Immune responses to SARS-CoV-2 in the lung

Prabhu S Arunachalam

Human immunity to SARS-CoV-2 has been characterised extensively; however, our understanding of the immune responses in the lung, the site of infection, is limited. A previous study assessing bronchoalveolar lavage (BAL) samples showed a higher proportion of inflammatory monocytes and macrophages in patients with severe COVID-19 disease. In contrast, the moderate patients showed an accumulation of clonally expanded CD8 T cells.[1] The data suggested an enhanced inflammation in the lungs, but paired analysis of peripheral blood and BAL is even more limited.[2]

In this issue, Saris *et al* present a study in which the authors characterised the cellular immune composition of paired blood and BAL samples from 17 patients with severe COVID-19 infection, of which 4 patients were deceased.[3] They observed a significant increase in monocyte populations in BAL of all patients, consistent with the idea that activated blood monocytes migrate to the lung in response to infection. The human leukocyte antigen class DR (HLA-DR) levels were also significantly higher in the BAL monocytes than in the peripheral blood mononuclear cell (PBMC) counterpart. These data support previous observations that severe COVID-19 disease results in migration of activated monocytes to the lung while the periphery is enriched in dysfunctional innate immune cells, including monocytes and dendritic cells expressing lower levels of activation markers.[4–6] It also becomes clear that several inflammatory cytokines such as interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and notably, IL-10 are more abundant in the BAL, suggesting their tissue origin.[7] While several studies have demonstrated an impaired type I interferon (IFN) response, there are contrasting results on the temporal kinetics of type I IFN in patients with severe COVID-19. Of note, the authors did not detect type I IFN in the BAL, possibly due to the timing of sample collection, a median of 13 days in mechanical ventilation during sample collection. However, it is intriguing that there was a detectable type I IFN in plasma despite their absence in BAL. Additional studies are warranted to investigate the kinetics of type I IFN response in the BAL and circulation.

The lymphopenia observed in SARS-CoV-2 infection has been attributed to the migration of T and B cells to the lungs. This study shows that there was no significant increase in the proportion of total T cells in BAL. While it is possible that the T cells were sequestered in pulmonary interstitium, precluding their sampling in the BAL fluid, whether there was a preferential induction of antigen-specific T cells is to be determined. The frequency and activation of T cells were also significantly reduced during an extended stay in the intensive care unit (ICU), potentially due to the increased accumulation of monocytes and neutrophils in the lung during the course of the disease. However, this is likely to be confounded by continuing treatments during the extended ICU stay. Furthermore, investigation on how the viral load in the BAL correlates with these immune responses should be ascertained in future studies.

Finally, the authors also characterised the differences in immune composition in survivors (n=13) and non-survivors (n=4). While this analysis is limited by too few patients, the complete absence of antibody-secreting cells and reduced proportion of T cell subsets are intriguing. These data complement another study in which the authors observed an accumulation of inflammatory innate immune cells in the lung tissue from deceased COVID-19.[8] These results strongly support the accumulation of inflammatory cells and cytokines in the lung as a major driving factor of severe COVID-19 disease.

Collectively, studies in the lung and lung-associated compartments such as BAL provide valuable insights to fully understand the pathophysiology of severe COVID-19. Of particular interest will be to determine if there are differences between the lung immune phenotypes of young, healthy adults versus elderly adults or individuals with comorbidities who are more prone to developing severe/lethal COVID-19 disease.

Institute for Immunity, Transplantation and Infection (ITI), Stanford University School of Medicine, Palo Alto, California, USA

Correspondence to Dr Prabhu S Arunachalam, Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Palo Alto, California 94304, USA; prabhusa@stanford.edu

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Arunachalam PS. *Thorax* 2021;**76**:961.

Accepted 19 May 2021
Published Online First 4 June 2021

Linked

► http://dx.doi.org/10.1136/thoraxjnl-2020-216256

Thorax 2021;**76**:961.
doi:10.1136/thoraxjnl-2021-217231

ORCID iD
Prabhu S Arunachalam http://orcid.org/0000-0003-0090-5689

REFERENCES

1 Liao M, Liu Y, Yuan J, *et al*. Single-Cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* 2020;26:842–4.
2 Xiong Y, Liu Y, Cao L, *et al*. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg Microbes Infect* 2020;9:761–70.
3 Saris A, Reijnders TDY, Nossent EJ, *et al*. Distinct cellular immune profiles in the airways and blood of critically ill patients with COVID-19. *Thorax* 2021;76:1010–9.
4 Arunachalam PS, Wimmers F, Mok CKP, *et al*. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science* 2020;369:1210–20.
5 Schulte-Schrepping J, Reusch N, Paclik D, *et al*. Severe COVID-19 is marked by a dysregulated myeloid cell compartment. *Cell* 2020;182:e23:1419–40.
6 Kuri-Cervantes L, Pampena MB, Meng W, *et al*. Comprehensive mapping of immune perturbations associated with severe COVID-19. *Sci Immunol* 2020;5. doi:10.1126/sciimmunol.abd7114. [Epub ahead of print: 15 Jul 2020].
7 Schultze JL, Aschenbrenner AC. COVID-19 and the human innate immune system. *Cell* 2021;184:1671–92.
8 Szabo PA, Dogra P, Gray JI, *et al*. Analysis of respiratory and systemic immune responses in COVID-19 reveals mechanisms of disease pathogenesis. *medRxiv* 2020. doi:10.1101/2020.10.15.20208041. [Epub ahead of print: 18 Oct 2020].