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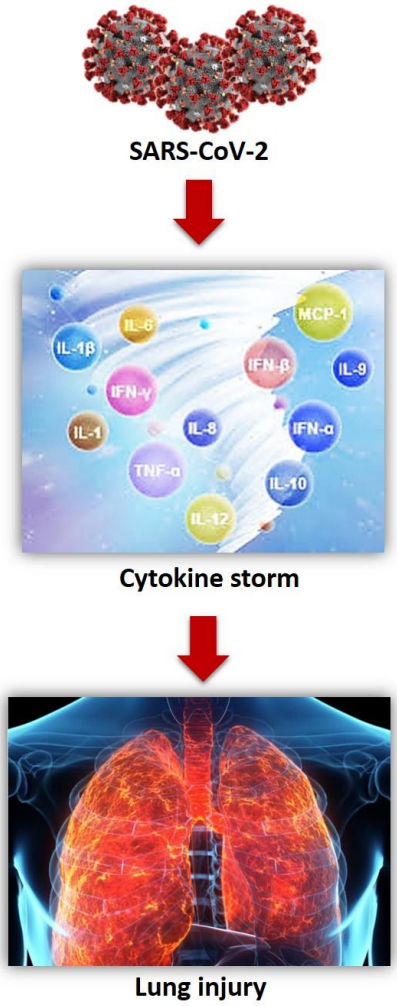
Cytokine storm in COVID-19: a severe immune situation

Italo Rossi Roseno Martins[a*] *and Joedna Cavalcante Pereira*[b]

[*a] *Campus Senador Helvídio Nunes de Barros, Universidade Federal do Piauí (UFPI), Picos, Piauí, Brazil.*
[b] *Unidade Descentralizada do Iguatu, Universidade Regional do Cariri (URCA), Iguatu, Ceará, Brazil.*
**Corresponding Author: italorossi@ufpi.edu.br*

Graphical Abstract



Abstract.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the greatest pandemic of the 21st century. Since December 2019 until now more than nine millions have been infected by the virus and almost five hundred thousand people lost their lives for Coronavirus disease 2019 (COVID-19). Some mechanisms were associated to COVID-19 pathophysiology and specially in severe cases a specific dysregulation in the immune system could be identified, the cytokine storm. In that situation occurs a decrease in the anti-inflammatory and protective immune compounds and an increase in peripheral blood of pro-inflammatory, such as interleukin-2 (IL-2), IL-6, IL-10 and interferon-gamma (IFN-γ) that cause lung injury and worsens the patient's prognosis. So, this work aimed to review the role played by cytokine storm in SARS-CoV-2 infection, in order to better understand the molecular events behind out-of-control cytokine response in severe COVID-19 patients.

Keywords: *coronavirus; SARS; cytokine release syndrome.*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first notified in Wuhan, China, in December 2019. It is a virus with greater transmissibility and pathogenicity than the severe acute respiratory syndrome coronavirus (SARS-CoV-2), that emerged in 2002. SARS-CoV-2 is the pathogen responsible for coronavirus disease 2019 (COVID-19) that has a wide range of clinical presentations since asymptomatic or with mild, moderate and severe symptoms.

Mild COVID-19 cases have a range of clinical manifestations, including cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia but without great complications. On the other hand, these critically ill and dead patients did not develop severe clinical manifestations in the early stages of the disease. However, the conditions of these patients deteriorated suddenly in the later stages of the disease or in the process of recovery. Pneumonia, acute respiratory distress syndrome (ARDS) and multiple-organ failure occurred rapidly, resulting in death within a short time [1].

COVID-19-induced severe respiratory symptoms are due to prominent alveolar damage with eosinophilic exudates, hyaline membrane formation, mononuclear inflammatory cells, multinucleated giant cells, severe pneumocyte hyperplasia, and interstitial thickening [2]. Furthermore, a subsequent peripheral flow cytometry analysis found a decrease in $CD4^+$ and $CD8^+$ T-cells but an increase in the Th17 cell proportion [3]. These findings indicate that a key mechanism associated with the deterioration of the COVID-19 is the cytokine storm [4], an exacerbated immune response of the host to some conditions, as already observed in some viral infections, e.g. H1N1 or H5N1 influenza viruses.

Therefore, this work aimed to review the role played by cytokine storm in SARS-CoV-2 infection, in order to better understand the molecular events behind out-of-control cytokine response in severe COVID-19 patients.

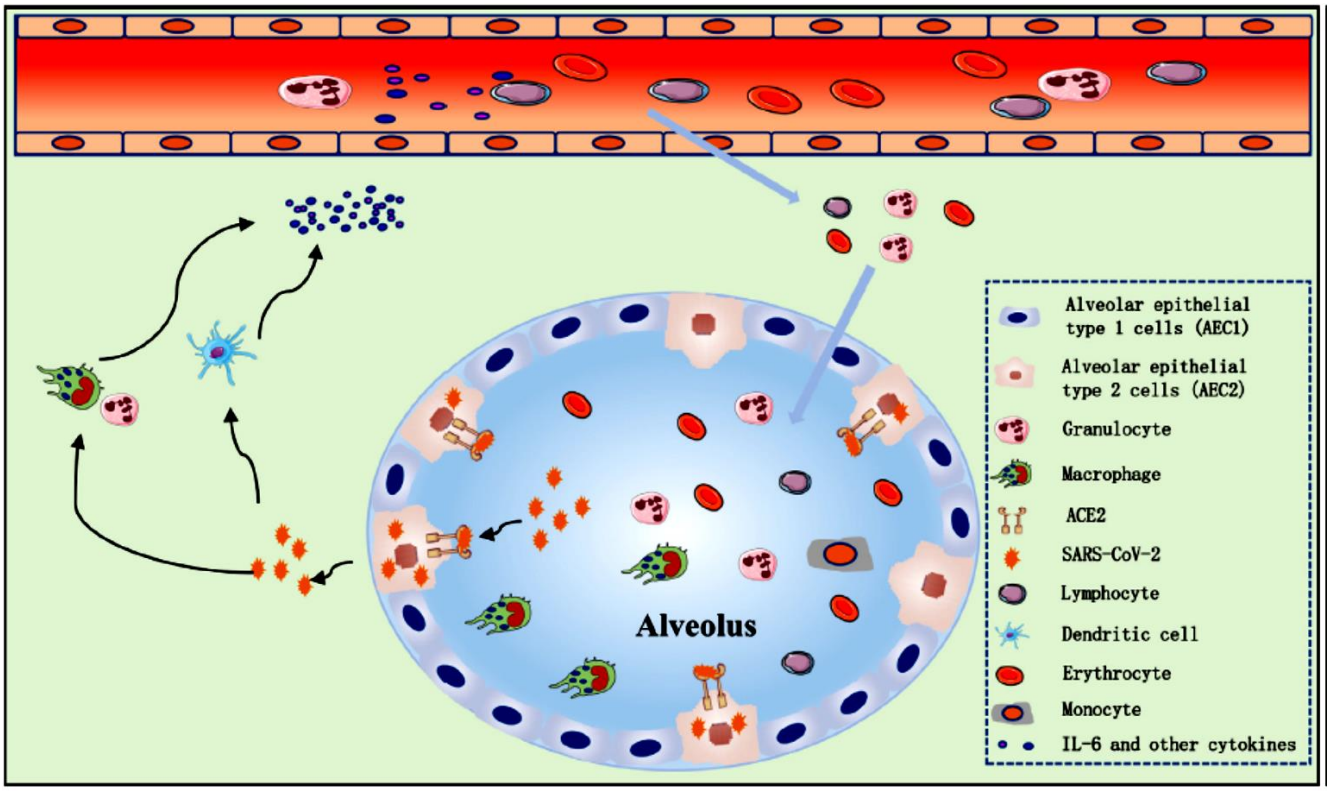
Results and Discussion

Cytokine storm or cytokine release syndrome (CRS) is a systemic inflammatory response that can be caused by infection, some drugs and other factors, characterized by a sharp increase in the level of a large number of pro-inflammatory cytokines. CRS is more common in immune system related diseases and immune-related therapy such as chimeric antigen receptor T-cell (CAR-T) therapy, organ transplantation sepsis and viral infections. SARS-CoV-2 binds to alveolar epithelial cells via angiotensin-converting enzyme 2 (ACE2) that is presents in these cells. The virus then activates the innate and adaptive immune systems, resulting in the release of a large number of cytokines, including IL-6. Then, vascular permeability is increased by pro-inflammatory factors, resulting in a large amount of fluid and blood cells entering the alveoli, resulting in dyspnoea and even respiratory failure [5] (Figure 1).

Another observed event is a significant reduction of the number of regulatory T cells. Severe lymphopenia is a very early sign of the disease, preceding pulmonary problems, and tends to normalize as the patient improves. Lymphopenia is included among diagnostic criteria in China. Despite low numbers, both CD4 and CD8 positive lymphocytes express the high amount of HLA-DR4 and CD38 showing hyperactivity [SOY].Generally, the number of CD8 T lymphocytes recovers in 2–3 months, whereas it may take nearly a year for the memory CD4 T lymphocytes to recover in SARS-CoV infection [6]. Additionally, monocytes and macrophages are increased, which may explain elevated levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)α, and IL-8, which

in some patients turn out to be a real cytokine storm, causing a harmful effects to lung and several body systems.

Figure 1. Illustrative mechanism of cytokine release syndrome in COVID-19 patients.



Adapted from Zhang et al., 2020 [7].

IL-6 plays a central role in the cytokine storm. It is a multi-effective cytokine with both anti-inflammatory and pro-inflammatory effects. IL-6 can promote T-cell population expansion and activation and B-cell differentiation, regulate the acute phase response, and affect the hormone-like properties of vascular disease, lipid metabolism, insulin resistance, mitochondrial activity, neuroendocrine system and neuropsychological behaviour. In addition, IL-6 promotes the differentiation of osteoclasts and angiogenesis, the proliferation of keratinocytes and glomerular membrane cells, and the growth of myeloma and plasmacytoma cells [8].

During COVID-19 infection, T lymphocytes could be hyperactivated, and there is an enormous amount of pro-inflammatory cytokines including, specially IL-6, which contribute to vascular permeability, plasma leakage, and DIC, thereby causing pulmonary damage and ARDS, as well as multi-organ failure. A rational strategy to combat this damage scenario could be use tocilizumab (TCZ), an IL receptor antagonist. Currently, TCZ is used for therapy of rheumatoid arthritis, temporal arteritis, and many other autoimmune rheumatic diseases [9], in addition to having already been reported to control cytokine storm, which may be induced by CAR-T treatment [10]. Some reports indicated that TCZ was used in patients with severe COVID-19 infection complicated with cytokine storm and ARDS and resolved the fever and hypoxemia and improvement in serum CRP levels and pulmonary CT findings [11].

A recent preliminary study from the UK showed that dexamethasone reduced deaths by one third in ventilated patients and by one-fifth in COVID-19 patients that were on oxygen only [12]. It was postulated that early treatment with corticosteroids in patients with rising C-reactive protein and worsening hypoxemia may help prevent or attenuate the hyper-inflammatory response associated with this condition. In this way, due to its abilities as immunosuppressive, the corticosteroids could be a plausible tool to control the cytokine storm in COVID-19 patients.

Conclusions

Taken together, the above observations indicates that cytokine storm can be improve the COVID-19 severity. Understanding the immune dysregulation in patients with COVID-19 not only provides a greater understanding of SARS-CoV-2 pathogenesis but also identifies targets for immune therapeutics. In special, drugs as the IL-6R antagonist tocilizumab and the corticosteroid dexamethasone may be an important drug to reduce infection symptoms and save patients' lives.

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