Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

REPLY TO: Interleukin-17: a potential therapeutic target in COVID-19

Text

We read with great interest the paper by Mendoza, which suggests the use of anti-IL-17 therapy in coronavirus disease 2019 (COVID-19) patients.[1] While agreeing on the potential role of anti-IL-17 drugs in controlling the excessive production of inflammatory cytokines, we would like to emphasize another possible relevant benefit that could derive from using these treatments in such patients.

As observed in the paper by Mendoza, IL-17 is thought to play a key role in the immune dysregulation observed in COVID-19 and in other severe coronavirus-mediated respiratory syndromes, therefore its inhibition has been suggested to determine a better outcome in these patients.[1] Basing on these assumptions, the use of the IL-17 inhibitor ixekizumab is currently being investigated for the acute phase of COVID-19.[3]

However, COVID-19, besides being associated with acute respiratory distress syndrome (ARDS), can also determine long-term sequelae. These will likely represent a considerable therapeutic challenge in the upcoming months, chronic lung fibrosis arguably being the most important.[2]

IL-17 is a cytokine with pleiotropic effects which might enhance the progression towards pulmonary fibrosis in COVID-19 patients.

IL-17 has been shown to exert direct pro-fibrotic effects on fibroblasts isolated from mouse and human lung through the activation of NF-kB, promoting production of TGF-β and expression of α-smooth muscle actin and eventually leading to collagen deposition.[5] Moreover, by acting on both epithelial cells and fibroblasts, IL-17 promotes epithelial to mesenchymal transition, as well as myofibroblast differentiation and extracellular matrix production, resulting in pulmonary fibrosis.[4]

Intriguingly, permanent pulmonary damage appears to be more severe in ARDS patients who have been mechanically ventilated.[5] Pulmonary fibrosis in SARS patients may be the result of the high inflammatory burden related not only to the anti-viral immune response, but also to ventilator-induced lung injury (VILI).

Neutrophilic inflammation in response to higher levels of IL-8 is a pivotal step in the pathogenesis of VILI[5] and higher concentrations of IL-6 and TNFα have been reported in the lungs of patients with VILI.[6] Although IL-17 levels have not been evaluated in specific studies, IL-17 represents a crucial molecule in IL-8-mediated neutrophil recruitment and its interplay with IL-6 and TNFα has been largely demonstrated.[1]

Moreover, IL-17 has been suggested to be involved in the endothelial dysfunction and thrombophilia that has been observed in COVID-19.[7] In fact, studies performed on both human patients and murine models have shown that IL-17 correlates with vascular dysfunction and induces platelet aggregation, facilitating arterial thrombosis.[7] Furthermore, IL-17 activates endothelial cells, stimulating the production of tissue factor and modulating thrombomodulin expression.[7] In turn, the activation of coagulation might enhance the fibrotic process. In fact, in the bronchoalveolar lavage of interstitial lung disease patients, tissue factor has been shown to be more active than in healthy controls.[8] The pro-coagulative cascade following the activation of tissue factor has been pathogenetically linked to the establishment of pulmonary fibrosis.[8] Notably, factor Xa and thrombin seem to activate protease-associated receptors which induce myofibroblast differentiation in lung fibroblasts. Moreover, anticoagulant therapies have been shown to ameliorate lung fibrosis in both murine models and human patients.[8] Therefore, it is conceivable that IL-17 inhibition could also contribute to fibrosis prevention in COVID-19 by interfering with the coagulative pathways.

Currently, IL-17 inhibitors like secukinumab and IL-17 receptor inhibitors like brodalumab are used for the treatment of psoriasis.[9] In psoriatic patients, secukinumab has been demonstrated to decrease serum levels of Krebs von der Lungen-6 (KL6), a marker of lung fibrosis.[10] Furthermore, in a case series of psoriatic patient with concomitant interstitial pneumonia, the inhibition of the IL-23/IL-17 pathway by ustekinumab, secukinumab or brodalumab correlated with a stabilization or an amelioration of lung fibrosis.[9]

In conclusion, IL-17 appears to be involved in several processes which might be relevant in the pathogenesis of COVID-19-induced pulmonary fibrosis. Notably, IL-17 could act both directly, by activating fibroblasts, and indirectly, enhancing virus-mediated and ventilator-mediated inflammatory processes. Furthermore, IL-17 could stimulate fibrogenesis through the activation of pro-coagulative pathways. Therefore, we suggest that IL-17 inhibitors may be helpful not only for the acute phase of COVID-19, but also for the prevention of its long-term fibrotic sequelae.

Contributions

SP conceived, wrote and performed the revision the paper
AM performed the researches and wrote the paper
FM performed the researches, wrote the paper and contributed to its revision
All authors approved the final version to be published.

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Declaration of Competing Interest

The authors declare no competing interests

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