



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



Letter to the Editor

PubChem

Fedratinib (PubChem CID: 16722836); IL-1 β (PubChem CID: 123872); IL-8 (PubChem CID: 44357137); PGE₂ (PubChem CID: 5280360); Plaquenil (PubChem CID: 3652)

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; PGE₂, Prostaglandin E₂; SARS, severe acute respiratory 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

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-1 β 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 "TOCOVID-19 Protocols" but further validation is still required. Interestingly, hydroxychloroquine (Plaquenil), an anti-malarial 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, $\gamma\delta$ 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 E₂ (PGE₂) [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 an extracellular inflammatory stimulus. However, an exacerbation of this type of stimuli, can induce an overproduction of IL-17, which may

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

<https://doi.org/10.1016/j.phrs.2020.104791>

Received 26 March 2020

Available online 14 April 2020

1043-6618/ © 2020 Elsevier Ltd. All rights reserved.

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 could be 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-1 β , 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-1 β , 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 a neutralizing antibody 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.

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.

Declaration of Competing 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.

Acknowledgment

This work was in part supported by MIUR (PRIN 2017; 2017A95NCJ/2017A95NCJ_002, “Stolen molecules - Stealing natural products from the depot and reselling them as new drug candidates”). AJI is supported by a Birmingham Fellowship.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

online version, at doi:<https://doi.org/10.1016/j.phrs.2020.104791>.

References

- [1] L. Runfeng, H. Yunlong, H. Jicheng, P. Weiqi, M. Qin Hai, S. Yongxia, L. Chufang, Z. Jin, J. Zhenhua, J. Haiming, Z. Kui, H. Shuxiang, D. Jun, L. Xiaobo, H. Xiaotao, W. Lin, Z. Nanshan, Y. Zifeng, Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2), *Pharmacol. Res.* 104761 (2020), <https://doi.org/10.1016/j.phrs.2020.104761>.
- [2] X. Peng, X. Xu, Y. Li, L. Cheng, X. Zhou, B. Ren, Transmission routes of 2019-nCoV and controls in dental practice, *Int. J. Oral Sci.* 12 (2020), <https://doi.org/10.1038/s41368-020-0075-9>.
- [3] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, *Lancet* 395 (2020) 507–513, [https://doi.org/10.1016/s0140-6736\(20\)30211-7](https://doi.org/10.1016/s0140-6736(20)30211-7).
- [4] Y. Gao, T. Li, M. Han, X. Li, D. Wu, Y. Xu, Y. Zhu, Y. Liu, X. Wang, L. Wang, Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19, *J. Med. Virol.* (2020), <https://doi.org/10.1002/jmv.25770>.
- [5] K.B. Adler, B.M. Fischer, D.T. Wright, L.A. Cohn, S. Becker, Interactions between respiratory epithelial cells and cytokines: relationships to lung inflammation, *Ann. N. Y. Acad. Sci.* 725 (1994) 128–145, <https://doi.org/10.1111/j.1749-6632.1994.tb00275.x>.
- [6] F. D'Acquisto, F. Maione, M. Pederzoli-Ribeil, From IL-15 to IL-33: the never-ending list of new players in inflammation. Is it time to forget the humble aspirin and move ahead? *Biochem. Pharmacol.* 79 (2010) 525–534, <https://doi.org/10.1016/j.bcp.2009.09.015>.
- [7] D. Wu, X.O. Yang, TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor fedratinib, *J. Microbiol. Immunol. Infect.* (2020), <https://doi.org/10.1016/j.jmii.2020.03.005>.
- [8] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Y. H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, Bin Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet* 395 (2020) 497–506, [https://doi.org/10.1016/s0140-6736\(20\)30183-5](https://doi.org/10.1016/s0140-6736(20)30183-5).
- [9] M. Sisay, Pp6 CLpro inhibitors as a potential therapeutic option for COVID-19: available evidence and ongoing clinical trials, *Pharmacol. Res.* (2020), <https://doi.org/10.1016/j.phrs.2020.104779> In Press.

Gian Marco Casillo

ImmunoPharmaLab, Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy

Adel Abo Mansour^{a,b,1}

^a *Institute of Cardiovascular Sciences (ICVS), College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK*

^b *Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid University, Guraiger, Abha, 62529, Saudi Arabia*

Federica Raucci, Anella Saviano, Nicola Mascolo

ImmunoPharmaLab, Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy

Asif Jilani Iqbal^{a,b,**}

^a *ImmunoPharmaLab, Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy*

^b *Institute of Cardiovascular Sciences (ICVS), College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK*
E-mail address: A.J.Iqbal@bham.ac.uk.

Francesco Maione*

ImmunoPharmaLab, Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Via Domenico Montesano 49, 80131, Naples, Italy

E-mail address: francesco.maione@unina.it.

** Corresponding author at: Institute of Cardiovascular Sciences (ICVS), College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK.

* Corresponding author.