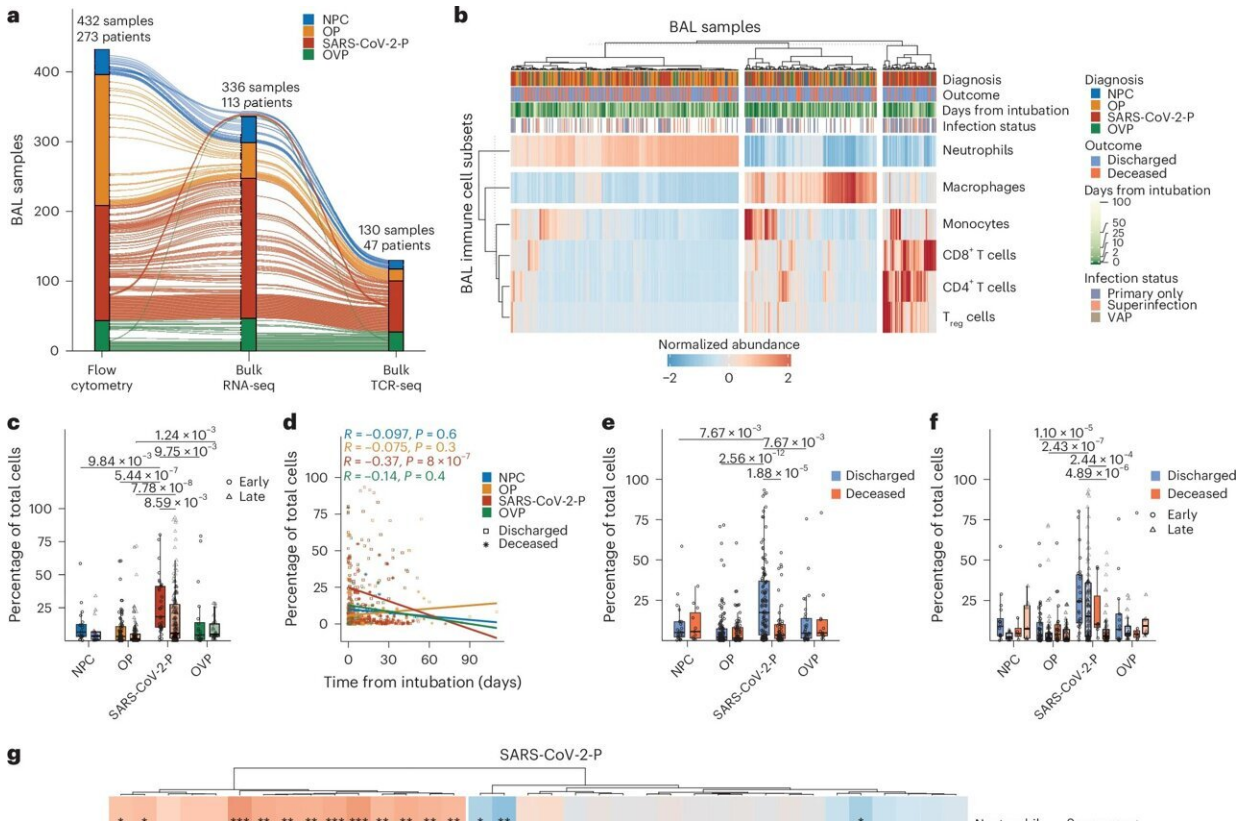
T-cell responses influence patient outcomes in SARS-CoV-2 pneumonia, study finds

September 4 2024, by Melissa Rohman



BAL T cell enrichment is associated with clinical outcome in SARS-CoV-2-P. Credit: *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01914-w

Northwestern Medicine investigators have identified distinct T-cell responses associated with patient outcomes in unvaccinated individuals

with severe SARS-CoV-2 pneumonia, according to findings published in *Nature Immunology*.

During the COVID-19 pandemic, severe pneumonia caused by the SARS-CoV-2 virus was the leading cause of prolonged respiratory failure and mortality, as demonstrated in previous work led by Northwestern Medicine scientists.

"What we saw during COVID-19 that was quite peculiar was that a lot of these patients with SARS-CoV-2 pneumonia were on the ventilator for 14 days or even longer, which was pretty surprising to us. Usually when people get pneumonia, they come to the ICU and are there for three or four days on the ventilator," said Luisa Morales-Nebreda, MD, '17 GME, assistant professor of Medicine in the Division of Pulmonary and Critical Care and senior author of the study.

This prompted Morales-Nebreda and her team to better understand how T-cells in the lungs behave differently in patients with SARS-CoV-2 pneumonia compared to pneumonia caused by other respiratory pathogens and how these immune responses determine favorable or poor patient outcomes.

"T-cells are one of the main immune cells that help patients be protected from pneumonia. We started digging into how lung-specific T-cells are distinct in different causes of pneumonia and to learn anything we can from the number and phenotype of T-cells in the lung; their gene expression profile; their antigenic target; and whether that correlates with clinical outcomes in patients," said Morales-Nebreda, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

In the study, the scientists performed bulk RNA sequencing and T-cell receptor (TCR) sequencing to study T-cells in nearly 400 lung fluid

samples from 273 patients with severe pneumonia, including unvaccinated patients with SARS-CoV-2 or with respiratory failure not caused by pneumonia.

In T-cells from patients with SARS-CoV-2 pneumonia who recovered, the investigators discovered increased activation of interferon signaling pathways, pathways that help interferon proteins activate the immune system to fight off infection and disease.

In T-cells from patients who died as a result of SARS-CoV-2 pneumonia, however, the investigators saw increased activation of the NF-kappa-B pathway, a signaling pathway that induces the activation and differentiation of inflammatory immune cells.

Additionally, T-cells from the lungs of patients who recovered from SARS-CoV-2 pneumonia were more likely to target structural proteins (spike and nucleocapsid proteins) on the SARS-CoV-2 virus, as compared to targeting non-structural proteins (ORF1ab), according to the authors.

"This brings up the concept of whether T-cells elicited by different parts of the virus lead to better or worse outcomes," Morales-Nebreda said. "Vaccines are based on spike proteins, and there has been this thought in the field that we should aim to broaden cellular immunity by including other immunogens into next-generation coronavirus vaccines, so I think this can also help inform that."

The investigators also identified a subset of T-cell receptors generated in response to different pneumonia etiologies that were associated with survival, suggesting these immune correlates of protection may be promising therapeutic targets, Morales-Nebreda said.

"This knowledge can be translated into finding better pharmacotherapies

that can specifically target these pathways and downregulate some of this unremitting inflammation that leads to more severe pneumonia," Morales-Nebreda said.

More information: Nikolay S. Markov et al, Distinctive evolution of alveolar T cell responses is associated with clinical outcomes in unvaccinated patients with SARS-CoV-2 pneumonia, *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01914-w

Provided by Northwestern University