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COVID-19: From viral infection to pulmonary failure

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Abstract

SARS-CoV-2 is a virus which promoted a worldwide pandemic outbreak in 2020. The virus is highly infectious and is able to contaminate a lot of people in a short time period. The disease promoted by the virus, named COVID-19, can cause different symptoms such as fever, cough, muscle pain, headache, prostration, diarrhea, neurological complications, dermic manifestations, pulmonary impairment, dyspnea, coagulopathies, organ failure, and death. Here, we show how the infection occurs and the major characteristics observed in the lungs of patients with COVID-19. In addition, we explored the immunological activation in this environment by the virus and some treatments used in the severe phase of the disease.

Keywords: COVID-19; Pulmonary impairment; SARS-CoV-2; Virus; Pandemic.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cause of the outbreak of severe pneumonia, called COVID-19 (Coronavirus Disease 2019) [1], is present in more than 200 countries [2-4]. According to a notification from the COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, by March 27, 2021, there were a total of 126,280,989 cases and 2,769,934 deaths worldwide [5].

The SARS-CoV-2 is believed to be able to disseminate through contaminated objects, respiratory droplets, and aerosols, where the virus can be suspended in the air for up to three hours [6,7]. The symptoms are commonly recognized as fever, dry cough, tachypnea, shortness of breath, sore throat, sneezing, nasal congestion, and other symptoms, including severe inflammatory responses with the evolution of cytokine storm, pneumonia, and sepsis [8,9].

Acute Respiratory Distress Syndrome (ARDS) is the most common complication in patients with COVID-19, with Acute Lung Injury (ALI) being the most serious form of viral infection [10]. Due to the clinical importance associated with the estab-

lishment and worsening of lung injuries in patients diagnosed with COVID-19, many studies have invested daily in testing prophylactic and therapeutic methods of treatment against acute lung injuries, through the administration of empirical antibiotics, antiviral drugs and systemic corticosteroids [6].

Cellular infection promoted by SARS-CoV-2 in respiratory tract cells

The upper airways are important entry regions of airborne pathogens, such as viruses, bacteria, and fungi. Some of these pathogens use this first environment to begin their multiplication process. The SARS-CoV-2 virus infects the host through ciliated and goblet cells in the nasopharyngeal region, using those cells for its replication and subsequent proliferation to other body regions [11]. Furthermore, the angiotensin-converting enzyme 2 (ACE2) is one of the receptors, present in those cells, that allow for viral entrance and favor viral fusion with the cellular membranes [12,13].

After virus-target cell fusion, the transmembrane serine protease type II (TMPRSS2) cleaves ACE2 and generates activation and conformational changes in virus protein S (through cleavage of the S1/S2 and S2' sites), allowing the virus to fully enter cells. Inside the cell, the virus will subsequently release its genetic material ($_{(+)}$ssRNA) into the cytoplasm and will use the cellular compounds to translate the viral proteins. In this context, both proteins (TMPRSS2 and ACE2) are the main determinants of the virus infection in the host [14-16].

Sungnak et al. (2020) [17,18] have shown that nasal epithelial cells present in the nasopharyngeal region, specifically goblet and ciliated cells, exhibit high expression of ACE2, followed by alveolar cells producing type 2 surfactant in the lower respiratory tract. This implies that the respiratory tract, especially the upper region, is an important repository for colonization of the virus at the beginning of infection [19,20].

ACE2 is also present in different organs and tissues of the body such as intestinal epithelial cells, in cardiac cells, in the vascular endothelium and in syncytiotrophoblastic cells in the placenta [21-23]. Moreover, at lower and non-ubiquitous levels, ACE2 is expressed in immune cells, such as monocytes/macrophages and T cells. To SARS-CoV-2 infection it is important to emphasize that other receptors and/or phagocytosis of viruses containing immune complexes may also be involved (Figure 1) [4,24,25].

Epithelial cells and macrophages when in contact with viral RNA normally activate Toll-like receptors (TLR) (3 and/or 7) in endosomes and cytosolic RNA sensors (RIG-I and MDA-5). This activation causes antiviral cellular events mediated by factors associated with the TNF receptor (TRAF). However, in SARS-CoV-2 infection, there is an effective suppression of the activation of factors associated with TRAF3 and 6, limiting the activation of the NFκ-B and IRF3/7 transcription factors, suppressing early pro-inflammatory responses by type-I Interferons (IFN) and stimulating other pro-inflammatory effector cytokines such as IL-1, IL-6 and TNF-α. In addition, SARS-CoV-2 also inhibits the activation of STAT transcription factors in response to activation of the type-I interferon receptor (IFNR), which further limits the mechanisms of antiviral response (Figure 1). Those parameters may be involved in the delay of virus containment in the host organism due to lower recruitment of immune cells and activation of immune checkpoints [26,27].

SARS-CoV-2 and its interaction with immune cells in the respiratory tract

Tissue monocyte/macrophages express less ACE2, this makes them less likely to be infected by this pathway. However, immune complexes consisting of circulating antibodies, recognize the virus particles and can be absorbed by macrophages through Fc gamma receptors (FcγR), resulting in their infection. This process is known as an Antibody-Directed Enhancement (ADE) and occurs due to interaction between virions complexed with antibodies, complement components, and target immune cells [28,29]. COVID-19 has been demonstrating a significant ADE response. These disease dynamics happen due to immunological antiviral program suppression, when virions inhibit type-I IFN signaling in infected macrophages, allowing pro-inflammatory expression of IL-1, IL-6 and TNF-α cytokines, which contributes to hyperinflammation and cytokine storm syndrome [30,31].

Huang et al., (2020) [20] found in an analysis of plasma from 41 patients with COVID-19 suffering from a cytokine storm, high levels of cytokines IL-1β, IL-6, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN -γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α and VEGF in patients admitted to an Intensive Care Unit (ICU). All patients included in the study had pneumonia and 1/3 of the patients were admitted to the ICU, where six of them died. IL-6 may be the major cytokine involved in the cytokine storm in COVID-19. A retrospective multicenter study of 150 patients with COVID-19 in China evaluated predictors of mortality for COVID-19 and showed that 68 deaths present higher levels of IL-6 [32]. Gao et al., (2020) [33] who evaluated 43 patients in China, also reported high levels of IL-6 in 33 patients.

The IL-1, TNF-α and IL-6 cytokines are produced by several cells, such as tissue macrophages, mast cells, endothelial and epithelial cells. The cytokine storm promotes in an influx of macrophages, neutrophils, and T cells from the circulation to the infection site with destructive effects on host tissues [34-37]. These higher inflammatory signals may result in destabilizing endothelial cell interactions, damaging the vascular barrier and diffuse alveolar capillarity, lowering oxygen saturation levels, resulting in failure of several organs and death [38,39].

Cytokines also regulate the activity of neutrophils and induce the expression of chemoattractants to those cells. In this context, as a result of the cytokine storm in the airways of patients with COVID-19, extracellular DNA was observed, partly originating from NETs (Neutrophil Extracellular Traps) released in response to persistent lung infections [2]. In addition, the excessive formation of NETs makes the mucus thick and viscous, not only impairing ventilation, but also facilitating the colonization of bacteria and, consequently, decreasing the patient's respiratory function [40-43].

The evident neutrophilia also brings as a consequence the formation of microvascular thrombi by the release of NETs by neutrophils mixed with platelets, evidenced in the post-mortem examination of the lungs of patients with COVID-19 (especially the patients who present rapid disease progression and sudden death), and in tracheal aspirates of intubated ICU patients [44-

48].

Although lymphocytes are blood circulation cells, they could be attracted to the inflammatory sites and display an increased immunological response. In fact, T cells play an important role in antiviral immunity, such as $CD8^+$ T and NK cells that are capable of secreting a series of molecules such as perforin, granzymes and IFN-γ to eliminate the virus and the infected cells, and $CD4^+$ T cells that can regulate T, B, and phagocytic cells, increasing their ability to eliminate different pathogens [49,50]. COVID-19 progression has shown a widespread lymphopenia status. Different studies point to possible T-cell exhaustion, due to the persistence of viral infection in the host, resulting in loss of cytokine production, lymphocyte apoptosis, and reduction of immune function [51-53]. Moreover, COVID-19-associated lymphopenia is promoted by NK cell reduction due to the increase of NKG2 expression (type C lectin receptor), which can stimulate or inhibit the cytotoxic activity of NK cells, being an important marker of exhaustion of these cells [54-56].

Histopathological findings of patients with COVID-19

The pathological and histological changes associated with the respiratory tract of patients infected by SARS-CoV-2 are poorly understood, so we have gathered some clinical information to facilitate the process of understanding. Ground-Glass Opacities (GGO) consolidation, pleural effusion and crazy-paving pattern are anomalies commonly found in pulmonary histopathology of COVID-19 patients [4,57,58].

Guan et al. (2020) [59], for example, demonstrated in a study of 47 patients with COVID-19 through CT scans (computed tomography) that 100% of them showed GGO, 89.36% crazy-paving and 63.83% had pulmonary consolidation. Pan et al., (2020) [60] analyzing pulmonary changes during the COVID-19 disease, from the initial diagnosis to recovery, used 82 chest CT scans from 21 patients (both sexes; aged 25 to 63 years). In the first 4 days, images showed severe but non-specific pulmonary anomalies and GGO. Over subsequent days (5-8 days) an increase in the mosaic paved pattern occurred. In the last stage (9-13 days), there was a consolidation predominantly in subpleural locations (mainly affecting the peripheral third of the lung) in the lower lobes. Similar results were found by Shi et al., (2020) [61] in a study involving 81 patients with COVID-19. The authors affirmed that pulmonary anomalies could be observed in asymptomatic patients and in more serious patients the evolution from focal unilateral to diffuse bilateral GGO occurred quickly, and it progressed to, or co-existed with, consolidations during the first 3 weeks.

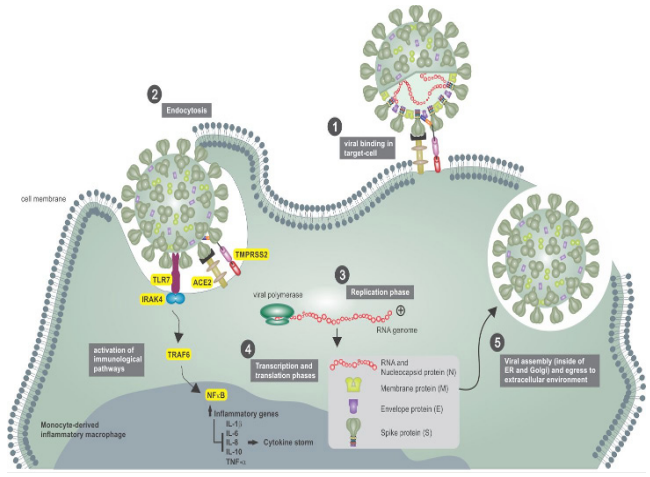

Figure 1: Infection mechanism by SARS-CoV-2 in epithelial and macrophage cells. 1) Virus attachment in target-cell is through ACE2 and TMPRSS2 proteins. 2) The endocytosis mechanism is activated and the virus is introduced into the cell also activating immunological pathways. In this way, inflammatory cytokines are produced by inflammatory gene activation and a cytokine storm can be triggered. 3) By the other way, the virus begins its replication phase. 4) Through the transcription and translation phases, the virus proteins and RNA are built into RE and Golgi compartments. 5) The final phase is characterized by egress of SARS-CoV-2 ready to infect another target-cell.

Pulmonary consolidation is a pathophysiological mechanism that may be present in patients with respiratory diseases, consisting of the replacement of body fluids, air by liquid or cells, or the coexistence of both in the alveoli [62]. In addition, pulmonary consolidation may be associated with the presence of diffuse alveolar damage and cellular infiltrates, and the mosaic paving pattern found in the results of chest CT may be related to hyperplasia of the inter- and intratubular interstices. These histopathological changes in pulmonary tissue, commonly found in cases of COVID-19, can also be observed in pediatric patients, even in milder cases of the disease (Figure 2).

Studies have often shown that children affected by the disease may have pulmonary anomalies, such as GGO and nodules, mostly located in the lower lobe of both lungs near the pleural area [63-65], in a study [66] with 20 pediatric patients, showed that 80% of those patients presented high levels of procalcitonin, a pre-hormone marker that may assist in the early detection of sepsis. This high level is not commonly observed in adult patients, demanding special attention for this group. Lung consolidation with surrounding halo was observed in 50% of those patients, suggesting parenchymal infection, a typical sign in pediatric patients also not often found in adults. Moreover, 15% presented pulmonary nodules and 60% GGO.

Regarding COVID-19 in children, another point is interesting to discuss, the multisystem inflammatory syndrome (MIS) in children. In a general manner, both adults and children with COVID-19 present GGO, GGO with consolidation and nodular opacities. However, bronchial wall thickening is more commonly found in pediatric patients [67]. Moreover, as mentioned above, some children present abnormal increase of inflammatory markers included serum lactate dehydrogenase, serum D-dimer, procalcitonin, thrombocytopenia, ferritin, creatine kinase, interleukin-6, cytokine storm and multiorgan failure. Clinical signals of MIS in children are dyspnea, vomiting, and diarrhea. White blood cell counts have significant lymphopenia (especially $CD16^+CD56^+$ natural killer cells) and changes were not found in platelets or liver function markers [68-70].

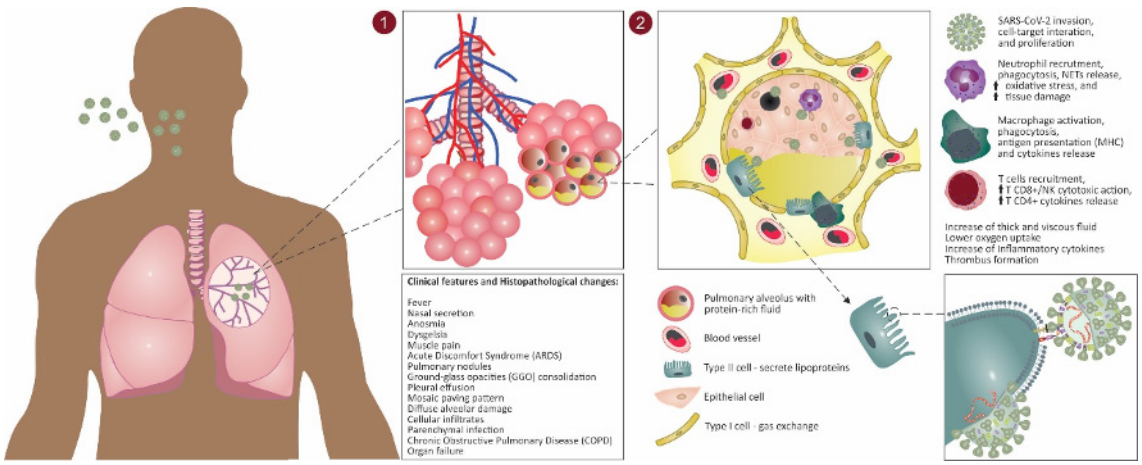

Figure 2: Briefing of SARS-CoV-2 infection in pulmonary tissues. 1) The virus invades the respiratory tract and goes to alveoli. 2) Type II cells and macrophages are targets of the virus, which is able to proliferate in those cells. Subsequently, the inflammatory site and its chemical signals attract new immunological cells to this microenvironment, promoting more oxidative stress, increase of fluid, release of neutrophil extracellular traps (NETs), and activating lymphocytes. These factors compromise the entire respiratory tract, leading to different clinical features and histopathological changes.

Pathological findings in a study by Wang et al. (2020) [71], investigating 151 COVID-19-infected patients, suggest that alveolar-arterial oxygen tension (A-aDO2) in terms of arterial blood gas tests is significantly affected by the abnormal presence of liver enzymes (A-aDO2 in patients with increased amount of liver enzymes: 202.0 vs. A-aDO2 in patients with normal liver enzymes: 27.6, p = 0.022). As for lung damage, postmortem biopsy of 2 patients in that study demonstrated the presence of diffuse alveolar damage, desquamation and hyaline membrane, multinucleated syncytial pneumocytes, as well as interstitial mononuclear infiltrates and hemorrhage. Peréz et al., (2020) [72] identified similar pulmonary histological findings in 14 of the 20 samples analyzed, with the addition of hyperplasia, and scattered thrombi.

These injuries found in the studies mentioned above indicate severe acute lung damage. It is also important point out that diffuse alveolar damage can be triggered by the presence of different pathogens in the host organism, including viruses. This type of lung injury is the same as that is found in patients with Acute Discomfort Syndrome (ARDS) and has been described in several autopsy studies of COVID-19 patients and in the acute (<11 days) and late stage of SARS [22,73-75].

More information is needed regarding the development of COVID-19 in patients with chronic lung disease. However, Chronic Obstructive Pulmonary Disease (COPD) in patients appears to be associated with a significant increase in the risk of developing severe complications of SARS-CoV-2 infection [76,77]. COPD is linked to decreased host immunity, increased local and systemic inflammation, exacerbated mucus production and promotion of microbiome imbalance [78]. More specifically for COPD patients affected by COVID-19, there is an increase in the levels of angiotensin-converting enzyme 2 (ACE2) [79].

Major treatments to prevent or decrease lung injuries in patients with COVID-19

From the studies analyzed, different treatment approaches were observed in patients affected by the disease, such as the use of a combination of antivirals (oseltamivir, arbidol or lopinavir/ritonavir) [80], immunoglobulin therapy, use of corticosteroids [81] and empirical antimicrobial therapy [66]. Those drugs have shown relevant results in reducing pulmonary complications and mortality rates in patients with COVID-19.

No pharmacological agent is capable of promoting an efficient humoral response against SARS-CoV-2 and we have few options for treatments to the lung injuries observed in COVID-19 patients. Thus, prophylactic, and supportive therapies can be used to reduce the progression of lung injury [82,83].

Some potential drugs, used to treat other viruses, have shown promising anti-SARS-CoV-2 effects. Studies have shown that Arbidol, an antiviral used to treat flu in Russia and China, is able to promote ACE2 receptor neutralization and the drugs Oseltamivir, Zanamivir and Peramivir, used to treat Influenza A and B, impair the SARS-CoV-2 flux among neighboring cells [84]. In addition, lopinavir/ritonavir, both HIV-1 protease inhibitors, are able to improve clinical signs during COVID-19 treatment and decrease the pulmonary damage by 3CLpro protease inhibition [85]. Azithromycin is an antibiotic that has a liposoluble mechanism of action and acts as a lysosomotropic agent, which are chemical agents that interfere in the process of the entire endocytic system [86]. It has been used against the disease due to its antimicrobial action and control of opportunistic multidrug-resistant bacterial infections [87].

Dexamethasone has been used in COVID-19 treatment due to its immunosuppressive action, inhibiting the activity of inflammatory cells such as neutrophils and promoting downregulation in Th1 and Th17 cytokines [88-90].

The immunotherapies against COVID-19 can be represented by Tocilizumab, a monoclonal antibody inhibitor of interleukin-6 and its signal transduction pathway observed in the cytokine storm; by Mepolizumab, a humanized anti-CD147 antibody used for asthma and which is able to block the entry of SARS-CoV-2 into the cell, and experimental studies with convalescent plasma from patients cured of COVID-19, to promote virus neutralization in the host organism [91-960].

Conclusion

SARS-CoV-2 can promote different reactions in the host organism. The virus has tropism to important physiological tar-

gets such as the neurological, respiratory, and gastrointestinal systems. Inside of those environments, the virus can promote an inflammatory reaction which can lead to death. The respiratory tract is the most affected system and presents differences between old and young people, requiring also different approaches in care. This study showed how virus infection occurs and the subsequent effects in the host. Unfortunately, we do not yet have the cure or specific treatment for COVID-19, but the significant advances in the knowledge of the disease have promoted better care of contaminated people and decreased deaths.

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