CHAPTER
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General aspects of the inflammatory reaction in COVID-19

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ABSTRACT
COVID-19 has become a challenge in recent times in different scenarios including areas of health, economy, and education, among others. In the years 2020 and 2021, the world experienced a pandemic caused by the SARS-CoV-2 virus that causes the disease. Since then, understanding the etiopathogenic mechanisms of the new coronavirus has become a challenge. Thus, it becomes the objective to present the role of TCD4+ and TCD8+ lymphocytes in COVID-19, studying the mechanism of action of these cells, their activation, effects on the body, and immunomodulation. A bibliographic review was carried out on the PubMed platform, using literature published between the years 2020 to 2023, and the keywords: COVID-19, T lymphocytes, inflammation, SARS-COV 2, and cytokines. Analyzing published data, we found that after virus infection, CD4+ T lymphocytes are induced to release pro-inflammatory cytokines, such as INF-gamma, which activate cytotoxic CD8+ T lymphocytes, which, as the name implies, cause cell toxicity that ends in lysis of infected cells and destruction of the machinery used by the virus to reproduce. Lysis is brought about by proteins, such as perforins, which induce the appearance of pores on the surfaces of cell membranes. Although the inflammatory response is important for fighting the virus, it can occur in an exacerbated way, releasing a harmful amount of the inflammatory cytokine IL-6 and this overexpression is responsible for decreasing the efficiency of TH 1 cells, TCD8+ lymphocytes, and immunoglobulins. In short, it is important to understand how knowledge of the immunopathogenic of COVID-19 can be fundamental to learning more about the disease itself and to pave the way for its resolution. Thus, the chances of death from the disease decrease, as professionals are aware of its effects and can indicate more accurate treatments for its resolution.

Keywords: COVID-19, T lymphocytes, Inflammation, SARS-COV 2, Cytokines

1 INTRODUCTION

Currently, we are faced with one of the most contagious viral infections in history, the pandemic produced by the SARS-CoV-2 coronavirus, the etiological agent of the disease identified by the WHO Organization as COVID-19. Coming to the knowledge of many at the end of 2019, COVID-19, already existing before that date, gained great prominence after promoting a pandemic that lasted the years 2020 and 2021 and claimed thousands of victims all over the world. Due to its pathogenesis and mechanism of attack being practically unknown and poorly studied so far, health organizations could do little in a short period, and many people from all over the world suffered the consequences of the disease, directly or indirectly. Side effects for each citizen were often different, ranging from the symptoms of a common cold to severe acute respiratory syndrome and becoming more lethal in patients with diabetes, high blood pressure, kidney failure, obesity, and cardiovascular disease. , among others. From then on, the existence of numerous clinical forms of COVID-19 was perceived, and the

need to carry out studies that elucidated how each one works by understanding the specific role of TCD4+ and TCD8+ lymphocytes in directing inflammation, in addition to understanding how the reaction happens and what "motivates" the lymphocytes to promote it (SURYASA et al., 2021; SETTE, CROTTY, 2021; GALVÃO, DELLALIBERA-JOVILIANO 2022).

2 OBJECTIVE

To evaluate the role of TCD4+ and TCD8+ lymphocytes in promoting an inflammatory reaction in COVID-19, studying the mechanism of action of these cells, their activation, effects on the body, and immunomodulation based on a bibliographic review.

3 METHODOLOGY

A retrospective study of the subject was carried out based on international literature found on the electronic platforms PubMed and SCIELO, using the keywords: COVID-19, inflammation, and TCD4+ and TCD8+ lymphocytes. The scientific articles chosen were published between the years 2020 and 2023, projects before 2020 were not chosen. The prerequisites for choosing the articles were recent publication dates, subjects that cover the proposed theme, and that demonstrate regulation of lymphocytes and pro-inflammatory markers. All information that did not embrace those previously selected was disregarded.

4 DEVELOPMENT

COVID-19 is a viral disease caused by the SARS-CoV-2 virus, with asymptomatic cases up to severe cases with a risk of death. It is often common for an inflammatory exacerbation to occur, occasionally excessive, related to the modifications that the virus causes to the leukocyte count, to the elevation of C-reactive protein, and to the viral load with which the individual is infected (the higher it is, the worse the infection will be) (PACES et al., 2020). It all starts with TCD4+ lymphocytes, which in the face of a new infection release pro-inflammatory cytokines into the circulation early, such as TNF-alpha and INF-gamma, which activate cytotoxic TCD8+ lymphocytes, cells of the adaptive immune system, which promote cell toxicity, destroying the infected cells and thus also the reservoir and machinery that the virus uses to replicate itself. Occasionally, cytokine release can be exacerbated, causing a so-called "cytokine storm", which in addition to causing tissue damage in patients can lead to septic shock. Cellular toxicity caused by lymphocytes occurs through cell lysis. Cytotoxic CD8+ T lymphocytes have cytoplasmic granules in their cytoplasm that contain proteins such as perforins and granzymes. These proteins are transported to the infected cell through contact between the membranes of the lymphocyte and the target cell, causing exocytosis and passage of proteins, which induce

cytotoxicity to the host cell. For example, perforins produce pores on the surface of the plasma membrane, which leads to lysis (COSTA SILVA et al., 2022).

Relating obesity as a potential risk factor for death in COVID-19, recent studies have found a close relationship between the lipid metabolism of the human body and the inflammatory reaction of the disease. This happens thanks to the existence of intracellular lipid droplets, which apparently can facilitate and enhance the viral replication of SARS-COV2 within the host cell, aggravating its pathogenesis (MUNAVALLI et al., 2022). Probably the virus regulates lipid metabolism and causes de novo synthesis and lipid remodeling to increase, increasing the number of droplets inside cells. How the virus accomplishes this feat is still unknown. In addition, there is a close relationship between lipid droplets and the production of inflammatory mediators and innate signaling of immune cells, producing a more pronounced inflammatory response through the greater release of pro-inflammatory cytokines and chemokines in obese and overweight patients. NADER, DELLALIBERA, DELLALIBERA-JOVILIANO, 2023; NADER et al., 2023). This explains why the population with these phenotypic characteristics suffers from such lethal cases of the disease. Monocytes infected with SARS-COV 2 have been shown to start synthesizing more leukotrienes (LTB4), more chemokines such as IL-8 and CXCL 10, more inflammatory cytokines such as IL-6, TNF-alpha, IL-10, and IL- 12, and decreased the manufacture of IL-4, an anti-inflammatory cytokine. Diacylglycerol acyltransferase 1 (DGAT-1) can be used to inhibit lipid droplets, making the infection milder and increasing the amounts of IL-4 (DIAS et al., 2020; PACES et al., 2020; NADER et al. ., 2023).

The exacerbated inflammation in COVID-19 may also be associated with the pro-inflammation cytokine IL-6, released during the illness. This cytokine has numerous functions in the immune system, promoting the differentiation of B lymphocytes, cytotoxic T lymphocytes, and the functions of macrophages and monocytes. However, many times, some individuals develop the severe form of the disease, producing high Il-6, which starts to influence a deficient and negative viral immune response, impairing the functionality of TH1 cells and cytotoxic CD8+ T lymphocytes in promoting cell lysis (MUNAVALLI et al., 2022). Furthermore, overexpression of IL-6 causes lymphocytopenia and a decrease in immunoglobulin production, which leads to further impairment in opsonization. To inhibit IL-6 and reduce its damage, a therapy using anti-IL-6 serum was developed, which showed positive results in interleukin blockade and does not seem to be harmful to SARS-COV-2 immunity in the long term. The anti-IL-6 serum declined inflammatory markers such as CRP and increased the rate of lymphocytes and antibodies, as well as their immune responses. The study showed that after one treatment with the serum, antibody levels remained high and much higher than in patients who did not undergo the therapy, with better INF-gamma responses and a lower propensity for infectivity (MASIÁ et al., 2022).

5 FINAL CONSIDERATIONS

Having seen how cellular immunity and inflammation occur in COVID-19, certain cases of aggravation that totalize the disease and require treatments that help improve clinical conditions and prevent sequelae and the chance of death. Analyzes of monocytes from patients infected with the pathology showed that these cells show accumulation of lipid droplets and the explanation is based on the summoning of transcription factors for lipogenesis after 24 hours of infection. This alteration in lipid metabolism could function as an important finding for the discovery of SARS-COV 2, as the droplets function as a “phenotype” for the disease. The use of DGAT-1 inhibits acyl-COA and interrupts lipid metabolism, preventing the prognosis of patients who use it. Likewise, therapy with anti-IL-6 serum prevents an inflammatory exacerbation by inhibiting IL-6 and its receptors and is recommended for the treatment of patients with the severe form of the disease. Thus, it is concluded that it is extremely important to know what happens in the human body when it is infected by the SARS-COV-2 virus, as a good understanding of this process can be crucial for finding key treatments for the various clinical forms of the disease. COVID-19.

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