



OPEN ACCESS

EDITED AND REVIEWED BY
Ilias C. Papanikolaou,
General Hospital of Corfu, Greece

*CORRESPONDENCE
Argyris Tzouvelekis
✉ atzouvelekis@upatras.gr

RECEIVED 10 September 2023
ACCEPTED 13 October 2023
PUBLISHED 03 November 2023

CITATION
Karampitsakos T, Spagnolo P and Tzouvelekis A
(2023) Editorial: Immune-mediated lung injury.
Front. Med. 10:1292074.
doi: 10.3389/fmed.2023.1292074

COPYRIGHT
© 2023 Karampitsakos, Spagnolo and
Tzouvelekis. This is an open-access article
distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use,
distribution or reproduction in other forums is
permitted, provided the original author(s) and
the copyright owner(s) are credited and that
the original publication in this journal is cited, in
accordance with accepted academic practice.
No use, distribution or reproduction is
permitted which does not comply with these
terms.

Editorial: Immune-mediated lung injury

Theodoros Karampitsakos¹, Paolo Spagnolo² and
Argyris Tzouvelekis^{3*}

¹Division of Pulmonary, Critical Care and Sleep Medicine, Ubben Center for Pulmonary Fibrosis Research, Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL, United States, ²Respiratory Disease Unit, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padova, Padova, Italy, ³Department of Respiratory Medicine, University Hospital of Patras, Patras, Greece

KEYWORDS

post-COVID, long-COVID, post-COVID-19-interstitial lung disease, idiopathic pulmonary fibrosis, immunity, monocytes

Editorial on the Research Topic
[Immune-mediated lung injury](#)

The dawn of a new immune-mediated lung disease: post-COVID-19 interstitial lung disease

The role of immunity in acute and chronic lung injury has been now established (Sweis et al.) (1, 2). With regards to interstitial lung diseases (ILDs), a possible association with immunity was first reported almost 50 years ago. In particular, Crystal et al. reported that “The fibrotic process is probably irreversible, however the inflammatory and immune processes causing it may be amenable to therapy if diagnosed early” (3). Despite further reports linking immune deregulation and chronic lung injury, the role of immunity had been severely underscored in the past mainly due to the disappointing results of immunosuppressive and immunomodulatory agents such as corticosteroids in patients with idiopathic pulmonary fibrosis (IPF) (4). Most recently, the interest has been revived. Clinical and translational observations fueled mechanistic discoveries on the role of immunity in lung injury. For example, cellular deconvolution of the 52-gene signature, a highly reproducible biomarker in IPF, showed that monocytes are the cellular source of the upregulated genes. This paved the way for clinical studies showing the prognostic potential of monocyte count in ILDs as well as mechanistic studies investigating the role of monocytes/myeloid derived suppressor cells in pulmonary fibrosis (5–9).

Given the increased interest for the association of immunity with lung injury, this Research Topic included articles presenting immune insights in the context of IPF as well as articles highlighting the impact of ILD in patients with connective tissue diseases such as scleroderma and myositis (Kirgou et al.; Liossis and Bounia; Liossis and Staveri; Karampitsakos et al.). Importantly, this Research Topic highlighted the dawn of a new immune-mediated lung disease, named post-COVID-19-ILD (Bernardinello et al.; Karampitsakos et al.). In particular, data from the Greek registry of patients with post-COVID-19-ILD showed that Forced Vital Capacity% predicted and Diffusing capacity for carbon monoxide% predicted were below 80% in 25.8 and 30.6% of patients in the 3-month follow up, respectively (Karampitsakos et al.). Of note, 5.6% of patients presented with “fibrotic-like” changes and persistent functional impairment at the 6-month follow-up leading thus to implementation of antifibrotics. Similarly, an Italian study demonstrated that 6.9% of the cohort had not recovered in terms of lung disease in the 1-year follow-up (Bernardinello et al.). Patients that did not recover in the 1-year follow-up were older, more

frequently current smokers and had worse PaO₂/FiO₂ on admission at the time point of hospitalization compared to patients that recovered (Bernardinello et al.). Given that both studies showed that a (not negligible) minority of patients with COVID-19 exhibit persistent lung disease even 1 year following acute infection, questions about the long-term trajectory of these patients arise. Taking into consideration that COVID-19 and fibrotic-ILDs have (1) common radiographic features and (2) common innate and adaptive immune responses [the aforementioned gene-signature that predicted outcomes in IPF, predicted outcomes in COVID-19, as well (10)], the following remain to be addressed:

- 1) Are “fibrotic-like” changes in patients with post-COVID-19 reversible? Does radiologic fibrosis necessarily mean histologic fibrosis? Will the treatment of “immature fibrosis” prevent irreversible disease or radiographic findings will resolve/not progress irrespective of treatment? Ongoing studies will hopefully shed light to these questions.
- 2) Are genes that predict mortality in IPF and COVID-19, still abundantly expressed in post-COVID-19-ILD? Extensive investigation of genes that predict mortality in IPF suggested that monocytes/myeloid derived suppressor cells persist during the disease course, while T cells might exhibit exhaustion (5–11). Similarly in COVID-19, myeloid cells have been shown to be highly activated (12), with dysfunctional HLA-DR^{lo}CD163^{hi} and HLA-DR^{lo}S100A^{hi} CD14⁺ monocytes being present in patients with severe disease (13). Moreover, T cell subpopulations of patients with SARS-CoV-2 infection had exhaustion features (14–16). However, further data are needed to understand if the aforementioned phenomenon persists in post-COVID-19-ILD. If not, a less abundant expression of genes that are directly related with monocytes, might mean a gradual “immune recovery” in post-COVID-19-ILD and probably a favorable long-term course. Contrary to IPF, persistence of monocytes and impaired T cell response might not be the case in post-COVID-19-ILD, as the epithelial injury happened only in the acute phase of infection and is not repetitive (17, 18). Studies implementing single-cell RNA-sequencing to compare

post-COVID-19-ILD and IPF could hopefully address this unmet need and help clinicians “predict” the long-term outcomes of patients with post-COVID-19-ILD.

Addressing the two aforementioned questions, will substantially contribute to the management of this new entity with unknown long-term consequences. Despite that the acute phase of the pandemic is thankfully over, clinicians should not forget that a minority of COVID-19 survivors have persistent lung disease. Timely and appropriate management of this new entity might positively impact patients’ health-related quality of life on a long-term basis.

Author contributions

TK: Conceptualization, Investigation, Writing—original draft. PS: Conceptualization, Investigation, Writing—original draft. AT: Conceptualization, Investigation, Writing—original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Kumar V. Pulmonary innate immune response determines the outcome of inflammation during pneumonia and sepsis-associated acute lung injury. *Front Immunol.* (2020) 11:1722. doi: 10.3389/fimmu.2020.01722
2. Karampitsakos T, Papaioannou O, Tsiri P, Katsaras M, Katsimpris A, Kalogeropoulos AP, et al. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial. *Clin Microbiol Infect.* (2023) 29:372–8. doi: 10.1016/j.cmi.2022.10.015
3. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Reynolds HY. Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. *Ann Intern Med.* (1976) 85:769–88. doi: 10.7326/0003-4819-85-6-769
4. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *The New England J Med.* (2012) 366:1968–77. doi: 10.1056/NEJMoa1113354
5. Scott MKD, Quinn K, Li Q, Carroll R, Warsinske H, Vallania F, et al. Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study. *Lancet Respir Med.* (2019) 7:497–508. doi: 10.1016/S2213-2600(18)30508-3
6. Karampitsakos T, Torrisi S, Antoniou K, Manali E, Korbila I, Papaioannou O, et al. Increased monocyte count and red cell distribution width as prognostic biomarkers in patients with idiopathic pulmonary fibrosis. *Respir Res.* (2021) 22:140. doi: 10.1186/s12931-021-01725-9
7. Kreuter M, Lee JS, Tzouveleki A, Oldham JM, Molyneux PL, Weycker D, et al. Monocyte count as a prognostic biomarker in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* (2021) 204:74–81. doi: 10.1164/rccm.202003-0669OC
8. Herazo-Maya JD, Sun J, Molyneux PL, Li Q, Villalba JA, Tzouveleki A, et al. Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study. *Lancet Respir Med.* (2017) 5:857–68. doi: 10.1016/S2213-2600(17)30349-1
9. Karampitsakos T, Juan-Guardela BM, Tzouveleki A, Herazo-Maya JD. Precision medicine advances in idiopathic pulmonary fibrosis. *EBioMedicine.* (2023) 95:104766. doi: 10.1016/j.ebiom.2023.104766
10. Juan Guardela BM, Sun J, Zhang T, Xu B, Balnis J, Huang Y, et al. 50-gene risk profiles in peripheral blood predict COVID-19 outcomes: a retrospective, multicenter cohort study. *EBioMedicine.* (2021) 69:103439. doi: 10.1016/j.ebiom.2021.103439

11. Desai SR, Hansell DM, Walker A, MacDonald SL, Chabat F, Wells AU. Quantification of emphysema: a composite physiologic index derived from CT estimation of disease extent. *Eur Radiol.* (2007) 17:911–8. doi: 10.1007/s00330-006-0369-0
12. Melms JC, Biermann J, Huang H, Wang Y, Nair A, Tagore S, et al. A molecular single-cell lung atlas of lethal COVID-19. *Nature.* (2021) 595:114–9. doi: 10.1038/s41586-021-03569-1
13. Schulte-Schrepping J, Reusch N, Paclik D, Baßler K, Schlickeiser S, Zhang B, et al. Severe COVID-19 is marked by a dysregulated myeloid cell compartment. *Cell.* (2020) 182:1419–40. doi: 10.1016/j.cell.2020.08.001
14. Kusnadi A, Ramírez-Suástegui C, Fajardo V, Chee SJ, Meckiff BJ, Simon H, et al. Severely ill COVID-19 patients display impaired exhaustion features in SARS-CoV-2-reactive CD8(+) T cells. *Sci Immunol.* (2021) 6:782. doi: 10.1126/sciimmunol.abe4782
15. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* (2023) 21:133–46. doi: 10.1038/s41579-022-00846-2
16. Alahdal M, Elkord E. Exhaustion and over-activation of immune cells in COVID-19: challenges and therapeutic opportunities. *Clin Immunol.* (2022) 245:109177. doi: 10.1016/j.clim.2022.109177
17. Mehta P, Estrada BS, Denny EK, Foster K, Turner CT, Mayer A, et al. Single-cell analysis of bronchoalveolar cells in inflammatory and fibrotic post-COVID lung disease. *medRxiv.* (2023) 2023:23287759. doi: 10.1101/2023.03.28.23287759
18. Tourki B, Vera I, Perrot C, Farsaei F, Arsenault A, Juan-Guardela B, et al. Peripheral Blood Gene Expression Changes Predict Mortality and Treatment Response in Acute COVID-19 and Associate with Lung Fibrosis. In: *c32 Interrogation of Genetic Variation, Gene Expression, and Other Biological Layers With Omics Techniques to Understand Respiratory Traits*. Washington, DC: American Thoracic Society (2022), p. A3929-A.