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Could IL-17 represent a new therapeutic target for the treatment and/or management of COVID-19-related respiratory syndrome?

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This paper is dedicated to Sofia Maione born during COVID-19 outbreak.

Abbreviations: BALF, bronchoalveolar lavage fluid; COVID-19, Coronavirus disease-19; FDA, Food and Drug Administration; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; Gro-α, growth-regulated oncogene-α; IL-, interleukin-; IP-10, interferon γ-induced protein 10; JEK2, Janus kinase 2; MCP-1, monocyte chemoattractant protein-1; MERS, Middle East respiratory syndrome; MIPs, macrophage inflammatory proteins; mRNA, messenger RNA; PGE_2, Prostaglandin E_2; SARS, severe acute severe syndrome; STAT3, signal transducer and activator of transcription 3; TLRs, toll-like

receptors; TNF-α, tumor necrosis factor-α; TREM-1, triggering receptor expressed on myeloid cells-1; WHO, World Health Organization.

Letter to the Editor

Since 2003, outbreaks of Coronavirus have caused multiple public health epidemics including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The first case of infection in response to a new strain of Coronaviridae, designated Coronavirus disease-19 (COVID-19) was recorded in Wuhan, China [1]. This virus appears to be weaker than SARS, in terms of pathogenesis but more sustained in its transmission behavior [2]. COVID-19 is transmitted through droplet inhalation, saliva, nasal and mucous membranes of eyes. Symptoms include fever, continuous coughing and shortness of breath. This has been shown to lead to a mild or severe respiratory illness and, in a number of cases, death. However, this is largely dependent upon the health status of the patient, with highest risk associated with those who have pre-existing respiratory tract pathologies [3]. As of April 2, 2020, the World Health Organization (WHO) reported 896,450 cases of COVID-19 and 45,525 deaths worldwide. The number is growing, and urgent clinical strategies are needed [supplementary materials 1].

The pathological presentation following COVID-19 infection in severe cases [supplementary materials 2] includes specific modulation and release, mainly by lung epithelial cells, of pro-inflammatory cytokines, such as interleukin-(IL-)6, IL-1β and tumor necrosis factor-α (TNF-α) which contribute to lung damage by further aggravating clinical features, such as pneumonia severity in patients affected by this virus [4].

From a cellular viewpoint, lung epithelial cells play a crucial role locally in the release of several pro-inflammatory cytokines such as IL-8 and IL-6. Recent studies have shown that the production of these mediators is regulated at the transcriptional level. Indeed, human lung epithelial cells turn from normo-responsive to hyper-responsive IL-8 and IL-6-producing cells when related messenger RNA (mRNA) degradation is reduced. Recent findings demonstrate the involvement of pro-inflammatory cytokines in several respiratory system diseases including asthma and chronic obstructive pulmonary disease. In particular, IL-6 has been shown to play a critical role in increasing airway resistance, thus increasing the risk of respiratory crisis [5].

Considering the role that IL-6 plays in airway disease, preliminary studies targeting this cytokine therapeutically in response to COVID-19 infection through the use of humanized monoclonal antibodies against the IL-6 Receptor (Tocilizumab), have demonstrated encouraging results as reported in "TOCIVID-19 Protocols" but further validation is still required. Interestingly, hydroxychloroquine (Plaquenil), an antimalarial drug, has also been reported to downregulate the expression of toll-like receptors (TLRs) and IL-6 production, and therefore may have potential anti-COVID-19 activity [supplementary materials 3].

However, other inflammatory cytokines require attention in this disease, and this has prompted investigators and clinicians around the world to set new mechanistical hypothesis/approaches. In this context, we would like to propose a potential interplay between IL-6 and IL-17 in COVID-19-related respiratory pathological events.

IL-17A is a pro-inflammatory cytokine mainly produced by Th17 cells, but also by innate and other adaptive immune cell components such as natural killer T cells, macrophages, neutrophils, $CD8^+$ T

cells, γδ T cells and innate lymphoid cells [supplementary materials 4]. The biological functions of this cytokine include i) the production of chemokines such as IL-8, monocyte chemoattractant protein-1 (MCP-1) and growth-regulated oncogene-α (Gro-α) which increase the recruitment of neutrophils and monocytes, ii) the production of IL-6, a cytokine produced by macrophages, epithelial cells and T cells in response to extracellular microorganisms, iii) the production of the hematopoietic cytokines such as granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage (GM)-CSF, that stimulate the expansion of myeloid lineages and the production of other mediators such as IL-1, TNF-α and Prostaglandin E_2 (PGE_2) [6]. Moreover, it has been reported that IL-17 is associated with several inflammatory respiratory diseases. Laan and colleagues reported that the autocrine action of IL-17 encourages the production of chemokines such as IL-8 in human bronchial epithelial and venous endothelial cells, thereby promoting the influx of neutrophils and exacerbating airway inflammation [supplementary materials 5].

Paradoxically, IL-17 plays a key role in defence from both extracellular bacteria and viruses that infect airway mucous membranes. In fact, this cytokine, in combination with IL-22, regulates homeostasis and contributes to the repair of epithelial cells, damaged previously by extracellular inflammatory stimulus. However, an exacerbation of this type of stimuli, can induce an overproduction of IL-17, which may tip the balance towards a more pro-inflammatory pathological activity, contributing to increased risk of airway diseases [supplementary materials 6].

Several studies, including those from our research group, have shown that IL-17 sustains rather than induces inflammation and promotes the recruitment of inflammatory monocytes which results in the release of a range of mediators including IL-16, triggering receptor expressed on myeloid cells-1 (TREM-1) and different cyto-chemokines which collectively are involved in lung-related inflammatory diseases [supplementary materials 7 and 8]. Interestingly, a recent study from Yuan and colleagues demonstrated that deletion of TREM-1 significantly reduced IL-1β, TNF-α, and IL-6 production and improved lung injury damage [supplementary materials 9].

As reported in the representative figure [supplementary materials 10], we would like to speculate that IL-17 could potentially enhance IL-8 and (more specifically) IL-6 production in both human lung epithelial cells and fibroblasts. This poses an interesting paradigm whereby IL-17 released from innate cellular components, may direct lung structural cells to respond more vigorously. Our hypothesis is also in accordance to a recent article from Wu & Yang [7] which reviewed Th17 responses in patients with SARS-CoV-2. They found that peripheral blood cells from patients with severe COVID-19 infection had strikingly high numbers of circulating Th17 cells which were associated with a "cytokine storm" including IL-1β, IL-2, IL-7, IL-10, IL-17, G-CSF, interferon γ-induced protein 10 (IP-10), MCP-1, macrophage inflammatory proteins (MIPs) and TNF-α. As a result of this hyper-inflammatory state, the authors suggested the use of Fedratinib, a Janus kinase 2 (JAK2) small molecule inhibitor which is involved in the suppression of signal transducer and activator of transcription 3 (STAT3), as a potential therapeutic agent for patients with elevated Th17 (but also Th1) type immune profiles [8,9].

It would therefore be of great interest to further strengthen this hypothesis by accessing bronchoalveolar lavage fluid (BALF) and plasma/serum samples from mild- and severe-infected COVID-19 patients to measure IL-17 levels. This would potentially provide a rationale for testing neutralizing antibodies targeting IL-17. Could targeting IL-17 alone or in combination with IL-6 supersede other therapeutic approaches? A global effort by the research community will certainly help to tackle such questions and we hope to be part of this.

Conflict of interest

This article has been conducted and written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

GMC, AAM, FR and AS drafted the manuscript. NM, AJI and FM wrote and revised the manuscript. All Authors gave final approval to the publication.

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Supplementary materials

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[supplementary materials 10] Schematic representation of inflammatory pathways involved in the COVID-19-related respiratory syndrome. The left part shows the inflammatory scenario induced by COVID-19 and potentially amplified by the presence of IL-17. The right part could represent the future therapeutic approach for COVID-19-releated syndrome using a combined IL-6 and IL-17 neutralizing antibodies.