NCT
Neumología y Cirugía de Tórax

COVID-19 SERIES REVIEW

Immunopathology of SARS-CoV-2 infection

Inmunopatología de la infección por SARS-CoV-2

*José A. Choreño-Parra[1], Gustavo Ramírez-Martínez[1], and Joaquín A. Zúñiga-Ramos[1,2]**

[1]Laboratorio de Inmunobiología y Genética, Dirección de Investigación, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas; [2]Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey. Mexico City, Mexico

Abstract

The loss of human life as well as the global economic costs because of COVID-19 are devastating. Despite having effective diagnosis, antiviral treatment, and vaccines to prevent infection, it is essential to delve deeper into the pathogenic mechanisms in the SARS-CoV-2 virus and its recent variants infection. Despite advances, the understanding of the pathobiology of COVID-19 remains incomplete, particularly due to the emergence of SARS-CoV-2 variants, with augmented transmissibility and pathogenicity. The analysis of the host immune responses in lung and other tissues induced by this virus has allowed us to partially understand the pathogenesis of severe forms of COVID-19, and distinguish it from other respiratory infections. The complex interaction between cytokines, other immune mediators and viral factors results in exacerbated, poorly regulated, inflammation which contributes to tissue damage and the appearance of severe forms of the disease. In this review, we provide an overview of the immunological mechanisms in SARS-CoV-2 infection and their role in severe disease. We analyzed the role of matrix metalloproteinases, transforming growth factor beta and other key immunological mediators in lung damage. Furthermore, we discuss their possible implications in the post-COVID-19 sequelae and highlight the study of these molecules as biomarkers for the diagnosis, prognosis and treatment of convalescent patients with COVID-19.

Keywords: *COVID-19. Immunopathology. SARS-CoV-2. Cytokines. Immune response.*

Resumen

Los costos económicos y humanos de la COVID-19 son devastadores. A pesar de contar con diagnóstico efectivo, tratamiento antiviral y vacunas para prevenir la infección, es indispensable profundizar en los mecanismos patogénicos del SARS-CoV-2 y sus variantes recientes. Aun con importantes avances, la comprensión de la biopatología de la COVID-19 sigue siendo incompleta, en particular por la aparición de variantes del SARS-CoV-2 con mayor capacidad de transmisión y más patoge nicidad. El análisis de la respuesta inmunitaria del huésped en el pulmón y otros tejidos inducida por el virus ha permitido comprender, en parte, la patogénesis de las formas graves de COVID-19 y distinguirla de otras infecciones respiratorias. La compleja interacción de mediadores inmunitarios y factores virales da como resultado una inflamación exacerbada, poco regulada, la cual contribuye al daño a los tejidos y la aparición de formas graves de la enfermedad. En esta revisión se proporciona una descripción general de los mecanismos inmunitarios en la infección por SARS-CoV-2 y su papel en la enfermedad grave. Se analiza el papel de las metaloproteinasas de la matriz, el factor de crecimiento transformante beta y otros mediadores inmunitarios clave en el daño pulmonar. Además, se discuten las posibles implicaciones en las secuelas post-COVID-19 y se destaca el estudio de dichas moléculas como biomarcadores para el diagnóstico, el pronóstico y el tratamiento de pacientes convalecientes de COVID-19.

Palabras clave: *COVID-19. Inmunopatología. SARS-CoV-2. Citocinas. Respuesta inmunitaria.*

***Correspondence:**
Joaquín A. Zúñiga-Ramos
E-mail: joazu@yahoo.com

Date of reception: 06-06-2025
Date of acceptance: 10-06-2025
DOI: 10.24875/NCTE.M26000009

Available online: 03-02-2026
Neumol Cir Torax (Eng). 2025;84(1):57-68
www.revistanct.org.mx

Introduction

COVID-19, associated with SARS-CoV-2, has caused millions of deaths worldwide. Unfortunately, the pandemic that emerged in 2019 in the Chinese province of Wuhan has spread for several years and new variants of the virus have appeared, such as Omicron and some of its variants. At the beginning of the pandemic, in February 2020, at the National Institute of Respiratory Diseases Ismael Cosío Villegas (INER), one of the first confirmed cases for this virus in Mexico was diagnosed, although very likely there were other cases that may have coexisted with this index case in southern Mexico City. A wise decision by the authorities and institutions, such as INER and other national health institutes in Mexico, was to anticipate and be prepared in response to reports of this outbreak that rapidly spread through China and other countries, and an alert that was issued in the final weeks of 2019 by the authorities of the Mexican Ministry of Health. This allowed the establishment of operational strategies for diagnosis and management of respiratory disease cases by coronavirus and the reestablishment of reference and sample confirmation systems through molecular biology techniques. At that time, INER, by order of the authorities, was converted into a hospital specifically dedicated to the diagnosis and management of severe COVID-19 cases. However, this did not occur in parallel at other levels of care. The lack of early diagnosis and confinement of new cases and their contacts at that time were factors associated with higher morbidity and mortality. Even now, preventing the spread of SARS-CoV-2 remains a public health challenge. The lack of access to specific antivirals and vaccines has also contributed significantly to the development of severe forms and poor clinical outcomes in COVID-19 patients.

The extensive research and literature on the characteristics of SARS-CoV-2, its origin, its mechanisms of infection, replication and cellular tropism, as well as on host characteristics and risk factors for infection and development of severe forms of the disease, has allowed the development of a series of prophylactic, therapeutic, and infection control strategies with a speed never before seen in the history of applied medicine. Despite this, understanding of the viral and host factors that determine the clinical behavior of the disease is still incomplete. Through advanced genome expression analyses, molecular signatures associated with severe disease have been identified that are currently used as prognostic biomarkers to guide therapeutic decisions[1-8].

The mechanisms of immune response have been identified, both the innate response of cells such as macrophages and the adaptive response of T and B lymphocytes that determine poorly regulated inflammatory responses that can contribute to tissue damage. An example of this is the histopathological evidence of hemophagocytosis in bone marrow and reticuloendothelial organs, and the macrophage activation syndrome observed in virus-induced hemophagocytic lymphohistiocytosis, which suggests that the host's innate immune system plays a crucial role in the immunopathology of COVID-19. In fact, several studies have highlighted the efficacy of some immunomodulatory agents that allow attenuation of the inflammatory response to SARS-CoV-2 and prevent lung injury.

It is important to note that an increasing incidence of sequelae was observed in patients recovering from COVID-19, including pulmonary fibrosis, especially among those who recovered from severe disease. These complications could permanently affect the respiratory function of patients, negatively impacting their quality of life. Therefore, it is a priority to study the pathogenic processes underlying excessive inflammation, tissue injury, and tissue remodeling mechanisms, including the extracellular matrix, after SARS-CoV-2 infection.

In this review, we present an overview of the mechanisms of SARS-CoV-2 infection and the immune processes of protection and damage associated with different clinical forms of COVID-19.

Biology of SARS-CoV-2

SARS-CoV-2 is a member of the human coronavirus (HCoV) group, consisting of HCoV-229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, SARS-CoV-1, and MERS-CoV[1]. These pathogens are single-stranded RNA coronaviruses belonging to the Coronaviridae family. Some of them have caused a variety of respiratory diseases of varying severity in the past; for example, SARS-CoV-1 infected more than 8,000 people in Asia in 2003[2], and MERS-CoV (Middle East respiratory syndrome coronavirus) originating in Saudi Arabia in 2012 had high mortality rates[3,4].

Through comparative studies of viral genome sequences, HCoVs can be grouped into four genera: alpha, beta, gamma, and delta. The novel SARS-CoV-2 is a *Betacoronavirus* genetically related to a bat coronavirus called BatCoV RaTG13, as well as to SARS-CoV-1[5,6]. Furthermore, SARS-CoV-2 shares genetic identity with some coronavirus isolated from pangolins[7,8]. Therefore,

COVID-19 is believed to be a zoonotic disease originating in bats with the pangolin as a possible intermediate host. The SARS-CoV-2 genome consists of an RNA strand of 29,903 base pairs that encodes a replicase-transcriptase and the structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N)[5].

Mechanism of SARS-CoV-2 infection

The initial step in the SARS-CoV-2 infection process is the recognition of its receptor on the membrane of host cells. This process is mediated by the S protein, which recognizes human angiotensin-converting enzyme 2 (ACE2), the same receptor for the SARS-CoV-1 S protein[9-11]. This protein has two functional domains: the S1 domain contains the receptor binding domain (RBD) that binds to ACE2, while the S2 domain performs fusion of the viral membrane with the target cell membrane[11]. Therefore, the distribution of the ACE2 receptor in different organs and tissues is crucial for determining the infectivity and tropism of the virus.

A key aspect of the infection process is the activation of the S protein. This process is mediated by different host proteases that cleave the S protein at its S1/S2 and S'2 sites. This protein processing allows full functional activity of the S2 domain of the S protein, so it can fuse the viral and cellular membranes. For this purpose, just as SARS-CoV-1 does, SARS-CoV-2 employs transmembrane protease serine 2 (TMPRSS2)[9,12,13]. Interestingly, the proteases TMPRSS4 and cathepsin L[14,15], as well as the human CD147 receptor[16], also promote SARS-CoV-2 infection. Therefore, the tissue expression pattern of these elements may determine viral tropism, and even some drugs that inhibit the activity of these proteases or the CD147 receptor have been proposed as therapeutic agents to prevent and treat COVID-19[9,15,16].

Another factor involved in the SARS-CoV-2 infection process is phosphatidylinositol-3-phosphate kinase (PIKfyve, phosphoinositide kinase, FYVE-type)[15]. This enzyme regulates the production of phosphatidylinositol-3,5-bisphosphate, a phospholipid that participates in the endosome maturation process. In fact, apilimod, a potent PIKfyve inhibitor, reduces SARS-CoV-2 infectivity and could be a candidate for therapeutic purposes[15].

Once the virus manages to enter cells, viral replication begins with translation of the replicase-polymerase gene and assembly of the replication-transcription complex. This complex transcribes the genomic regions of the virus that encode structural proteins. In this way, new virions are produced in the endoplasmic reticulum and Golgi apparatus and are then released from the cell[1]. A particular characteristic of SARS-CoV-2 is that it possesses a polybasic furin cleavage sequence at the S1/S2 site, absent in other related coronaviruses[6,11]. This sequence is processed in the Golgi apparatus during the biosynthesis of the S protein of new virions[11]. Therefore, new SARS-CoV-2 virions possess an activated S protein ready to bind to the ACE2 receptor, without requiring the activity of other host proteases. Since virtually all human cells express furin, the insertion of a furin cleavage sequence could increase the transmission capacity and tropism of SARS-CoV-2.

Immune response against SARS-CoV-2

It is known that once SARS-CoV-2 achieves its first phase of replication in the upper respiratory tract, it spreads early to the lower respiratory tract, where it triggers a pronounced innate immune response that, in symptomatic cases, leads to the onset of clinical manifestations. Among the most frequent signs and symptoms observed in people with COVID-19 are fever, dry cough, fatigue, headache, diarrhea, dyspnea, anosmia, and loss of taste[17,18]. However, the disease has a heterogeneous clinical spectrum that includes asymptomatic cases, patients with mild manifestations, and patients with moderate to severe symptoms who develop acute respiratory failure, multiorgan dysfunction, and risk of fatality[19,20]. Fortunately, 85% of people infected with SARS-CoV-2 do not present clinical manifestations or suffer mild disease, while only 5-30% of cases may present a critical form21-23. This means that, in the vast majority of COVID-19 cases, the immune system is effective in controlling the infection and eliminating the virus. However, as already mentioned, the immune components that participate in protective responses against SARS-CoV-2 are still under study.

Traditionally, it is believed that defense against viral infection involves activation of mechanisms such as the production of type I interferons, which limit pathogen replication within infected cells and prevent its spread to healthy cells. Likewise, a robust humoral response with production of high-affinity antigen-specific antibodies is required to neutralize viral particles. Finally, cellular immunity plays a key role in identifying and lysing infected cells to eliminate intracellular reservoirs of the pathogen. All these mechanisms may be important for protection against COVID-19: the current evidence on the role of different immune factors during SARS-CoV-2 infection is summarized below.

Innate immune response

The innate immune system provides nonspecific protection against a wide variety of microorganisms. Its main components include epithelial and mucosal barriers, as well as humoral and cellular factors that together can recognize pathogens and initiate an inflammatory response that, in most cases, is sufficient to eliminate the infection. Mucosal barriers, such as the respiratory epithelium, have a series of mechanisms that prevent the adhesion of pathogens to the surface of epithelial cells and the initiation of infection. The respiratory mucosa is important because any alteration of its integrity, as in the case of people with chronic bronchial and pulmonary diseases, confers a greater risk of contracting COVID-19 and presenting a severe form of the disease.

Among the barrier mechanisms that protect the host is the production of mucus in the airways, which traps and allows the elimination of viruses and bacteria, as well as the production of surfactant in the alveolar epithelium, which contains some protein defense factors that allow neutralization of different microorganisms. Such is the case of surfactant protein D (SP-D), which can bind to the S protein of SARS-CoV-2 and neutralize it, inhibiting virus entry into epithelial cells[24]. However, some studies suggest that, in severe cases of the disease, the virus is able to counteract the effects of surfactant by suppressing SP-D production[25,26]. Other molecular elements produced by the respiratory epithelium that are suppressed during infection include some cytokines with antimicrobial properties, such as the chemokine CXCL17[27].

Once SARS-CoV-2 overcomes the barrier mechanisms, the next step in defense against the virus includes recognition of pathogen-associated molecular patterns, such as the viral single-stranded RNA or envelope proteins, by surface or intracellular pattern recognition receptors expressed on epithelial cells, alveolar macrophages, and other cells of the phagocytic-mononuclear system. Currently, not all innate immune receptors that recognize viral infection and initiate immune responses against SARS-CoV-2 are known. Since this virus is genetically related to SARS-CoV-1, it is presumed that both share infection mechanisms. In this sense, SARS-CoV-1 is recognized by Toll-like receptors (TLR) TLR3 and TLR4, which induce an immune reaction through the MyD88 and TRIF pathways[28,29]. Furthermore, SARS-CoV-1 triggers the production of interleukin (IL)-1β through inflammasome activation[30], with the aim of triggering an inflammatory response against the virus. In this regard, recent research indicates that TLR2 is another innate sensor capable of recognizing the virus through its binding to the envelope protein. Once this recognition occurs, TLR2 induces an inflammatory reaction through the MyD88-dependent signaling pathway[31]. Inflammasome activation is also likely to occur during SARS-CoV-2 infection, as high levels of IL-1β have been observed in patients with COVID-19, as described below[32]. Studies have shown that SARS-CoV-2 infection induces activation of NLRP3 inflammasomes and release of IL-1β in monocyte cultures and peripheral blood mononuclear cells from COVID-19 patients; however, excessive inflammasome activation can also lead to the development of severe forms of the disease[33,34].

Another crucial innate mechanism in defense against viral infections is the production of type I interferons (IFN) (primarily IFN-α and IFN-β), which bind to membrane surface receptor complexes known as the IFN-α/β receptor (IFNAR), consisting of IFNAR1 and IFNAR2 chains. Once bound to their receptor, type I IFNs can interfere with virus replication in host cells, activating different signaling pathways involving antiviral proteins such as PKR. *In vitro* studies indicate that type I IFN activity is effective in inhibiting SARS-CoV-2 replication in human cells[35]. In primate COVID-19 models, it has been observed that the IFN-mediated response is widely induced in the lungs and is crucial for defense against infection[36]. However, it is possible that suppression of type I IFN is a SARS-CoV-2 strategy to evade the innate antiviral immune response, as some studies have shown very low production of IFN-α and IFN-β in the plasma of Mexican and French patients with severe forms of COVID-19[37,38].

Finally, some cells of the innate immune system could play an important role in host defense. Among these cells are alveolar macrophages, which are presumed to be the first immune system cells to come into contact with SARS-CoV-2. Although these cells can recognize the virus, their response is manipulated by the pathogen[39,40]. Other crucial cells in defense against viral infections are NK (natural killer) cells, but their role in COVID-19 is not yet fully understood. In general, most studies characterizing the immunological profile of COVID-19 patients show that NK cells are decreased in the blood of those with severe disease[41,42]. It is believed that some deficiencies in the expression of NK cell receptors, such as NKG2C, could be associated with a higher risk of severe infection[43]. This suggests a possible protective role of NK cells in the immune response against SARS-CoV-2.

Adaptive immune response

The adaptive immune system provides a second line of defense against pathogens mediated by lymphocytes that possess antigen-specific receptors capable of undergoing genetic recombination. Therefore, adaptive immunity against viruses is capable of controlling infection effectively in most cases, through mechanisms specifically directed at the attacking pathogen. Adaptive immunity cells can promote protective responses against pathogens through the production of proinflammatory and antiviral cytokines by CD4+ helper T lymphocytes, or through the destruction of infected cells mediated by CD8+ cytotoxic T lymphocytes. These cells are believed to play a fundamental role in defense against SARS-CoV-2, as it has been observed that in other coronavirus infections, antigen-specific T lymphocytes are crucial for conferring protection. In fact, in people who were affected by SARS-CoV-1 in 2003 and survived the disease, it has been proven that different virus-specific memory T lymphocyte clones survive and are capable of responding to the virus up to 17 years after the primary infection44. Some studies suggest that individuals infected with SARS-CoV-2 develop CD4+ and CD8+ memory T lymphocytes, which persist in circulation for up to 8 months[45]. These memory responses also include follicular T lymphocytes, which are crucial for supporting B lymphocytes in the production of protective antibodies. Despite the above, current data on the role of cellular immunity in COVID-19 pathogenesis are still unclear and controversial. For example, some researchers have found that patients with severe forms of the disease have reduced numbers of T lymphocytes in circulation, but the antigen-specific T lymphocytes of these individuals develop more potent cytokine production responses[46].

The humoral response is also important for controlling viral infections in humans. In this sense, B cells from individuals infected with SARS-CoV-2 undergo immunoglobulin (Ig) class switching from IgM to higher affinity IgG and IgA. Thus, sera from patients recovering from COVID-19 contain anti-S protein IgG, IgM, and IgA antibodies and anti-nucleocapsid IgG antibodies. However, elevated titers of IgG and IgM antibodies have been found in patients with severe disease, which questions the protective capacity of antibody responses in COVID-19[47]. It is important to address the neutralizing capacity of antibodies induced by natural infection and vaccination, especially to improve the protective capacity of the humoral response elicited by vaccines. A study by Dan et al.[45] reveals that even when there are different kinetics of neutralizing antibodies against different components of SARS-CoV-2, antigen-specific memory B cells remain detectable for more than 8 months after symptom onset in some COVID-19 patients. Ellebedy et al. have observed different clones of long-lived plasma cells and memory B lymphocytes in the bone marrow and blood of people who recovered from COVID-19 up to 11 months after infection. These plasma cells and memory B lymphocytes can respond to secondary encounters with SARS-CoV-2 and produce neutralizing antibodies[48]. Finally, the importance of adaptive immune memory responses mediated by B lymphocytes for defense against COVID-19 is also highlighted in studies that have shown that the germinal center reaction in lymph nodes is abolished or altered in severely ill people after SARS-CoV-2 infection[49].

The defense mechanisms against SARS-CoV-2 are summarized in figure 1.

Immunopathology of severe forms of COVID-19

Cytokine storm and immunosuppression

People who progress to severe COVID-19 develop pneumonia within 10-20 days after symptom onset, which is associated with reduced oxygen saturation, acute respiratory distress syndrome, and prominent lung damage with ground-glass opacities. Acute respiratory distress syndrome is characterized by increased pulmonary permeability, severe hypoxemia, and non-cardiogenic pulmonary edema. These conditions alter the alveolar-capillary barrier and are a consequence of a systemic hyperinflammation process[50-52.]

For guiding immunotherapeutic interventions in critically ill patients, a better understanding of host factors involved in protective versus pathogenic immunity against SARS-CoV-2 is crucial. Unfortunately, what we understand today about the immunopathology of severe COVID-19 is a paradox: the adaptive response is hyperactive but unable to control the virus. In fact, COVID-19 patients present a profile of proinflammatory cytokines (IL-1β, IL-2, IL-6, IL-7, IL-8, IL-9, FGF, G-CSF, GM-CSF, IFN-γ, CXCL10, CCL2, CCL3, CCL4, PDGF, TNF-α, and VEGF) and regulatory cytokines (IL-10 and TGF-β)21[,53-55],53-55. This phenomenon has been termed “cytokine storm” and mediates tissue damage in COVID-19 patients who progress to severe disease[55,58]. Of these factors, IL-1β, IL-6, CXCL10, and TNF-α are the cytokines most strongly associated with tissue

damage in different organs, including the brain, due to their inflammatory properties. For example, IL-1β and IL-6 have been implicated in neurotoxicity associated with chimeric antigen receptor T cell therapy in patients with hematologic neoplasms[59,60]. These cytokines possess detrimental effects on endothelial function in various vascular niches, which may be implicated in the pathophysiology of thrombotic and neurological complications of COVID-19. In this regard, it is important to mention that other organs, in addition to the lungs, can also be affected by SARS-CoV-2, such as the brain, heart, intestines, kidneys, and liver, among others.

This generalized inflammatory reaction also induces the production of several acute phase reactants, such as C-reactive protein and ferritin in the liver, which further increase the release of inflammatory mediators and enrich cytokine release in patients with severe COVID-19[61,62]. In fact, elevated ferritin levels predict the risk of death in these patients[62]. Furthermore, the hyperinflammation observed in critically ill COVID-19 patients may be associated with the development of thrombotic events. In this sense, abnormal coagulation parameters, such as higher D-dimer levels and longer prothrombin and activated partial thromboplastin times, have been associated with unfavorable prognosis. These abnormal coagulation parameters occur shortly after hospitalization, and in some patients, fibrinogen concentrations and antithrombin activity decrease over time[63-65].

Interestingly, unlike other cytokine storm syndromes, the polyfunctional immune activation of COVID-19 is accompanied by lymphocytopenia and strong infiltration of immune cells, primarily mononuclear (lymphocytes and macrophages), into the lung interstitium[66-68]. In patients with severe SARS-CoV-2 infection, a wide range of immune cell subtypes is decreased in circulation. These cells include monocytes, dendritic cells, CD4+ and CD8+ T cells, and NK cells[41]. Furthermore, the few adaptive lymphocytes remaining in the blood express markers of functional exhaustion[69]. These data suggest that severe COVID-19 produces an immunosuppression state similar to that induced by sepsis[70]; it is also possible that robust recruitment of functional immune cells to SARS-CoV-2 infection sites may explain the leukocytopenia observed during COVID-19. A recent study by Remy et al.[71] has demonstrated that immunosuppression observed in COVID-19 is even more profound than that of critically ill patients with sepsis from other causes. These researchers observed that IFN-γ production by peripheral blood T cells from COVID-19 patients was impaired compared to T cells from healthy individuals and sepsis patients after stimulation with anti-CD3/anti-CD28 antibodies; reduced TNF-α production was found by stimulated monocytes from COVID-19 patients. These findings led the researchers to propose that the primary immune mechanism underlying COVID-19 morbidity and mortality is immunosuppression rather than hyperinflammation.

The immune profile in severe COVID-19 shows distinct features compared to other respiratory infections, such as pandemic influenza A (H1N1). Among the immune factors found only in critically ill COVID-19 patients, and not in influenza patients, are IFN-γ, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-1β, CCL11, VEGF, TWEAK, TSLP, MMP-1, and MMP-3[38]. These molecules could play a specific role in COVID-19 and are potential targets for reducing its morbidity and mortality. It is noteworthy that higher levels of Th2 cytokines, particularly IL-4 and IL-5, could inhibit protective Th1 antiviral responses in COVID-19 patients. Therefore, the lack of immune balance in the type of effector response is another crucial determinant of the collapse of protective immunity in the host against SARS-CoV-2. This Th2-skewed response can generate interstitial infiltrates of Th2 cells, neutrophils, eosinophils, and type 2 innate lymphoid cells, which mediate pulmonary inflammation and tissue damage. Critically ill COVID-19 patients often show interstitial pulmonary infiltrates, some of which resemble various forms of progressive interstitial lung disease, such as cryptogenic organizing pneumonia and nonspecific interstitial pneumonia[21,72-74]. These harmful effects of Th2 responses could also explain the abnormalities in lung function and progression to pulmonary fibrosis observed in more than 45% of COVID-19 patients discharged from hospitals[75], particularly elderly subjects. Therefore, it would be of great interest to characterize the cytokine profile of COVID-19 patients who subsequently develop any form of interstitial lung disease, as they would benefit from specific antifibrotic therapies.

Neutrophil infiltration and lung damage

A variety of inflammatory mediators released excessively during severe SARS-CoV-2 infection function to mediate the recruitment of myeloid cells to sites of inflammation. One of the cells that heavily infiltrate the lungs of patients with severe COVID-19 is neutrophils, probably following a chemotactic gradient generated by high concentrations of IL-8, CXCL10, CCL2, and CCL3 released into circulation[21,53-55]. Neutrophils are the

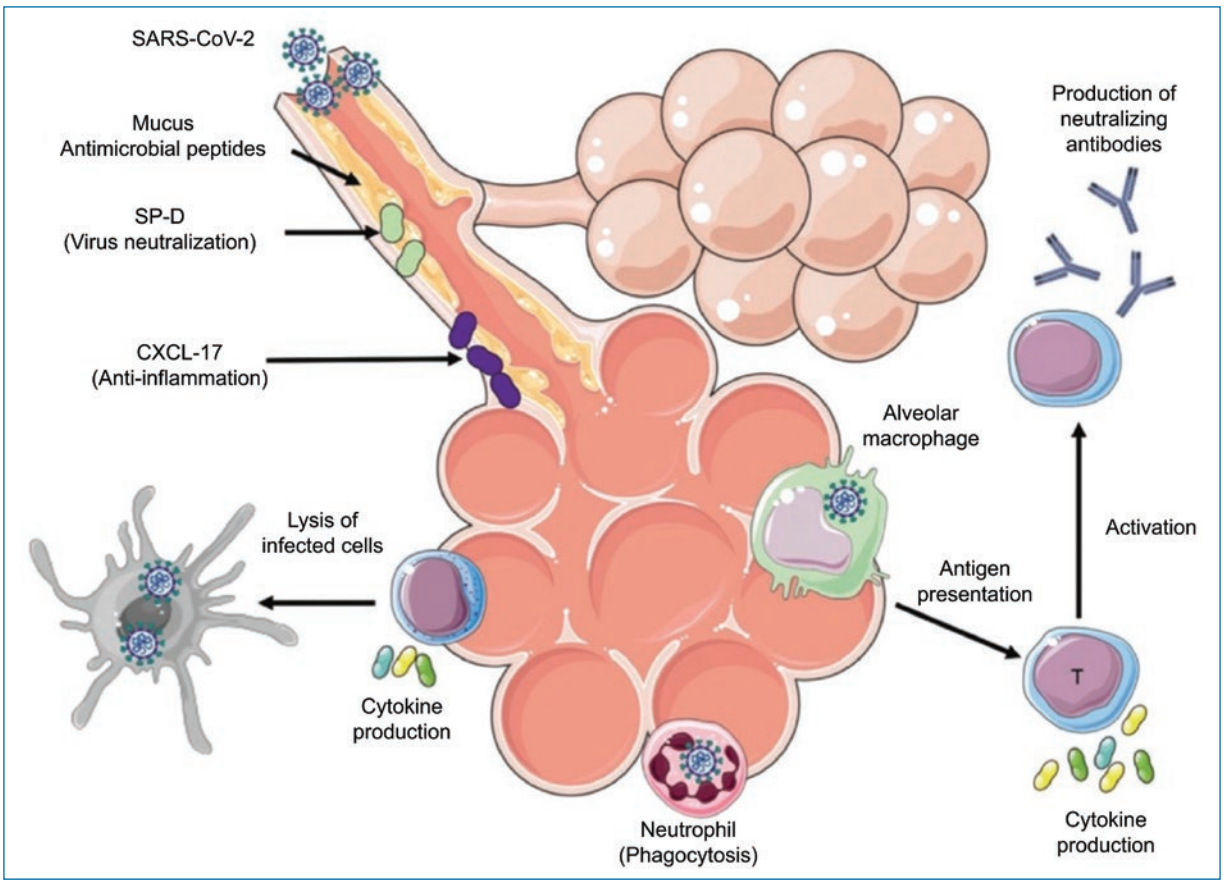

Figure 1. Defense mechanisms of immune immunity against SARS-CoV-2. NK: natural killer cell; SP-D, surfactant protein D.

most abundant leukocytes in blood and have a short half-life. Due to their mobility, they can easily infiltrate inflamed tissues and contribute to the defense response against different microorganisms. Their main function is to mediate phagocytosis of pathogens, as well as release cytokines and proteolytic substances contained in their granules. Neutrophils can exert a protective role in defense against viral infections[76]; it is well known that neutrophils are always present in the lungs of patients with different respiratory infections associated with the development of acute respiratory distress syndrome, especially due to their capacity for degranulation and lysis, promoting tissue damage.

In line with these findings, in animal models of macaques, it has been observed that neutrophils infiltrate the lung rapidly during SARS-CoV-2 infection[36]. This is also observed in COVID-19 patients, in whom it has been found that neutrophilia and a higher neutrophil ratio is a distinctive characteristic of severe cases and those occurring in elderly patients, associated with unfavorable prognosis[36,77]. In patients who died from severe COVID-19, intense neutrophil infiltration has been observed in pulmonary capillaries, extravasation into alveolar spaces, and neutrophilic mucositis in the airways[78]. Within sites of SARS-CoV-2 infection, neutrophil degranulation results in the release of proteases capable of amplifying the inflammatory response. For instance, cathepsin G stimulates increased production of cytokines and chemokines, promoting recruitment of monocytes, macrophages, and neutrophils, as well as increased endothelial and epithelial permeability[36,79]. Cathepsin G also activates some matrix metalloproteinases (MMP)[80], initiating the alteration of mechanisms that regulate the composition of the extracellular matrix (ECM) and are associated with the appearance of sequelae characteristic of post-COVID-19 syndrome, as described below. Finally, neutrophils are a source of excess extracellular traps, which further exacerbate the cytokine storm and perpetuate a vicious cycle of inflammation and neutrophil recruitment to the lung[78].

Therefore, the search for new strategies to reduce COVID-19 morbidity and mortality focusing on interrupting neutrophil recruitment to the lung and limiting lung damage induced by the contents of these cells' granules is justified.

Immune mechanisms associated with post-COVID-19 syndrome

Post-COVID-19 syndrome or post-acute sequelae of COVID-19 (PASC) is defined by disease persistence for more than 28 days after symptom onset. Various longitudinal studies suggest that this process can be observed in 30% to 80% of individuals who suffer SARS-CoV-2 infection. In this regard, a notable characteristic of the COVID-19 convalescent phase is that many patients who suffered severe lung damage remain with permanent pulmonary dysfunction. Many of the chronic deleterious effects of COVID-19 are related to pulmonary fibrosis following injury. The mechanisms underlying the development of these complications have not been well defined until now. In patients with severe pneumonia of other etiologies, severe epithelial and endothelial damage accompanied by extensive fibrosis has frequently been observed. Patients presenting greater fibrotic changes are those who required prolonged periods of mechanical ventilation (~12 days) and developed more severe systemic organ failure[50,81]. Interestingly, pulmonary fibrosis is also a long-term sequela in patients with pandemic influenza A (H1N1). Several mechanisms, including barotrauma associated with mechanical ventilation, oxygen toxicity, and hyperinflammation, are crucial in determining sequelae in these patients after recovery from severe disease[82]. These factors cause mild epithelial lesions that are not adequately repaired, leading to fibroblast hyperactivation, excessive ECM deposition, and pulmonary parenchyma remodeling[83].

It is not understood to what extent mechanical injury and hyperinflammation contribute to pulmonary fibrosis in COVID-19. A significant number of severely ill COVID-19 patients with acute respiratory distress syndrome require critical care and respiratory assistance, and those who survive show persistent ground-glass opacities, chronic pulmonary dysfunction, and pulmonary fibrosis that affect their quality of life[84-86]. On the other hand, hyperinflammation in severe COVID-19 also includes the release of inflammatory chemokines such as CCL2, CCL3, and IP-10. These chemotactic factors are associated with dysregulated activation of cells in the mononuclear phagocyte compartment, which could further promote hyperinflammation in COVID-19 patients. In fact, bronchoalveolar fluid from severe COVID-19 patients contains high concentrations of CCL2, CCL3, CCL4, and CCL7, and a decreased proportion of tissue-resident alveolar macrophages, but large amounts of monocyte-derived inflammatory macrophages[87]. Interestingly, this macrophage subpopulation expresses RNA transcripts that have been previously associated with tissue repair and promotion of fibrosis in liver cirrhosis[88,89].

Surprisingly, during fibrosis, many types of collagen can modulate cellular functions and the physiological processes of leukocytes and parenchymal cells. Furthermore, in response to inflammation, ECM degradation by MMPs generates small peptides that can act as chemotactic factors for leukocytes, thereby increasing disease immunopathology. These mechanisms further promote MMP hyperactivity, causing progressive destruction of pulmonary parenchyma[90]. Therefore, MMPs and other ECM components could act as readouts of ongoing profibrotic activity and lung injury in severe COVID-19 patients, as discussed below.

An important controversy that has recently emerged is whether pulmonary fibrosis is an exclusive sequela of severe SARS-CoV-2 infection or whether patients with mild to moderate disease are also at risk. In this regard, evidence from recovering COVID-19 patients, both adult and pediatric, suggests that older patients and those with more severe disease develop fibrosis[91-93]. Similarly, a study conducted in Italy between March and April 2020 found that patients with non-severe manifestations showing pulmonary opacities showed complete remission of these lesions and no fibrosis during follow-up. In contrast, Dadhwal et al.[94] reported five cases of patients with asymptomatic or mild symptomatic COVID-19 presenting dyspnea and chest images suggesting resolution of ground-glass opacities who subsequently developed fibrosis 4 to 8 weeks after diagnosis.

Despite all the studies conducted to understand the immunopathological bases of pulmonary and extrapulmonary chronic sequelae observed in patients with PASC or prolonged COVID-19, their etiology remains unclear. One of the essential characteristics of PASC is viral persistence in various tissues, such as lung, central nervous system, kidneys, and intestine[95,96]. It has been suggested that patients who develop PASC may have aberrant, poorly regulated immune responses, and overactivation of cell populations such as myeloid cells and T and B lymphocytes that infiltrate tissues, generating tissue scenarios rich in

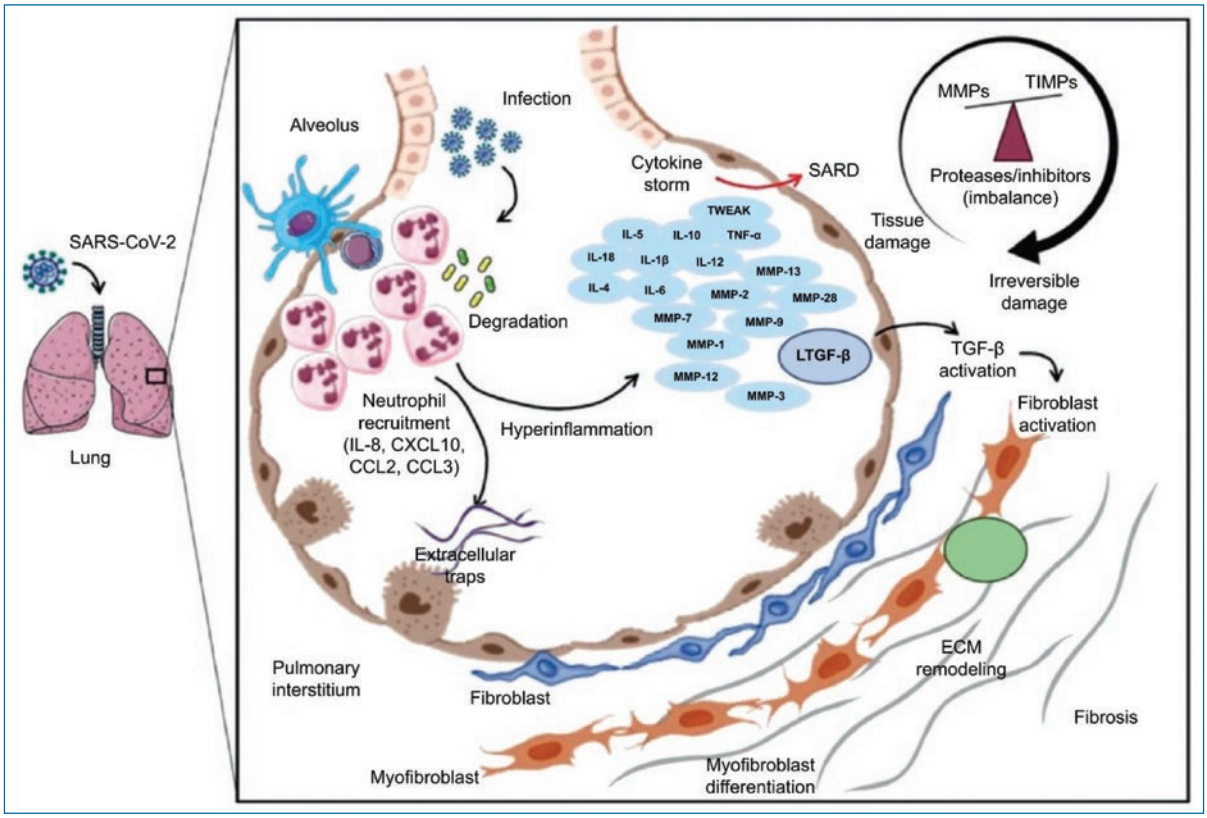

Figure 2. Immunopathology of severe forms of COVID-19 and their sequelae. ECM: extracellular matrix; MMPs: matrix metalloproteinases; ARDS: acute respiratory distress syndrome; TIMPs: tissue inhibitors of MMPs.

proinflammatory or profibrotic cytokines, as is the case of post-COVID-19 pulmonary fibrosis, characterized by elevation of TGF-β and hyperactivation of myofibroblasts producing extracellular matrix[97].

In post-COVID-19 syndrome, persistent dyspnea, frequently accompanied by fatigue, chest discomfort, and cough, affects approximately 20% of patients 3 months after the initial SARS-CoV-2 infection[98]. Furthermore, a considerable number of patients, particularly those who overcome COVID-19 acute respiratory distress syndrome and require treatment with high-flow nasal oxygen or mechanical ventilation, present chronic pulmonary sequelae, as demonstrated by pulmonary function tests and radiological changes on chest computed tomography, such as ground glass and fibrosis[99]. Interestingly, some studies have shown that the use of antifibrotic drugs, such as pirfenidone and nintedanib, has positive clinical and functional effects for treating pulmonary sequelae of COVID-19[100,101].

Post-viral pulmonary sequelae are not exclusive to SARS-CoV-2 and have been described after several other respiratory viral infections, possibly also associated with inflammatory alterations that lead to chronic pulmonary damage.

Taken together, these data highlight the need for further research studies in patients recovering from COVID-19 to establish better preventive, therapeutic, and rehabilitation strategies against pulmonary fibrosis. For these purposes, new biomarkers with predictive value will also be required to allow early detection of lung lesions and fibrosis.

The mechanisms involved in the pathophysiology of severe forms of COVID-19 and their sequelae are summarized in figure 2.

Conclusions

The spread of SARS-CoV-2 in various countries has caused possibly the greatest global health crisis of the last 100 years. Although the vast majority of COVID-19 cases present asymptomatically or with mild manifestations, sometimes the disease has severe manifestations, such as viral pneumonia that can evolve to respiratory failure and death in a short period of time. The natural evolution of infection by this virus includes

an initial stage of respiratory epithelium infection and viral replication that can be followed by a second stage of immunopathology driven by a hyperinflammatory response that has systemic manifestations. The syndrome shares overlapping features with virus-induced hemophagocytic lymphohistiocytosis, including evidence of macrophage activation with a cytokine storm, and impairment of T lymphocyte and NK cell function. Understanding the pulmonary and extrapulmonary immunopathology of COVID-19 will enable the identification of biomarkers in an attempt to classify the disease as mild, moderate, severe, and critical, as well as for the development of new therapeutic strategies aimed at reducing generalized and pulmonary hyperinflammation in severe COVID-19.

Funding

The Laboratory of Immunobiology and Genetics of the National Institute of Respiratory Diseases Ismael Cosío Villegas received funding from the E022 fund for research from the Ministry of Health.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of people and animals. The authors declare that no experiments were conducted on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data from patients nor require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence for writing this manuscript.

References

1. Lim YX, Ng YL, Tam JP, Liu DX. Human coronaviruses: a review of virus-host interactions. Diseases. 2016;4:26.
2. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;348:1986-94.
3. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814-20.
4. de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol. 2013;87:7790-2.
5. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-3.
6. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med. 2020;26:450-2.
7. Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr Biol. 2020;30:1346-51.e2.
8. Liu P, Chen W, Chen J-P. Viral metagenomics revealed sendai virus and coronavirus infection of Malayan pangolins (Manis javanica). Viruses. 2019;11:979.
9. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181: 271-80.e8.
10. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;426:450-4.
11. Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 Spike glycoprotein. Cell. 2020;181:281-92.e6.
12. Matsuyama S, Nao N, Shirato K, Kawase M, Saito S, Takayama I, et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. Proc Natl Acad Sci U S A. 2020;117:7001-3.
13. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol. 2011;85:4122-34.
14. Zang R, Gomez Castro MF, McCune BT, Zeng Q, Rothlauf PW, Sonnek NM, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Sci Immunol. 2020;5:eabc3582.
15. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat Commun. 2020;11:1620.
16. Wang K, Chen W, Zhang Z, Deng Y, Lian J-Q, Du P, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. Signal Transduct Target Ther. 2020;5:283.
17. Huang C, Wang Y , Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
18. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10:102-8.
19. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-9.
20. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 Patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323:1574-81.
21. Hernández-Cárdenas CM, Choreño-Parra JA, Torruco-Sotelo C, Jurado F, Serna-Secundino H, Aguilar C, García-Olazarán JG, et al. Clinical Risk Factors for Mortality Among Critically Ill Mexican Patients With COVID-19. Front Med (Laussane). 2021;8:699607.
22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382:1708-20.
23. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-9.
24. Hsieh M-H, Beirag N, Murugaiah V, Chou Y-C, Kuo W-S, Kao H-F, et al. Human surfactant protein D binds spike protein and acts as an entry inhibitor of SARS-CoV-2 pseudotyped viral particles. Front Immunol. 2021;12:641360.
25. Choreño-Parra JA, Jiménez-Álvarez LA, Ramírez-Martínez G, Cruz-Lagunas A, Thapa M, Fernández-López LA, et al. Expression of surfactant protein D (SP-D) distinguishes severe pandemic influenza A(H1N1) from COVID-19. J Infect Dis. 2021;224:21-30.
26. Islam ABMMK, Khan MA. Lung transcriptome of a COVID-19 patient and systems biology predictions suggest impaired surfactant production which may be druggable by surfactant therapy. Sci Rep. 2020;10:19395.
27. Choreño-Parra JA, Jiménez-Álvarez LA, Ramírez-Martínez G, Sandoval-Vega M, Salinas-Lara C, Sánchez-Garibay C, et al. CXCL17 is a specific diagnostic biomarker for severe pandemic influenza A(H1N1) that predicts poor clinical outcome. Front Immunol. 2021;12:633297.
28. Sheahan T, Morrison TE, Funkhouser W, Uematsu S, Akira S, Baric RS, et al. MyD88 is required for protection from lethal infection with a mouse adapted SARS-CoV. PLoS Pathog. 2008;4:e1000240.
29. Totura AL, Whitmore A, Agnihothram S, Schafer A, Katze MG, Heise MT, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio. 2015;6:e00638-15.
30. Shi CS, Nabar NR, Huang NN, Kehrl JH. SARS-coronavirus open reading frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov. 2019;5:101.
31. Zheng M, Karki R, Williams EP, Yang D, Fitzpatrick E, Vogel P, et al. TLR2 senses the SARS-CoV-2 envelope protein to produce inflammatory cytokines. Nat Immunol. 2021;22:829-38.

32. Ong EZ, Chan YFZ, Leong WY, Lee NMY, Kalimuddin S, Haja Mohideen SM, et al. A dynamic immune response shapes COVID-19 progression. Cell Host Microbe. 2020;27:879-82.e2.
33. Ferreira AC, Soares VC, de Azevedo-Quintanilha IG, Dias SdSG, Fintelman- Rodrigues N, Sacramento CQ, et al. SARS-CoV-2 engages inflammasome and pyroptosis in human primary monocytes. Cell Death Discov. 2021;7:43.
34. Rodrigues TS, de Sá KSG, Ishimoto AY, Becerra A, Oliveira S, Almeida L, et al. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med. 2021;218:e20201707.
35. Mantlo E, Bukreyeva N, Maruyama J, Paessler S, Huang C. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Res. 2020;179:104811.
36. Rosa BA, Ahmed M, Singh DK, Choreño-Parra JA, Cole J, Jiménez-Álvarez LA, et al. IFN signaling and neutrophil degranulation transcriptional signatures are induced during SARS-CoV-2 infection. Commun Biol. 2021;4:290.
37. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020;369:718-24.
38. Choreño-Parra JA, Jiménez-Álvarez LA, Cruz-Lagunas A, Rodríguez-Reyna TS, Ramírez-Martínez G, Sandoval-Vega M, et al. Clinical and immunological factors that distinguish COVID-19 from pandemic influenza A(H1N1). Front Immunol. 2021;12:593595.
39. Dalskov L, Møhlenberg M, Thyrsted J, Blay-Cadanet J, Poulsen ET, Folkersen BH, et al. SARS-CoV-2 evades immune detection in alveolar macrophages. EMBO Rep. 2020;21:e51252.
40. Lv J, Wang Z, Qu Y, Zhu H, Zhu Q, Tong W, et al. Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages. Cell Discov. 2021;7:24.
41. Wang W, Su B, Pang L, Qiao L, Feng Y, Ouyang Y, et al. High-dimensional immune profiling by mass cytometry revealed immunosuppression and dysfunction of immunity in COVID-19 patients. Cell Mol Immunol. 2020;17:650-2.
42. Maucourant C, Filipovic I, Ponzetta A, Aleman S, Cornillet M, Hertwig L, et al. Natural killer cell immunotypes related to COVID-19 disease severity. Sci Immunol. 2020;5:eabd6832.
43. Vietzen H, Zoufaly A, Traugott M, Aberle J, Aberle SW, Puchhammer- Stöckl E. Deletion of the NKG2C receptor encoding KLRC2 gene and HLA-E variants are risk factors for severe COVID-19. Genet Med. 2021; 23:963-7.
44. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020;584:457-62.
45. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371:eabf4063.
46. Anft M, Paniskaki K, Blázquez-Navarro A, Doevelaar A, Seibert FS, Hoelzer B, et al. COVID-19 progression is potentially driven by T cell immunopathogenesis. medRxiv. 2020:2020.04.28.20083089.
47. Weisberg SP, Zhu Y, Baldwin MR, Lin WH, Wontakal S, Szabo PA, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. 2021;22:25-31.
48. Turner JS, Kim W, Kalaidina E, Goss CW, Rauseo AM, Schmitz AJ, et al. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. Nature. 2021;595:421-5.
49. Kaneko N, Kuo HH, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, et al. Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. Cell. 2020;183:143-57.e13.
50. Cabrera-Benítez NE, Laffey JG, Parotto M, Spieth PM, Villar J, Zhang H, et al. Mechanical ventilation-associated lung fibrosis in acute respiratory distress syndrome: a significant contributor to poor outcome. Anesthesiology. 2014;121:189-98.
51. Guillamat-Prats R, Camprubí-Rimblas M, Bringué J, Tantinyà N, Artigas A. Cell therapy for the treatment of sepsis and acute respiratory distress syndrome. Ann Transl Med. 2017;5:446.
52. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:818-24.
53. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130:2620-9.
54. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:332-9.
55. Yang Y, Shen C, Li J, Yuan J, Yang M, Wang F, et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. medRxiv. 2020:2020.03.02.20029975.
56. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34:327-31.
57. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020;19:102537.
58. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). medRxiv. 2020.02.10.20021832.
59. Gust J, Hay KA, Hanafi LA, Li D, Myerson D, González-Cuyar LF, et al. Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T Cells. Cancer Discov. 2017;7:1404-19.
60. Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. Cancer Discov. 2018;8:958-71.
61. Meng J, Ma Y, Jia J, Wang M, Teng J, Shi H, et al. Cytokine storm in coronavirus disease 2019 and adult-onset still's disease: similarities and differences. Front Immunol. 2021;11:603389.
62. Ruscitti P, Berardicurti O, Barile A, Cipriani P, Shoenfeld Y, Iagnocco A, et al. Severe COVID-19 and related hyperferritinaemia: more than an innocent bystander? Ann Rheum Dis. 2020;79:1515-6.
63. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7.
64. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-7.
65. Becker R. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis. 2020;50:54-67.
66. Pacheco-Hernández LM, Ramírez-Noyola JA, Gómez-García IA, Ignacio-Cortés S, Zúñiga J, Choreño-Parra JA. Comparing the Cytokine Storms of COVID-19 and Pandemic Influenza. J Interferon Cytokine Res. 2022;42(8):369-392.
67. Ahmadpoor P, Rostaing L. Why the immune system fails to mount an adaptive immune response to a COVID-19 infection. Transpl Int. 2020;33:824-5.
68. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368:473-4.
69. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol. 2020;11:827.
70. Ono S, Tsujimoto H, Hiraki S, Aosasa S. Mechanisms of sepsis-induced immunosuppression and immunological modification therapies for sepsis. Ann Gastroenterol Surg. 2018;2:351-8.
71. Remy KE, Mazer M, Striker DA, Ellebedy AH, Walton AH, Unsinger J, et al. Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. JCI Insight. 2020;5:e140329.
72. Polak SB, Van Gool IC, Cohen D, von der Thusen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol. 2020;33:2128-38.
73. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis. 2020;20:1135-40.
74. Cui N, Zou X, Xu L. Preliminary CT findings of coronavirus disease 2019 (COVID-19). Clin Imaging. 2020;65:124-32.
75. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;55:2001217.
76. Camp JV, Jonsson CB. A role for neutrophils in viral respiratory disease. Front Immunol. 2017;8:550.
77. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol. 2020;17:533-5.
78. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. J Exp Med. 2020;217:e20200652.
79. Steinwede K, Maus R, Bohling J, Voedisch S, Braun A, Ochs M, et al. Cathepsin G and neutrophil elastase contribute to lung-protective immunity against mycobacterial infections in mice. J Immunol. 2012;188:4476-87.
80. Son ED, Kim H, Choi H, Lee SH, Lee JY, Kim S, et al. Cathepsin G increases MMP expression in normal human fibroblasts through fibronectin fragmentation, and induces the conversion of proMMP-1 to active MMP-1. J Dermatol Sci. 2009;53:150-2.
81. Ichikado K, Muranaka H, Gushima Y, Kotani T, Nader HM, Fujimoto K, et al. Fibroproliferative changes on high-resolution CT in the acute respiratory distress syndrome predict mortality and ventilator dependency: a prospective observational cohort study. BMJ. 2012;2:e000545.
82. Xing ZH, Sun X, Xu L, Wu Q, Li L, Wu XJ, et al. Thin-section computed tomography detects long-term pulmonary sequelae 3 years after novel influenza A virus-associated pneumonia. Chin Med J (Engl). 2015;128:902-8.

83. Yang J, Pan X, Wang L, Yu G. Alveolar cells under mechanical stressed niche: critical contributors to pulmonary fibrosis. Mol Med. 2020; 26:95.
84. Ahmad Alhiyari M, Ata F, Islam Alghizzawi M, Bint I Bilal A, Salih Abdulhadi A, Yousaf Z. Post COVID-19 fibrosis, an emerging complicationof SARS-CoV-2 infection. IDCases. 2020;23:e01041.
85. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8: 807-15.
86. Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, et al. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. J Infect. 2020;80:394-400.
87. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med. 2020;26:842-4.
88. Merad M, Martin JC. Pathological inflammation in patients with COVID19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20:355-62.
89. Ramachandran P, Dobie R, Wilson-Kanamori JR, Dora EF, Henderson BEP, Luu NT, et al. Resolving the fibrotic niche of human liver cirrhosis at single-cell level. Nature. 2019;575:512-8.
90. Karsdal MA, Nielsen SH, Leeming DJ, Langholm LL, Nielsen MJ, Manon-Jensen T, et al. The good and the bad collagens of fibrosis. Their role in signaling and organ function. Adv Drug Deliv Rev. 2017;121:43-56.
91. Chu WC, Li AM, Ng AW, So HK, Lam WW, Lo KL, et al. Thin-section CT 12 months after the diagnosis of severe acute respiratory syndrome in pediatric patients. AJR Am J Roentgenol. 2006;186:1707-14.
92. Antonio GE, Wong KT, Hui DS, Wu A, Lee N, Yuen EH, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. Radiology. 2003;228:810-5.
93. Ooi GC, Khong PL, Müller NL, Yiu WC, Zhou LJ, Ho JC, et al. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. Radiology. 2004;230:836-44.
94. Dadhwal R, Sharma M, Surani S. Restrictive lung disease in patients with subclinical coronavirus Infection: are we bracing ourselves for devastating sequelae? Cureus. 2021;13:e12501.
95. Rogliani P, Calzetta L, Coppola A, Puxeddu E, Sergiacomi G, D'Amato D, et al. Are there pulmonary sequelae in patients recovering from COVID-19? Respir Res. 2020;21:286.
96. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27:601-15.
97. Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol. 2022;23: 210-6.
98. Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Uribe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Chron Respir Dis. 2021;18:14799731211002240.
99. Mylvaganam RJ, Bailey JI, Sznajder JI, Sala MA; Northwestern Comprehensive COVID Center Consortium. Recovering from a pandemic: pulmonary fibrosis after SARS-CoV-2 infection. Eur Respir Rev. 2021;30: 210194.
100. Shu Y, He L, Liu C. Impact of anti-fibrotic medications on post-COVID-19 pulmonary fibrosis: a systematic review and meta-analysis. Int J Infect Dis. 2024;147:107193.
101. Sansores RH, Ramírez-Venegas A, Montiel-López F, Domínguez-Arellano S, Alva-López LF, Falfán-Valencia R, et al. Prolonged-release pirfenidone in patients with pulmonary fibrosis as a phenotype of post-acute sequelae of COVID-19 pneumonia. Safety and efficacy. Respir Med. 2023;217: 107362.