

Is Interstitial Macrophage Mainly Responsible for Lung Injury in SARS-CoV-2 Infection?

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Abstract

The course of the COVID-19 pandemic has led to high mortality rates worldwide, which justifies the development of various research studies aimed at elucidating the physiopathological mechanisms involved in the development of lung injury associated with this disease. The angiotensin-converting enzyme 2 (ACE2) receptor plays a leading role as the viral anchoring point necessary for viral replication to begin, so a thorough understanding of the regulatory mechanisms of this receptor is vital. Similarly, the distribution of ACE2 will justify the injury caused by SARS-CoV-2. Macrophages play a more significant role in lung injury since they allow the SARS-CoV-2 virus to reach tissues lacking ACE2 receptors and cause significant tissue damage. Therefore, all factors that influence macrophage migration and mobilization will be considered risk factors for the development of severe lung injury in COVID-19.

Keywords: COVID-19, SARS-CoV-2, ACE2, Macrophage migration, Lung injury, IL-6, Type 2 alveolar cells, Macrophage activation, Cytokine storm

Introduction

The development of the COVID-19 pandemic has led to a high number of deaths from respiratory failure due to the magnitude of lung damage. However, microbiological studies conducted to understand the behavior of the SARS-CoV-2 virus have demonstrated the scarcity of viral receptors in lung tissue, which suggests that there must be different mechanisms that allow for cellular entry and associated injury in this infection. In addition, it has been shown that during the phase of respiratory failure, viral replication is almost undetectable, suggesting adjuvant mechanisms that favor definitive lung injury.

Understanding the mechanisms involved in the development of respiratory failure responsible for the mortality associated with this disease would be beneficial for deploying new measures to contain the course of the pandemic, from preventive approaches to new therapeutic options during critical phases of this disease.

Physiopathological Approach

SARS-CoV-2 infection results in the manifestation of severe respiratory failure, which can ultimately be fatal. This fulminant respiratory clinical picture constitutes the last step of SARS-CoV-2 infection, which is why most patients do not develop it.

The entry of the SARS-CoV-2 pathogen into the body is followed by binding to its receptor, the angiotensin-converting enzyme 2 (ACE2) membrane protein [1].

This protein is widely expressed by the gastrointestinal system, followed by the urinary and reproductive systems. A striking fact is the low expression of this protein in the respiratory system, where histological studies have shown its presence in the nasopharynx and bronchi, and a low presence in lung parenchyma. When the search is performed as mRNA sequencing, the results continue to show the enzyme's great predilection for the gastrointestinal system and a low presence of mRNA in type 2 alveolar cells in the respiratory system.

In addition to tissue expression, this enzyme also has expression in the membranes of macrophages and dendritic cells, which play an important role in the development of respiratory failure [2].

After the binding of the SARS-CoV-2 virus, through the S protein, to the ACE2 transmembrane receptor, it requires binding with the type 2 transmembrane serine protease (TMPRSS2) to facilitate entry into the host cell. Similarly, the distribution of this protease TMPRSS2 is widely expressed in the gastrointestinal system, urinary system, and reproductive system, with low expression, almost absent, in the respiratory system. The mRNA sequencing demonstrates its presence in type 2 alveolar cells [3-5].

Other target cells for SARS-CoV-2 infection are macrophages and dendritic cells, and they play an important role in recognition by the immune system. Initially, the reticuloendothelial system, monocyte-macrophage, recognizes the entry of the SARS-CoV-2 virus and the binding with its specific receptor and initiates the response. Macrophages and dendritic cells are responsible for phagocytosis and antigen presentation so that a specific cellular response can be developed by specialized Th1 and Th2 lymphocyte signaling [6].

Role of Macrophage

Macrophages are widely distributed cells throughout the body and are specialized in some tissues. In the respiratory system, there are two types: M1, classically activated macrophages mediated by PAMPs (Pathogen Associated Molecular Patterns) as well as Th1, and class M2, activated by Th2. M1 macrophages are distributed in the proximity of alveolar type 1 and 2 epithelial cells, while M2 macrophages are widely distributed in the lung parenchyma. Class M1 macrophages recruit immune response cells in the lung parenchyma, while class M2 macrophages secrete anti-inflammatory interleukins to maintain balance [2].

Antigen presentation, carried out by dendritic cells, results in the activation of lymphocytes, which, through lineage differentiation, will produce a specialized cytotoxic or antibody-mediated inflammatory response. Both macrophages and dendritic cells play an important role in signaling the immune response, and both are target cells in SARS-CoV-2 infection. Cellular interference mediated by intracellular viral replication results in prolonged and persistent activation of macrophages, allowing the release of chemokines that increase the number of macrophages in the lung parenchyma, culminating in macrophage hyperactivation, similar to secondary hemophagocytic lymphohistiocytosis syndrome [7].

This prolonged macrophage activation leads to an increase in pro-inflammatory interleukins such as IL-1, IL-6, IL-18, along with type 2 and type 7 chemokine ligands (CCL2 and CCL7) and CXCL10, which is called a cytokine storm, associated with the macrophage activation syndrome.

The term cytokine storm has been widely criticized, as evidence from cytokine quantification studies carried out prior to the COVID-19 pandemic shows that the elevation, specifically of IL-6, is approximately 20 times below the highest value obtained for hyperinflammatory acute respiratory distress syndrome (ARDS). The high mortality associated with SARS-CoV-2 infection throughout the pandemic has forced the questioning of why, despite producing such a small elevation of IL-6, it is capable of producing a severe inflammatory response that results in lung parenchyma injury and ultimately organ failure [6].

Discussion

One hypothetical explanation for the significant lung injury with relatively low IL-6 counts associated with SARS-CoV-2 infection is macrophage invasion. Based on what has been seen so far, the cell that is becoming increasingly relevant in this infection is the macrophage, not only statically but also dynamically, from its precursor, the monocyte. The reticuloendothelial system, the immune surveillance system, has the ability to produce monocytes that will respond to chemokines in specific infection sites, turning them into specialized cells in each tissue. These cells, loaded with viral replicas, can carry the virus to every tissue in the body, which explains why it can cause such severe lung damage despite the low presence of ACE2 receptors in the lungs. In this way, the SARS-CoV-2 virus could reach any organ, regardless of whether or not it has ACE2 receptors, because it already travels inside each infected macrophage, emulating the mythical Trojan Horse [2].

The hypothetical explanation for believing that SARS-CoV-2 is not directly responsible for lung injuries is based on the normal distribution of its receptor. If we start from the fact that a microorganism requires a specific receptor to enter the cell and cause injury, COVID-19 should mainly have gastrointestinal manifestations (since the ACE2 receptor is widely distributed in the gastrointestinal tract), something that was not observed throughout the pandemic. Although there were gastrointestinal symptoms associated with the infection, no affected individual died from that cause. In addition to this, the mechanism associated with the ACE2 receptor involves, first, its inactivation by the virus, which unbalances the system towards an increase in the function of ACE1, favoring the pro-inflammatory effect of the angiotensin II receptor. This fact would be enough to justify the development of respiratory distress syndrome, but we would be ignoring the effect of a disintegrin and metalloproteinase 17 (ADAM-17). This metalloproteinase, present in membranes with ACE2 receptors, is responsible for reactivating this protein, restoring balance to the system, and thus limiting the direct viral effect on its receptor. This first observation forces us to think of an alternative mechanism that justifies the high mortality seen in some countries [2,4].

On the other hand, viral infection, invasion, and replication within macrophages justify the presence of viral copies in regions lacking its receptor. Considering that, in SARS-CoV-2 infection, the macrophage is responsible for the virus's arrival in all tissues, macrophage immunomodulation plays an important role in disease severity. Immune modulation, carried out through signaling by interleukins, is responsible for persistent macrophage activation. This begins with antigen presentation by dendritic cell, resulting in an increase in the concentration of IL-6 that activates macrophages. Normally, these should be presented to T lymphocytes and receive the signal to self-destruct, but thanks to cellular interference by the virus, the process is not completed, and they remain activated, releasing cytokines that initiate the storm. The lack of response from the macrophage forces the immune system to get rid of them by force, so they are destroyed by the ever-reliable cytotoxic lymphocytes. It is precisely this order that causes cellular injury, so the magnitude of the injury will be directly related to the number of activated macrophages present. For the specific case of lung tissue, the presence of ACE2 receptors in alveolar macrophages is too low to justify injury, so it can be inferred that macrophage migration guided by chemotaxis to the lung interstitium is primarily responsible for the magnitude of the injury [3,4].

Knowing this, it is easy to understand the various factors that influence the development of lung injury with macrophage migration being the cornerstone. IL-6 plays a crucial role, so much so that if there is increased secretion of IL-6, which occurs at the moment of antigen presentation normally handled by dendritic cells, the disease prognosis will be worse. This justifies the early use of anti-IL-6 drugs such as tocilizumab and sarilumab. The pathophysiological study of this disease would help understand the reasons for therapeutic failure seen with these drugs when used late. Similarly, some antibiotic, such as azithromycin, produce greater chemotaxis of alveolar macrophages, which would bring more virus to the lung parenchyma, darkening the prognosis. Ivermectin, an antiparasitic, has an immunomodulatory effect, increasing the expression of T lymphocytes and the secretion of interferons (IFN), thus activating more macrophages that will distribute viral replicas throughout the body [8].

Observing the development of this disease throughout the pandemic allowed us to differentiate several phases. Understanding the evolution of each of these would allow us to choose the best therapeutic option in each case. For example, antiviral replication drugs such as Remdesivir will be useful within the viral replication phase and not outside it, so limiting the start and end of this phase would provide an excellent therapeutic option. However, since viral replication begins up to 48 hours before the onset of symptoms, knowing the exact starting point of the replication phase borders on the impossible [9].

After this phase, the symptoms phase overlaps with the early

inflammation phase in which viral replication reaches its peak. Observationally, the onset of the early inflammation phase was associated with the development of respiratory failure. Therefore, we could limit the use of antiviral replication drugs to the appearance of hypoxemia. If we start from the hypothesis that macrophage activation and subsequent migration are responsible for cell injury, the start of the first, marked by the secretion of IL-6, provides an appropriate therapeutic window for drugs such as tocilizumab. The downside is the constant need for IL-6 measurement during the development of the replication phase, which is economically unsustainable for the vast majority of countries. On the other hand, macrophage migration involves an increase in the chemotaxis of monocytes and activation of macrophages systemically. The invasion of hepatocytes by these macrophages must precede pulmonary invasion, due to vascular anatomical caprice. The increase in the concentration of lactate dehydrogenase (LDH), transaminases, and gamma-glutamyltransferase (GGT) is the waving flag of hepatic invasion, therefore measuring LDH, GGT, and transaminases is much more cost-effective and useful in clarifying the onset of the early inflammation phase. Marking this milestone is of vital importance because it would imply the useful limit of the use of drugs responsible for blocking the effect of IL-6. Once the infected individual has crossed the LD and transaminases waving flag limit, the use of drugs such as Remdesivir, Colchicine, Tocilizumab, etc., makes little sense, limiting us to the use of oxygen and the always controversial corticosteroids [4,9].

Finally, the high mortality caused by COVID-19 is not only associated with the viral capabilities to evade the immune system defenses, but it is also supported by different mechanisms that paradoxically favor its transport and replication, as described here. If macrophage migration is responsible for lung injuries, we would have misjudged SARS-CoV-2, granting it capabilities it never actually had. Demonstrating the presence of high concentration of interstitial macrophages in the lung parenchyma could corroborate this hypothesis and bring us closer to understanding the pathophysiological process behind SARS-CoV-2 infection.

Conclusions

The lung injury caused during SARS-CoV-2 infection is not directly related to the presence of ACE2 receptors in lung tissue, which justifies the presence of an alternate mechanism to explain the damage produced.

The presence of ACE2 receptors in macrophages and viral replication within them provides SARS-CoV-2 with an unrestricted pathway to enter various tissues lacking ACE2 receptors. The immune modulation altered by intra-macrophage viral replication results in sustained macrophage activation. This persistent macrophage activation leads to cytotoxic destruction by T lymphocytes, thus producing lung injury.

The elevation of IL-6 justifies the use of anti-IL-6 drugs before the development of the early inflammation phase characterized by respiratory failure. The elevation of LDH, transaminases, and GGT would indicate macrophage migration, marking the inevitable progression towards the early inflammation phase.

The demonstration of the presence of interstitial macrophages in lung parenchyma lesions of individuals infected with SARS-CoV-2 would corroborate the hypothesis of macrophages as the main responsible for lung injury.

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