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PULMONARY INFLAMMATION IS MEDIATED BY CYTOKINES IN COVID-19

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ABSTRACT

The immune system is activated in response to pathogens (bacteria, viruses, or fungi), toxins, or physical trauma. Alveolar macrophages and epithelial cells recognize foreign antigens through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). Immune cells activated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) release pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6), causing a strong inflammatory response. In serious cases, a cytokine storm may occur in which excessive cytokine production causes uncontrollable systemic inflammation. Additionally, elevated levels of interferon-γ (IFN-γ) and inflammatory chemokines attract neutrophils and other immune cells to the lungs, contributing to tissue damage. Immune activation in COVID-19 leads to the recruitment of inflammatory cells and the release of harmful mediators that lead to fibrosis and respiratory failure. Impaired tissue damage and lung function causes respiratory failure that, if untreated, can result in death.

KEYWORDS: *Pulmonary inflammation, cytokine, COVID-19, SARS-CoV-2, virus, coronavirus, infection*

INTRODUCTION

Viral lung infections can be caused by pathogenic viruses such as respiratory syncytial virus (RSV) or coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can induce a cascade of inflammatory cytokines that damage the lungs (1). The immune system fights viral infection and triggers inflammatory pathways to contain and eliminate the virus (2). However, in some cases, excessive or dysregulated inflammation can cause diseases such as viral pneumonia or acute respiratory distress syndrome (ARDS), which can result in fluid accumulation in the lungs with poor oxygenation and multiorgan failure from systemic inflammation (3).

Coronaviruses are a group of similar RNA viruses that cause diseases in mammals and birds (4). They cause diarrhea in cows and pigs and hepatitis and inflammation in mice (5). In human beings, the virus can cause mild respiratory diseases but also causes severe diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 (6,7).

COVID-19 disease is an infectious pathology caused by the Sars-Cov-2 virus. It first appeared as cases of acute pneumonia of viral origin in December of 2019 in China (8). Most individuals affected by COVID-19 show mild to moderate symptoms that heal with special care.

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Sars-Cov-2 is mainly transmitted through salivary droplets from infected individuals by sneezing or exhalation (9). Others can become infected by inhalation if they are in close proximity to someone who has COVID-19, or by touching their eyes, nose, or mouth after having touched a contaminated surface (10).

During SARS-CoV-2 infection, the activated immune system produces several mediators such as cytokines, that cause inflammation if secreted in excessive quantities (11).

DISCUSSION

Lung inflammation can be induced by the immune response to SARS-CoV-2 infection. This can lead to tissue damage, lung irritation, and edema, which are potentially serious complications that may be fatal (12). The virus activates immune cells such as macrophages, neutrophils, lymphocytes, and mast cells (MCs), which release signaling molecules, including cytokines, that increase lung inflammation. COVID-19, caused by SARS-CoV-2, primarily affects the respiratory system, especially the lungs. In severe cases, the virus can cause acute lung injury and lead to ARDS (13).

SARS-CoV-2 enters cells by binding the ACE2 receptor which is found in large quantities in lung tissue (14). The infection can trigger excessive immune responses, particularly in the lower airways, leading to lung inflammation and difficulty in exchanging oxygen (15).

Cytokines are protein signaling molecules that help regulate the immune system's response to infection. They play a critical role in the severity of COVID-19 and, in some cases, can contribute to fatal outcomes (16). This occurs due to a phenomenon called the 'cytokine storm', which is a severe reaction by the immune system where there is an excessive release of inflammatory molecules, including pro-inflammatory cytokines, which provokes severe inflammation and tissue damage (17). This overproduction of cytokines causes increased vascular permeability which leads to fluid accumulation in the lungs that results in low oxygen levels (hypoxia) and further lung injury (18).

In COVID-19, the cytokine storm has been described as one of the critical mechanisms that leads to disease progression and death. In fact, when severe disease affects vulnerable individuals, such as immunocompromised patients and the elderly, COVID-19 can also lead to death (19). Therefore, when SARS-CoV-2 infects the body, it triggers an immune response that can successfully contain and eliminate the virus in mild cases but can overreact in some severe cases and release large amounts of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) (20). In the latter case, inflammation is not limited to the site of infection but becomes systemic, affecting multiple organs and tissues.

In severe, virus-induced lung inflammation, coagulation is dysregulated and thrombin is activated, which disturbs the balance between coagulation and fibrinolysis (21). Excess fibrin deposition in the alveoli impairs gas exchange and contributes to alveolar damage (22). In these cases, microvascular thrombosis may occur, leading to hypoxia (23). Inflammatory cytokines such as TNF and IL-1 damage the endothelium of pulmonary blood vessels, increasing vascular permeability (24) (Fig.1). This phenomenon allows plasma proteins and immune cells to leak into the interstitial and alveolar spaces. In addition, endothelial damage also impairs the production of nitric oxide (NO), causing vasoconstriction and pulmonary hypertension (25). Infiltration of immune cells contributes to the formation of edema, with accumulation of fluid in the alveoli, impairing oxygen exchange.

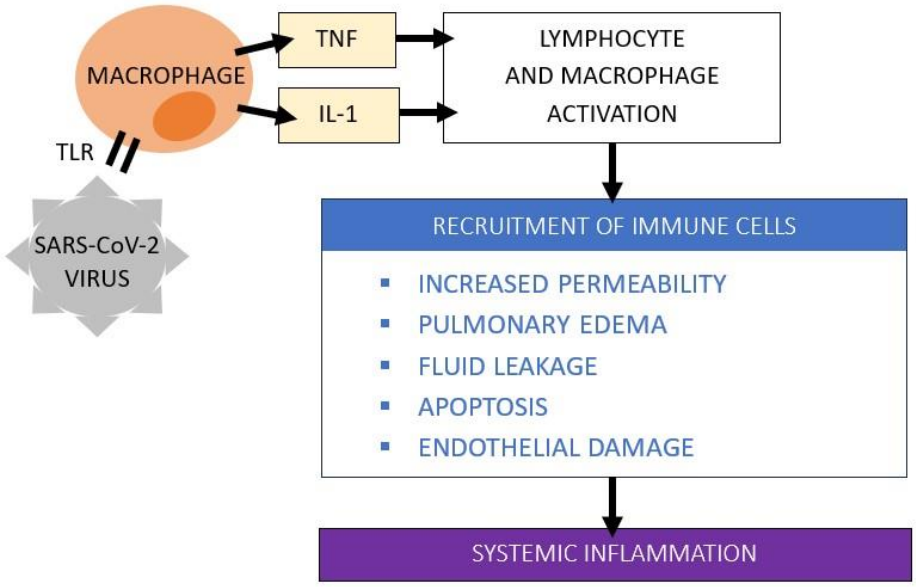

Fig. 1. *SARS-CoV-2 binds the Toll-like receptor (TLR) on macrophages. Macrophages secrete tumor necrosis factor (TNF) and IL-1, inflammatory cytokines that activate immune cells, producing increased permeability, pulmonary edema, fluid leakage, apoptosis and endothelial damage. These effects cause systemic inflammation.*

IL-1 is one of the first cytokines released after pulmonary viral infection as part of the body's innate immune response. This cytokine produces fever, promotes the production of other pro-inflammatory cytokines, and recruits immune cells (e.g., neutrophils and macrophages) to the lungs to fight the infection (26). Excessive IL-1 production has the potential to cause harmful levels of inflammation which damages lung tissue and worsens respiratory symptoms.

IL-6 is a major pro-inflammatory cytokine that has a wide range of effects, including promoting immune cell differentiation and stimulating the acute phase response such as C-reactive protein production in the liver (27). It acts both locally in the lungs and systemically and contributes to fever and systemic inflammation. High levels of IL-6 are associated with severe lung inflammation and tissue damage and are often implicated in a hyperinflammatory state seen in severe viral infections such as SARS-CoV-2 (28).

TNF is a critical cytokine released during viral infections, and it can also be induced by IL-1, which fuels the inflammatory situation (29). TNF helps activate immune cells and increases the permeability of blood vessels in the lungs, allowing immune cells induced by chemokines to migrate to the site of infection (30). This cytokine is also involved in the regulation of apoptosis and the control of viral replication. Excess TNF can cause hyperactivation of immune responses, increasing vascular permeability to the point of edema and contributing to acute lung injury or ARDS in severe cases of viral infection (31).

Cytokine storms can lead to coagulopathies with complications such as pulmonary embolism, stroke, or, in severe cases of COVID-19, heart attack (32). Systemic inflammation can cause damage to organs such as the heart, liver, and kidneys (33). Studies show that corticosteroids (for example, dexamethasone) reduce mortality in severe cases by moderating the immune response (34). IL-6 inhibitors, such as tocilizumab, are used to block the action of IL-6, one of the key cytokines implicated in the cytokine storm (35). In addition, janus kinase (JAK) inhibitors, which block cytokine signaling pathways, have been explored to control excessive inflammation (36). Although they do not directly target the cytokine storm, antiviral drugs can help reduce the viral load, which could potentially prevent excessive levels of cytokines (37).

Supportive care for COVID-19 includes oxygen therapy, ventilation, and organ support for those with severe symptoms. Some individuals will experience mild symptoms from a cytokine storm, while others rapidly worsen to severe conditions. The immune dysregulation triggered by this overreaction highlights the importance of finding the correct balance in immunomodulation during treatment (38).

SARS-CoV-2-induced lung inflammation is a severe and often life-threatening condition, in which inflammation in the lungs leads to respiratory failure, multi-organ damage, and ultimately death. Lung inflammation involves a complex interplay of immune responses, cellular damage, and dysregulation of multiple molecular pathways.

Vaccine

The purpose of the COVID-19 vaccine is to prevent infection or reduce the severity of the disease by providing immunity against SARS-CoV-2 (39). Work to develop a vaccine for coronavirus diseases was already underway before the COVID-19 pandemic, with efforts aimed at preventing SARS and MERS. Research in this field provided a better understanding of the structure and function of coronaviruses and enabled the accelerated development of various vaccines (40).

Many countries have implemented phased distribution plans for the COVID-19 vaccine that prioritize those who are at highest risk of complications, such as the elderly, the immune-compromised, and those who are at high risk of exposure and transmission, such as healthcare workers.

mRNA vaccines use messenger RNA which instructs cells to produce a piece of the virus's spike protein, which triggers an immune response (41). Viral vector vaccines use a modified adenovirus to provide instructions for making the spike protein; while protein subunit vaccines contain harmless pieces of the virus to stimulate an immune response (42). COVID-19 vaccines have been highly effective at reducing severe disease and preventing hospitalizations and deaths, although their effectiveness may be reduced by new variants. Because immunity can wane over time and due to the emergence of variants such as Delta and Omicron, booster doses are recommended to maintain strong protection (43). Vaccines have played a crucial role in controlling the spread of COVID-19, reducing the burden on healthcare systems and saving lives (44).

CONCLUSIONS

The production of pro-inflammatory cytokines is a crucial factor in severe COVID-19 disease. When the immune system becomes overactive and produces a cytokine storm, there can be significant damage to the lungs that results in respiratory failure. The excessive inflammatory response in COVID-19 is a critical and highly complex component, and treatments that target this phenomenon can help improve the clinical condition of this disease that has caused millions of deaths globally.

Conflict of interest

The authors declare that they have no conflict of interest.

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