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COMMENTARY

Targeting the interleukin-17 pathway to prevent acute respiratory distress syndrome associated with SARS-CoV-2 infection

Key words: acute respiratory distress syndrome, COVID-19, cytokine.

The novel coronavirus causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19) pandemic. This is spurring a global response and accelerating trials of a panoply of antivirals, antibiotics, cell therapies, anticoagulants, convalescent plasma infusion and immune modulation using steroids and anti-cytokine therapies. In the absence of SARS-CoV-2-specific interventions to treat the infection, there are urgent needs to identify adjunctive treatments that prevent or counteract the 'cytokine storm' underlying the severe acute respiratory distress syndrome (ARDS) manifestations.[1,2] Trials underway using immune modulation focus on targeting interleukin (IL)-6, IL-6 receptor (IL-6R), tumour necrosis factor-alpha (TNF-α), IL-1R, granulocyte-macrophage colony-stimulating factor (GM-CSF) and janus kinase (JAK) inhibition among others. Here, we provide the rationale for considering clinical trial testing of IL-17 blockade as a therapeutic strategy for overt pulmonary inflammation caused by SARS-CoV-2 infection.

IL-17 plays a key role in the cytokine storm observed in ARDS of any cause and is associated with alveolar inflammation and a poor prognosis.[3–5] In mouse models, both the direct IL-17 blockade and the upstream blockade of histone acetyltransferase p300 and transcription factor retinoic acid receptor-related orphan receptor gamma t (RORγt), which upregulate IL-17 production, resulted in an attenuation of the lung injury.[6,7] Consistently, peripheral blood mononuclear cells (PBMC) from ARDS patients have an increased expression of p300 and RORγt, especially among non-survivors.[7]

In severe compared to non-severe COVID-19, different studies found increased levels of IL-17-regulated cytokines, including IL-6, monocyte chemoattractant protein-1 (MCP-1), IL-8, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein (MIP)-1-α and TNF-α; however, IL-17 was only increased in severe cases compared to non-infected controls.[2,8,9] Another study observed that IL-17 distinguished between mild and severe cases and correlated positively with an increased lung injury severity score.[10] A pathological assessment found a high frequency of peripheral T-helper (Th) 17 in a patient with severe COVID-19 who did not survive.[11] Furthermore, IL-17 plays a role in facilitating early neutrophil recruitment into the lungs, a deleterious phenomenon associated with poor prognosis in severe cases of COVID-19.[12]

Activation of the IL-17 pathway is also a marker of severity in various other known viral infections. Infections due to the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012 were associated with a pro-inflammatory Th1 and Th17 cytokine profile and IL-17 responses.[13–15] In the 2009 influenza A (H1N1) pandemic, the IL-17 response played a detrimental role in lung injury and was higher in patients with ARDS who did not survive.[16,17] In childhood respiratory syncytial virus (RSV) infections, high IL-17 expression was associated with a poor interferon (IFN) production, abrogated type I IFN (IFN-I) responses and RSV infection severity.[5,18,19] IFN-I is implicated in reducing viral spread, and high levels of IFN-I seem particularly relevant in the early infection phase for disease control. Indeed, in mice, early IFN-I administration was protective against MERS-CoV lung disease.[20,21] Noteworthy, our observations revealed that IL-17A decreased IFN-I responses in intestinal epithelial cells, thus favouring human immunodeficiency virus type 1 (HIV-1) cell-to-cell spread.[22] Similarly, in simian

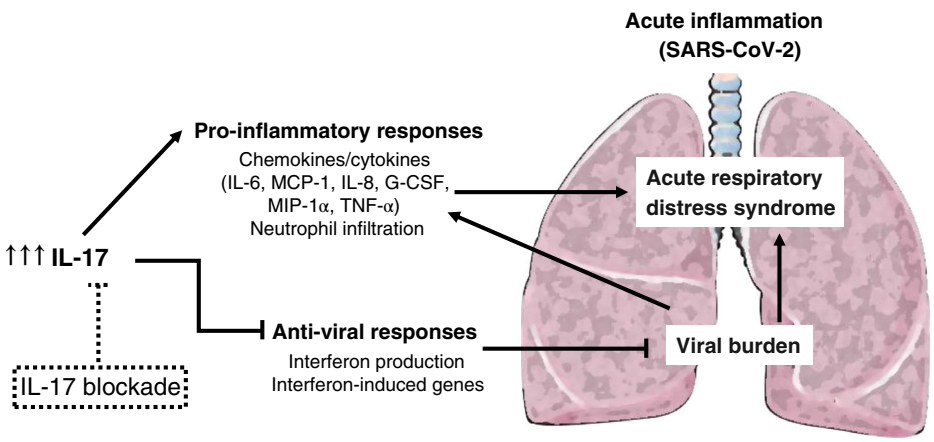

Figure 1 Blocking interleukin (IL)-17 as a strategy to boost antiviral responses and diminish exacerbated lung inflammation leading to acute respiratory distress syndrome in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.

immunodeficiency virus (SIV) infections, mucosal IFN-I responses only developed at late time points post-infection and coincided with a vanished IL-17 response.[23] These results point to the detrimental role of IL-17 in mounting a rapid IFN-I-mediated antiviral response. However, the beneficial impact of IFN-I on human lung diseases remains under investigation. A recent trial in ARDS patients reported an absence of benefit,[24] although this was not in the context of a viral infection.

Finally, while IL-6 has garnered much interest as a potential target to improve COVID-19 outcomes,[25,26] it is important to emphasize that it has interdependent relationships with IL-17. IL-6, along with pro-inflammatory IL-23 and other molecules, are upstream inducers of Th17 differentiation and subsequent IL-17 production. IL-17 then has diverse downstream pro-inflammatory effects increasing neutrophil activity, TNF-α secretion and inducing IL-6 production.[5] This all leads to a positive inflammatory feedback loop.[27] In fact, the rationale for the current interest with JAK blockade in COVID-19 derives from its role in mediating cytokine production, with JAK 2 mediating Th17 responses.[28] Moreover, IL-17 and IL-6 synergistically promote viral persistence.[29] In mice, IL-17 blockade improved H1N1-induced acute lung injury and decreased the levels of cytokines IL-1β, G-CSF, MCP-1, MIP-1-α, MIP-1-β and TNF-α.[16] Additionally, in viral myocarditis, IL-17 blockade abolished viral replication and decreased levels of IL-6.[30] Noteworthy, in COVID-19, myocarditis was observed in the context of ARDS.[31] Thus, IL-17 blockade may be beneficial in controlling the cytokine storm while boosting antiviral IFN-I responses during SARS-CoV-2 infection (Fig. 1). Consideration of IL-17 blockade is strengthened by the relative absence of adverse inflammatory lung manifestations when these therapies are used for autoimmune conditions such as psoriasis.[32,33] Since the initial submission of this commentary, other groups supported the idea of blocking IL-17 for controlling overt inflammation in COVID-19 patients.[28,34] In addition to its pro-inflammatory role, our most recent studies originally support a pro-viral role of IL-17 by interfering with IFN-I production/responses.[22] Therefore, we consider that early IL-17A blockade will also boost the control of viral replication by the host.

In conclusion, as we rapidly explore existing immunotherapies to be repurposed as adjunctive treatments for SARS-CoV-2-associated ARDS, IL-17 blockade may represent an interesting avenue that deserves testing, especially in people with pre-existent pathologies associated with exacerbated IL-17 responses. Monoclonal antibodies against IL-17A (secukinumab and ixekizumab) and IL-17r (brodalumab) may represent possible therapeutic options.

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