more pathogenic and deadly. Due to globalization the virus spread across international borders and WHO declared a pandemic (Khan & Naushad, 2020). In corona virus illness the efficacy of the treatment totally relies on the critical condition of patient health status and disease stage (Cascella et al., 2020).

Brief Overview of Corona Virus

SARS-CoV-2 Pathology

Coronaviridae family, having a total of thirty nine species, (Gorbalenya et al., 2020). Few of these species are zoonotic in nature (Schoeman & Fielding, 2019). Origin and transmission patterns of the virus, still remain as unidentified to world audience, recently, it is believed that SARS-CoV-2 has been transmitted to human being from mysterious animal and further transmitted from one individual to another (Xu et al., 2020). Coronaviruses affecting human being are causative of upper respiratory tract diseases limiting from minor to moderate symptoms together with common cold (Woelfel et al., 2020). Human might be infected with more than one species of this coronaviridae family at any stage during their life span (Killerby et al., 2018). Two main etiological agents of severe pneumonia are MERS-CoV and SARS-CoV (Zhu et al., 2020). There are sight variations among the signs and symptoms of MERS, SARS, COVID-19 and common flu that has been expressed below in the form of a table (Table 1). The World Health Organization, publically named this viral disease COVID-19 on 11, February 2020 (Shen et al., 2020). This new virus was named as SARS-CoV-2 by the research group of the International Committee on Taxonomy of Viruses (Gorbalenya et al., 2020). In arrays of serious outbreaks SARS-CoV first appeared in 2002. 8000 infections and 774 deaths were recorded across 35 countries during its course of infection (Peiris, Guan, & Yuen, 2004). Followed by the outbreak of MERS-CoV, responsible for infection of 2500 people and 858 dead in golf states (Zaki, Van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012). Similarly, the newly emerged SARS-CoV-2 transmitted from animals to human beings in December 2019. Currently 34,170,356 people are infected and reported deaths are 1,018,899 worldwide. Incubation period of SARS-CoV-2 is about 14 days. It replicates in the lower and upper part of respiratory tract as a result produced lesions in the affected areas (Chan et al., 2020). Most common clinical signs and symptoms found are cough, low to high grade fever, dyspnea and lesions in lungs (Wu et al., 2020). There may be development of

pneumonia in the later stages that leads to (ARDS) acute respiratory distress syndrome and severe pneumonia which follows into life-support to save the life of infected individual (Heymann & Shindo, 2020). Generally, the HCoVs are long single-stranded positive-sense RNA viruses (30,000 bp). HCoVs characterize by two groups of proteins; non-structural proteins and the structural proteins as RNA dependent RNA polymerase (RdRp) (nsp12) (Elfiky, 2020).

Therapeutic Interventions for Corona Virus

Modulation of Immune system

Neither anti-viral therapeutic agents nor any effective vaccines have been approved for the treatment of any human CoV disease or COVID-19 till date. Coronaviruses like MERS and SARS are specifically capable of dampening immune responses and evading immune detection. It is not still understandable as to how COVID-19 affects the immune response (Nikolich-Zugich et al., 2020). During this viral disease, some host factors evoke immune reaction against the viruses. Particularly, T cells (CD8+ & CD4+) play a critical antiviral response to raise the risk of expanding inflammation or autoimmunity and combat the pathogens (Cecere et al., 2012).

In addition, CD8+ T cells destroy virus infected cells and are cytotoxic. More than 80% of total inflammatory cells are CD8+ T cells in the lung's interstitial tissue in SARS-CoV cases, also show a dynamic response in reducing coronaviruses in diseased cells and prompting immune damage. However, CD4 + T cells improve the growth of particular antibodies by stimulating T cell-dependent B cells (Maloir, Ghysen, von Frenckell, Louis, & Guiot, 2018). Moreover, T helper cells produce pro-inflammatory cytokines through NF-kB signaling (Manni et al., 2014). Cytokines (IL-17) convert neutrophils & monocytes to the infected spot executing swelling and stimulates other downstream cataracts of chemokines and cytokines,

containing TNF-β, MCP-1, IL-1, IL-6, IL-8 and IL-21 (Bunte & Beikler, 2019). Different research studies revealed that, a unique BH3-like region to be found in the C-terminal cytosolic field of SARS-CoV protein facilitated by Bcl-xL induced T cell apoptosis (Yang et al., 2005). It was also revealed that response of T cell to basic proteins comprising the N, M and S is persistent, long-term and offers indication for preparing novel vaccines and drugs for SARS-CoV-2 comprised of basic viral fundamental proteins that can produce active, long lasting and dominant memory cell reactions in contradiction of virus. On the other hand, earlier researches have described a critical role of both CD4+ and CD8+ T cells in COVID-19 clearance, (Zhou & Zhao, 2020) observed that CD4+ T helper cells are compulsory for development of SARS-CoV-2 specific neutralizing antibodies. Furthermore, the ACE2 protein attached to a human IgG Fc (ACE2-Fc) domain of SARS-CoV-2 patients can have the advantages of a conventional counteracting antibody that might be used as a treatment for the disease. conclusively, there will be a necessity for medical trials to define any exact side effect or reactions of ACE2-Fc treatment (Kruse, 2020). Uncertainty, the function of ACE2-Fc is inhibited, then ACE2-Fc might perform an essential role in the treatment of SARS-CoV-2. Recent immunological research trials reveal how important it is to recognize the fundamentals of the immune responses in SARS-CoV-2, so these immune cells can be prompted to more attack on causative agents with better accuracy. In addition to the immune system, researchers have also established a possible effect of the SARS-CoV-2 in the central nervous system (Vellingiri et al., 2020).

Recent approach to coronavirus disease management concentrates on supportive therapy. Fast public health involvements with anti-viral, antibodies or novel vaccine approaches are extremely important to contain the virus and disease transmission. COVID-19 epidemics can be limited by passive antibody therapy. Immunoglobulins or convalescent plasma have been injected as a last possibility to boost the survival ratio of patients with

SARS whose situation sustained to decline in spite of treatment with pulsed methylprednisolone (Chen, Xiong, Bao, & Shi, 2020). Moreover, many studies revealed a limited hospital stay and lesser mortality in patients cured with convalescent plasma. The administration of convalescent plasma collected from individuals who had cured from Ebola virus disease was suggested by World Health Organization as an experiential treatment throughout outbreaks in 2014 (L. Chen et al., 2020).

In 2015 for the treatment of Middle East respiratory syndrome coronavirus, standard operating procedures for use of convalescent plasma were established (Zumla, Hui, & Perlman, 2015). According to World Health Organization, management of SARS-CoV-2 has primarily focused on prevention of infection, case monitoring & detection and supportive therapy. On the other hand, lack of evidence, no specific anti-COVID-19 treatment is suggested. Most importantly, the recent directions give emphasis to systematic corticosteroids would not be administered regularly for the treatment of COVID-19 (L. Chen et al., 2020). Research studies show that convalescent plasma obtained from patients who have cured from viral diseases may be used as a treatment without the incidence of severe contrary effects. Therefore, it could be valuable to test the efficacy and safety of convalescent plasma transfusion in SARS-CoV-2-infected patients. Li et al., (2020) described the medical characteristics & cytokine structural profile of serious patients in Wuhan, China with COVID-19 and recommended that a cytokine storm (i.e. interferon gamma-induced protein 10, higher concentrations of granulocyte-colony exciting factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α and tumor necrosis factor α) might be related with the severity of disease (Zhao, 2020). A different research study from China described that improved expression of interleukin (IL-6 & IL-2R) in serum acts to anticipate the severity and prognosis of patients with SARS-CoV-2. Furthermore, histopathological analysis of a biopsy section/sample obtained from a patient who expired from COVID-19

showed that interstitial mononuclear inflammatory infiltrates dominated by lymphocytes, in right and left lungs (Zhao, 2020). Additionally, Krebs et al., (2013) reported that marginal blood flow cytometric analysis revealed that the over activation of T cells accounted for the serious immune damage in the diseased person. Therefore, cytokine storms would not be ignored in the treatment of novel COVID-19. Immunomodulatory therapy to down-regulate the cytokine storm can facilitate insights into the treatment of COVID-19 (Zhao, 2020). In immunomodulatory therapy of infectious diseases, corticosteroids are among the most normally used medicines. However, in the treatment of COVID-19 the use of corticosteroids can cause host immune suppression and postponed viral clearance. Recently Liu et al., (2020) reported that chloroquine and its derivative like hydroxychloroquine have been used in the treatment of SARS-CoV-2. In February 2020, outcomes from more than hundred Chinese patients with COVID-19 presented that chloroquine phosphate had better effectiveness against the virus. Additionally, their anti-inflammatory properties, their antiviral and antimalarial effects have been confirmed in the treatment of autoimmune diseases such as lupus erythematosus and rheumatoid arthritis. Hydroxychloroquine and chloroquine can prevent the main histocompatibility complex class II expression, immune stimulation (reducing CD154 expression by T cells) and antigen appearance through cGAS activation of interferon genes and Toll-like receptor signaling (Rainsford, Parke, Clifford-Rashotte, & Kean, 2015). Thus, hydroxychloroquine and chloroquine can decrease the growth of numerous pro-inflammatory cytokines, such as interferon-α, IL-6, IL-1 and tumor necrosis factor associated in the cytokine storm.

The virus completes its cycle in following five stages: attachment, penetration, biosynthesis, maturation and release. The COVID-19 virus binds with its spine proteins (S protein) to the angiotensin exchanging enzyme-2 receptor (ACE2), (X. Chen et al., 2020) whose expression levels are higher in lungs, heart, ileum, kidneys and bladder could explain the involvement of

multiorgan failure in COVID-19 patients (X. Chen et al., 2020). Within lungs, ACE2 receptors are greatly expressed on apical aspect of lung epithelium in alveolar space (Ziegler et al., 2020). This initial binding of the virus with the ACE2 receptors initiate the cleavage of the S proteins by host proteases such as furin or TMPRSS2 which presumably result in the exposure of the fusion sequence of viral protein with cell membranes of host cell, a mechanism necessary for entry of the virus into the host cell (Yuki, Fujiogi, & Koutsogiannaki, 2020). The SARS-CoV-2 preferably attacks the alveolar cells type II compared to type I cells (Lopes et al., 2020).

The alveolar units situated under the pleura are the ones that are affected first. The virus then multiplies inside type II cells and multiple copies of the virus are then released, resulting in the apoptosis and death of these type II cells with the new viruses attacking nearby type II cells and this process goes on (Danser, Epstein, & Batlle, 2020). The SARS-CoV-2 also infects alveolar endothelial cells and hence compromises epithelial-endothelial barrier resulting in endothelialitis and infiltration of mononuclear cells edema of the alveolar space (Li et al., 2020). Moreover, type II alveolar cells are also the precursors of type I cells, hence after their destruction, the regeneration mechanism of alveolar units is severely impaired (Wiersinga, Rhodes, Cheng, Peacock, & Prescott, 2020). Much of the damaged inflicted by SARS-CoV-2 is presumably due to a robust immune reaction called cytokine storm with IL-6 as a major protagonist. This IL-6 is also a major culprit implicated in production of acute phase proteins, thermoregulation fever and multiple organ dysfunction.

Moreover, inhibition of ACE2 receptor by the virus further promotes lung injury as occupied ACE2 receptors fail to breakdown angiotensin II that leads to severe respiratory distress syndrome & multiorgan dysfunction (Gupta, 2020). These events cause diffuse alveolar injury with fibrin rich hyaline membranes and a few multi-nucleated giant cells. In terminal stages of COVID-19 patients, consumption of clotting factors and stimulation of coagulation

occur with resultant diffused intravascular coagulation (Andreakos & Tsiodras, 2020). Swollen lung parenchyma and pulmonary endothelial cells may cause the thrombi formation. Viral sepsis that is one of the complications associated with COVID-19 is caused by dysregulated reaction of host defense system and this sepsis could also play its part in multiorgan failure (Yuki et al., 2020).

Specific strategies to combat

The choice of whether to admit a patient in the hospital or not depends on the extent of progression of virus in the respiratory tract (Thomas-Rüddel et al., 2020). The patients in which the COVID-19 has just spread to upper and conducting part of respiratory airways exhibit mild symptoms, such as fever, cough and do not need immediate hospitalization. Instead they need to be isolated at home to contain and mitigate the spread of the disease and such house-quarantined patients should receive much of their treatment at home including spirometry or breathing exercises, rest, and adequate fluid intake and antipyretics. It is only in severe case in which the virus has acquired access to gas exchange area of the respiratory airways and other parts of the body where the situation gets complicated with sepsis, severe respiratory distress syndrome, multiorgan failure and septic shock including cardiac and renal failure (Zaim, Chong, Sankaranarayanan, & Harky, 2020), that the patient should be admitted to the hospital and be treated according to the complications involved. The severity of the disease is assessed by the development to of ARDS which is a syndrome described by sudden commencement of hypoxemic respiratory failure along with bilateral infiltrates (Coperchini, Chiovato, Croce, Magri, & Rotondi, 2020). The COVID-19 patients who suffer from other comorbid conditions such as diabetes and cardiac diseases also require immediate medical intervention as the chances of complication are elevated in these patients (Guan et al., 2020). The most common condition for requiring extensive care has been respiratory support. Therefore, those patients who develop respiratory distress, hypoxia or shock should

immediately be given supplemental oxygen therapy and their SpO2 should be tried to maintain at >94% (Alhazzani et al., 2020). If the patients continue to develop hypoxemia even after oxygen therapy should be opted to treat with mechanical ventilation with prone ventilation of 12-16 hours is recommended (Bhatraju et al., 2020). Similarly, those individuals who suffer from co-infections should be empirically treated with antimicrobial within an hour of their assessment.

Availability of Targeted Drugs

Ivermectin is a potential drug of choice against parasites and it is also proposed for treatment against SARS-CoV-2 (Caly, Druce, Catton, Jans, & Wagstaff, 2020). The concentration at 5 mmol/L causes the disappearance of RNA of virus and it is 50 times over higher after 700 lg/kg attained (Muñoz et al., 2018). Ivermectin showed a great anti-viral activity (broad spectrum) in vitro and it prevents COVID-19 with addition Vero-hSLAM cells. Its affects showed activity 2 hours after post infection and reduced the viral RNA ~5000-fold in 48 hours.

A nucleoside analogues drug, Remdesivir has antiviral activety and used for treatment of infections caused by Nipah and Ebola virus (Lo et al., 2019). Remdesivir has greater effects on SARS-CoV-2 as it is an RNA virus and has great potential candidate drug for treatment of COVID-19 (Cao, Deng, & Dai, 2020). The mechanism of action Remdesivir which targets the divergent RNA-dependent RNA polymerase (RdRp) of host viral replication and its nucleoside analogues shows the antiviral results as in HIV, hepatitis C and B. it is used with ribavirin and mutation was increased by 9.7-fold reduce infection at 99.3% (Crotty, Cameron, & Andino, 2001). Azidothymidine loses its 3′-hydroxyl group which is necessary for synthesis of additional DNA. Remdesivir blocks the transcription process at 3′-hydroxyl and produced phosphodiester bond with nucleotide. Patient infected with COVID-19 received Remdesivir 200 mg I/V in 1 day up to 10 days. So, 61 patients recovered successfully as they belong from different countries as Europe, United States, Canada and Japan.

Favipiravir inhibited the RNA-dependent RNA polymerase (RdRp) (Dong, 2020) and block the replication of alpha-, flavi-, bunya-, filo-, noro-, arena-, and other RNA viruses (Delang, Abdelnabi, & Neyts, 2018). Many clinical trials are undergoing for the use of treatment of COVID-19. 120 patients of COVID-19 treated with Favipiravir and compared Arbidol. Recovery rate is day 7 and recovery rate was 0.0954; 95%. Serum uric acid was raised by using of Favipiravir and it helps to relief from cough and pyrexia and adverse effects can be manageable.

MK-4482 is an emerging drug which has antiviral potential, so it can be used for treatment of COVID-19 (Vasudevan et al., 2020). A new route has been developed for MK-4482 from cytidine which is desirable for many reasons. It emits *O*-acylation which is undesirable and less chemical esterification plan. Further trails are necessary to check its effectiveness for the treatment of COVID-19. MK-4482 shows more better results than that of remdesivir for the treatment of COVID-19 patients and its trials have been completed in mice (Cross, 2020).

Conclusion

The COVID-19 pandemic is an ongoing problem that disturbs the lives of most people around the world. Most countries of the world are now semi-closed, strict travel regulations have been passed, international dealings have been affected, and humans are experiencing an exceptional regime, which has changed the normal life. Immune system plays a significant role in combating COVID-19, paradoxically it could also be dangerous. Now a day's target drugs are available and due to limitation of choice being catagories as best treatment for corona virus. It is compulsory to find effective drugs and vaccines to return to the normal situation and reduce the mortality rate.

Conflict of interest

The authors declare that they have no conflict of interest.

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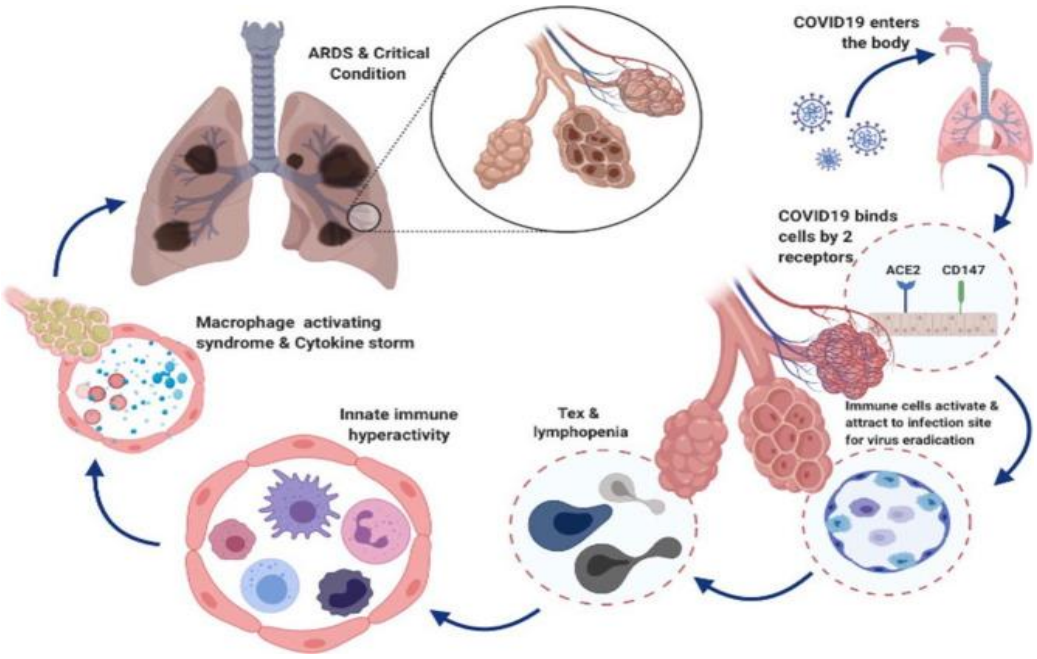


Fig. 1 Illustration indicating the pathogenesis and role of immune system in combating with viral load

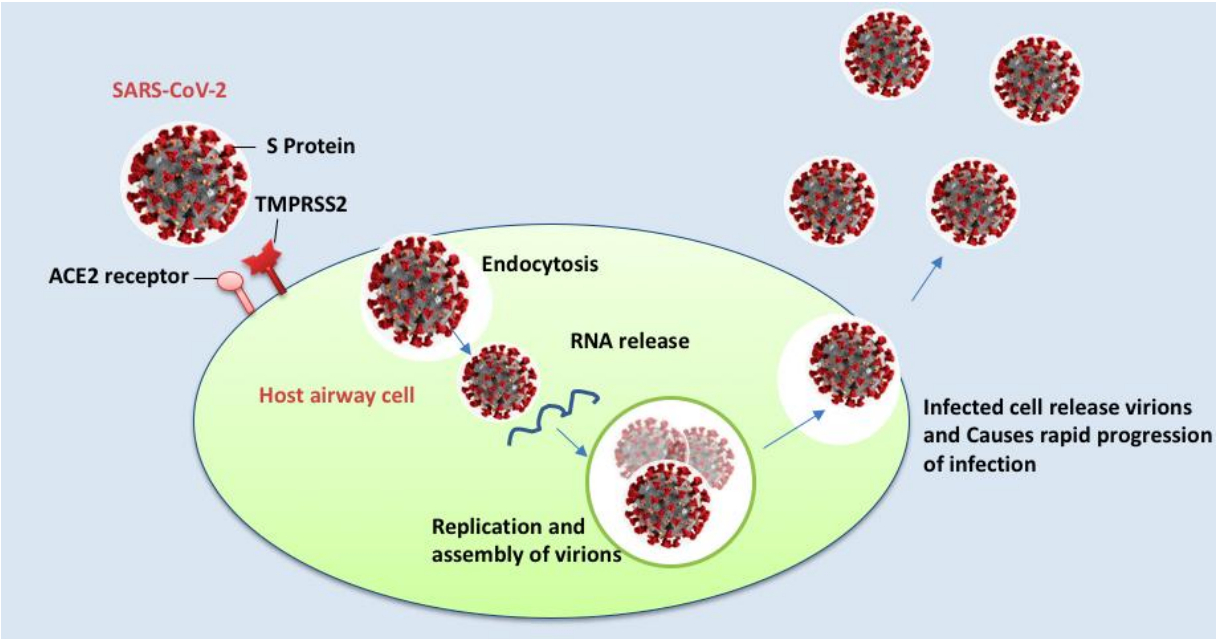
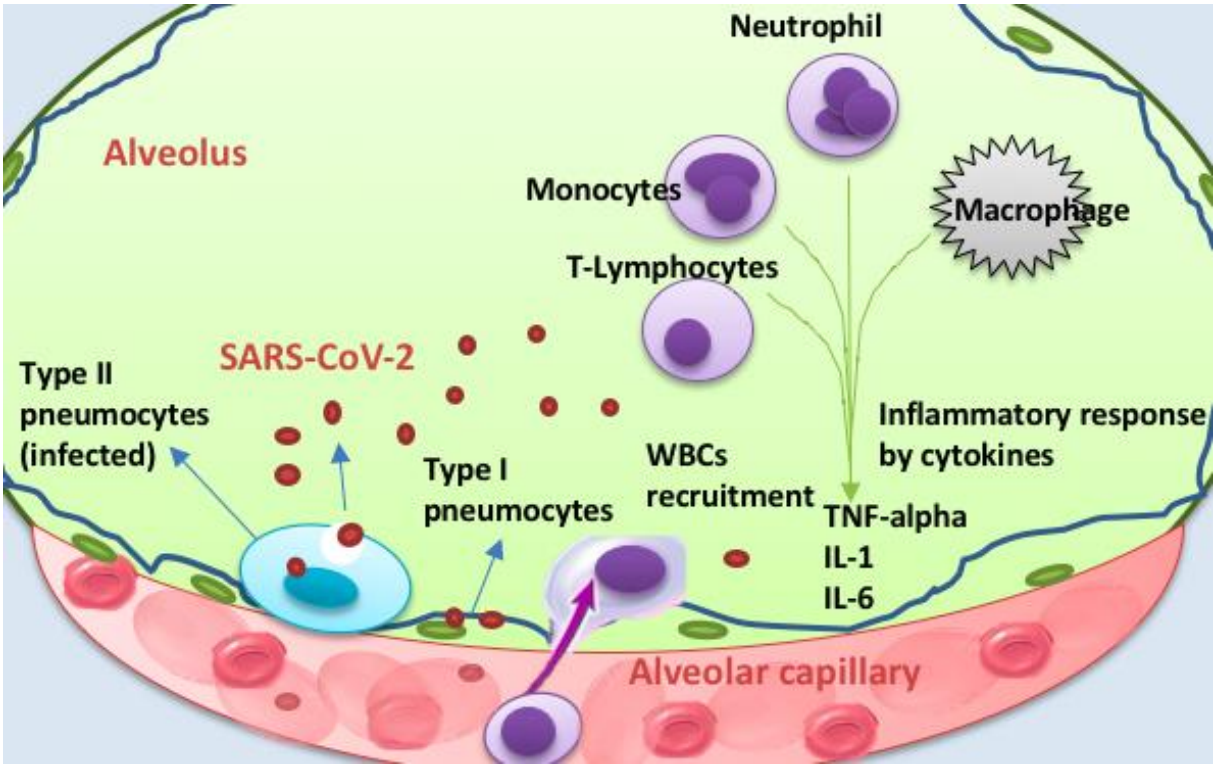


Fig. 2 SARS-CoV 2 virus infection in host cell; TMPRSS2 activates S protein of virus and cleaves ACE2 membrane receptors of host airway cell, virus enter host cell through endocytosis, releases RNA and utilize host cell machinery for replication and assembly of more viruses



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437 Fig. 3 Early stage SARS-CoV 2 virus infection; capillary endothelium and alveolar
438 pneumocytes (type I and II) are infected with SARS-CoV 2 virus and inflammatory
439 response initiates via cytokine release by recruitment of monocytes, neutrophil and
440 T-lymphocytes

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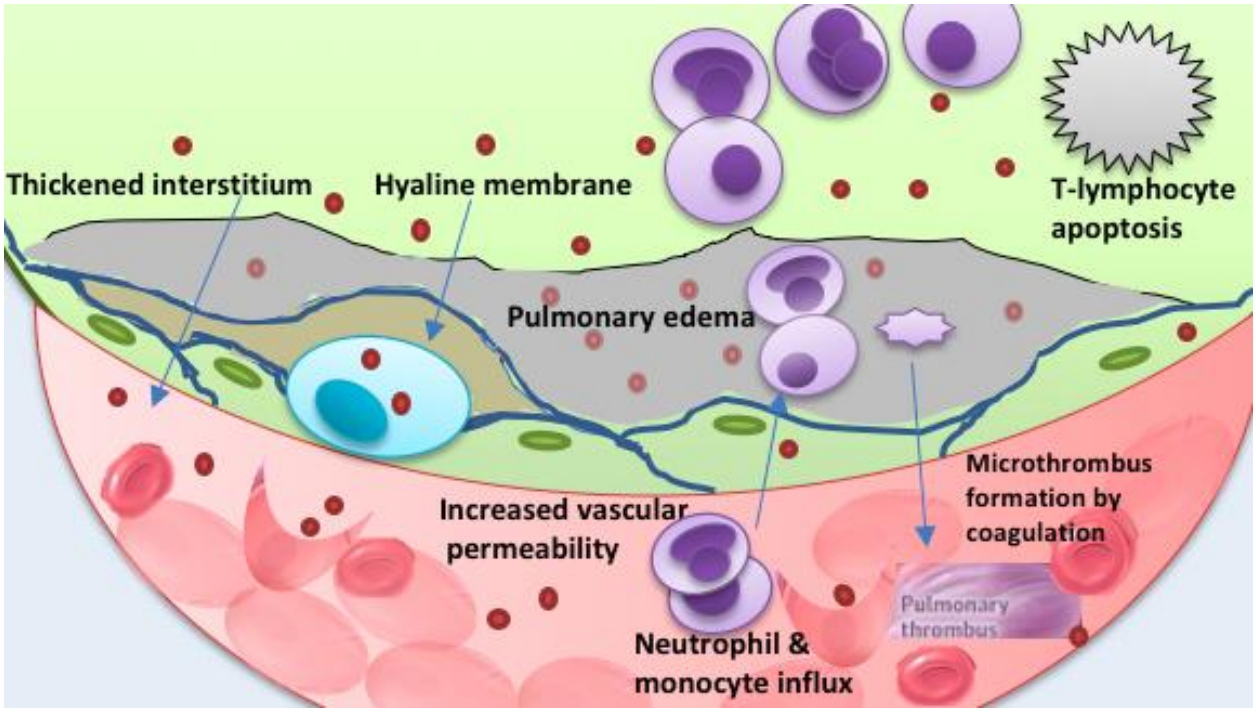

Fig. 4 Increased vascular permeability and alveolar interstitial thickening due to continues inflammatory response