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The role of Th17 cells in SARS-CoV-2 infection: implementation for the therapy of severe COVID-19 cases

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Abstract

Objective: **In this opinion paper, we discuss the implementation of Th17 cells in the pathophysiology of SARS-CoV-2 infection, with regard to cytokine storm, acute respiratory distress syndrome (ARDS), and other COVID-19 complications. Indeed, the imbalance of IL-17 cells and the consequent inflammatory process are key players in the persistent immune activation and development of cytokine storm. We also discuss the different treatment modalities for targeting the Th17 pathway, which may be helpful in managing severe COVID-19 patients with a prominent Th17 profile.**

The majority of patients with coronavirus disease 2019 (COVID-19) exhibit mild symptoms or remain asymptomatic. In contrast, about 15% of COVID-19 patients develop serious illness. Around 5% of patients experience severe organ dysfunction such as acute respiratory distress syndrome (ARDS) and/or multiorgan failure[1]. It was shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) stimulates cytokine storm development, manifested with elevated serum levels of a huge range of cytokines. Amongst them, it is worth mentioning interleukin (IL)-1b, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, interferon (IFN)-g, tumor necrosis factor (TNF)-a, as well as the growth factors granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and other proinflammatory mediators such as IFN-g-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1-alpha (MIP1a) and -beta (MIP1b). ARDS usually leads to pulmonary edema and lung failure associated with the cytokine storm development, also damaging the liver, heart, and kidneys[2,3].

From an immunologic perspective, type I IFNs, released by infected fibroblasts and epithelial cells, along with their other antiviral activities aimed to inhibit viral replication and spread, increase the process of antigen presentation in infected macrophages and dendritic cells, as well as the production of cytokines and chemokines[4]. This enhanced antigen presentation leads to T-helper (Th) cell differentiation and cytokine secretion and B-cell differentiation and antibody production (mostly immunoglobulins IgM and IgG). All these events reflect the adaptive (specific) immunity to SARS-CoV-2[4,5].

The enhanced effector function of different T cells, including Th17 cells, and the massive release of proinflammatory mediators, contribute to the pathophysiology of acute lung injury observed in severe COVID-19 cases. We have recently discussed the known immunological aspects of COVID-19 infection[6], although we did not focus on Th17 cells with regard to SARS-CoV-2 infection. It is well-known that Th17 cells and IL-17 can speed up the apoptosis of alveolar epithelial cells and the development and progression towards pulmonary fibrosis after resolving the infection. Thus, Th17

cells might be involved in the alteration of the typical alveolar architecture, leading to disruption of the alveolar-capillary gas exchange. Then, as the oxygenation of the blood is disturbed, symptoms of the respiratory system prominently arise[7]. Furthermore, Th17 cell numbers correlate with the extent of inflammation, tissue destruction and remodeling[7]. Xu et al[3] also demonstrated increased numbers of CCR6+ Th17 cells in the peripheral blood of patients with severe COVID-19. Not surprisingly, elevated Th17 cells along with Th1 cells were also observed in patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV infection[8,9], where the constellation of high IL-17 with lower IFN-g and IFN-a was associated with a worse prognosis. IL-22, a cytokine related to Th17 cells, was shown to support the edema formation, along with mucins and fibrin production, associated with the life-threatening features of severe acute respiratory syndrome occurring in patients with SARS-CoV and SARS-CoV-2 infections[10].

Notwithstanding, upon activation, IL-17 downstream signaling further promotes the production of a vast number of proinflammatory cytokines from several cell types. In such a way, mediators including chemokines (CXCL1, CXCL5, CXCL12, MIP3A), growth factors (i.e., G-CSF, GM-CSF) and cytokines (i.e., IL-1, IL-6, IL-8, TNF-α) contribute to inflammation via further recruitment of immune cells to the site of infection. However, although these factors are essential for microbial clearance and mucosal defense, they lead to severe tissue damage and destruction if their regulation is not sufficient. Moreover, it is hypothesized that the significant number of cytokines involved is the culprit of the hyperinflammatory state that SARS-CoV-2 infection causes in our body[11].

Interestingly, a strong Th17 cell response was also observed in the pandemic H1N1 influenza virus[12]. Muyayalo et al[13] highlighted another detrimental role of Th17 cells in COVID-19 during pregnancy. In their study[13], the investigators suggested that the increased ratio of Th17/Tregs may be associated with systemic inflammatory state and development of complications in women (ARDS, multiorgan failure, and death), along with adverse pregnancy outcomes (miscarriage, preterm birth, fetal distress, preeclampsia, and intrauterine growth restriction). However, authors did not exclude the vertical transmission of SARS-CoV-2 infection, leading to chorioamnionitis, premature rupture of membranes, stillbirth, neonatal asphyxia, pneumonia, and neonatal death[13]. In line with this, it might be beneficial to assess the Treg/Th17 ratio and target the imbalance between these cells to prevent pregnancy complications.

Thus, the imbalance of IL-17 and the consequent inflammatory processes are key players in the persistent immune activation and cytokine storm development during pulmonary viral infection. Consequently, instead of coping with the infection, Th17 cells play a paradoxical role by contributing to the disease severity[14]. For these reasons, some scientists suggest that targeting the Th17 pathway may be helpful in managing severe COVID-19 patients with a prominent Th17 profile. The blockade of Th17 cells was suggested during the Th17 cell-mediated inflammation. A feedback loop was formed where the continuous activation and recruitment of effector immune cells lead to the production of large amounts of proinflammatory mediators, further sustaining the hyperinflammatory state. Although lymphopenia is observed in most COVID-19 patients, disruption of the usual proportion of different cells causes an uncontrolled immune response, resulting in cytokine storm development. Therefore, patients with COVID-19 could obtain benefits from a treatment that modulates Th17 immune responses. Effects of IL-17 (and related cytokines) can be downregulated by blocking the cytokine itself, its receptor, or second messengers of the IL-17 signaling pathway[1]. The use of different monoclonal antibodies has been discussed so far: secukinumab (anti-IL-17), brodalumab (anti-IL-17 receptor), fedratinib (JAK2 inhibitor), anakinra (anti-IL-1), tocilizumab (anti-IL-6 receptor), ustekinumab (anti-IL-12 and anti-IL-23). Furthermore, Guaraldi et al[15] demonstrated that the use of tocilizumab could significantly reduce invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia. Based on the observation of the skewing of T-cell activation towards the Th17 functional phenotype in patients with COVID-19, the same group also suggested the IL-17 inhibition as an additional strategy for treating severe COVID-19 patients[16].

Although there are many treatment modalities, all of them can exert immunosuppression that can be harmful during the viral infection, including blocking the immune responses of other critical cell types such as Th1 cells. Besides, antibody-based therapy is still expensive, while providing narrow effects.

For this reason, all the immune effects should be taken into account when considering biologic therapies targeting the Th17 cell subpopulation. However, amongst the all above mentioned, Janus kinase 2 (JAK2) inhibitors are the most promising agents because they do not affect type I IFN production and action while inhibiting the Th17 pathway[12]. Targeting JAK2/Signal transducer and activator of transcription 3 (STAT3) is also considered cost-effective, safe and successful. Furthermore, it is also thought that JAK2 inhibitors prevent SARS-CoV-2 to enter the cells and counteract the overall immune stimulation in the early stages of COVID-19[1]. Still, more research is needed, especially randomized controlled trials enrolling many patients, to establish the role of JAK2 inhibitors as the first choice in COVID-19. The biological rationale for considering JAK2 inhibitors in the treatment of COVID-19 is that both IL-6 and IL-23 activate STAT3 through JAK2, whereas IL-21 activates STAT3 through JAK1 and JAK3. However, IL-6 also uses JAK1 to exert its functions. This complex network works perfectly for JAK2 inhibitors, which succeed in restricting only the existing Th17 cells[1]. Fedratinib also suppresses IL-22 expression by Th17 cells. Thus, the FDA-approved STAT3 inhibitors can not surpass JAK2 inhibition in its selective modulation of Th17 responses, because blocking STAT3 will also affect IL-21 signals in B cells. On the other hand, it was shown that JAK2 inhibition downregulates GM-CSF functions, which may also be beneficial in patients with COVID-19.

Other transcription factors with crucial significance for Th17 cell differentiation are the retinoic acid receptor-related orphan receptor gamma t (RORgt) and the retinoic acid-related orphan receptor α (RORα), which promote thymocyte differentiation into Th17 cells and their specific cytokine production. Although several RORgt and RORα inhibitors are being investigated in clinical trials and results are expected shortly, JAK2 inhibitors are very promising in preventing the Th17 exaggerated response and cytokine storm during severe viral infections, including COVID-19. The good news is that JAK2 inhibitors can also be combined with antiviral drugs and supportive therapy. Moreover, the inhibition of JAK2 is reversible. Thus, transient pharmacological inhibition of JAK2 in the early stages of COVID-19 may prevent the progression towards severe manifestations of the disease. Then, the vital participation of Th17 cells in fighting extracellular and pathogenic fungi will be preserved.

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