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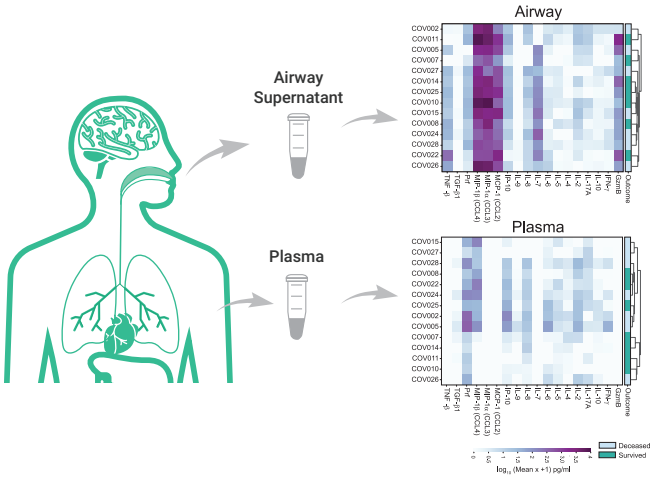
Immune-cell functional profiling sheds light on the pathogenesis of severe COVID-19

As of April 2021, COVID-19 has resulted in over two million deaths worldwide. Immune response dysfunction has been implicated in severe COVID-19. However, the precise nature of these pathogenic systemic immune responses remains unclear. In a recent study published in *Immunity*, researchers used high-dimensional phenotypic, transcriptomic, and functional profiling techniques to identify key disease drivers in patients with severe COVID-19. The study found evidence for myeloid cell-driven lung inflammation in severe COVID-19 and revealed potential therapeutic targets for reducing lung damage by inhibiting airway-specific inflammatory processes.



Highly multiplexed bulk secretome solution provides measurements in paired airway and plasma samples from COVID-19 patients and demonstrates MCP-1, MIP-1α, and MIP-1β, granzyme B, IL-7, and TNF-β were significantly increased in airways compared to blood.[1]

The mechanisms behind pathogenic immune responses

COVID-19 manifests in a wide variety of ways: 90% of patients develop a self-limiting disease and recover, but 5-10% suffer severe lung disease that can progress to acute respiratory distress syndrome (ARDS). Paradoxically, the immune response plays a role in both situations, acting in either a coordinated fashion to clear infection and establish virus-specific immunity, or advancing harmful cytokine storms. This makes it critical to find the specific mechanisms responsible for provoking a pathogenic immune response—as opposed to a disease-clearing one—to SARS-CoV-2.

The team next set out to define the dynamic immune processes associated with severe COVID-19. To do this, they obtained airway and blood samples from fifteen patients with severe COVID-19. These individuals all exhibited clinical features of ARDS and required mechanical ventilation. The team started acquiring samples from these individuals 24-36 hours after intubation and continued sample acquisition for up to ten days or until patients were removed from mechanical ventilation.

An airway-specific cell signature

With these samples, the researchers directly analyzed cellular composition profiles using flow cytometry, single-cell RNA sequencing, and highly multiplexed proteomics. High-dimensional analysis of flow cytometry data showed that although the proportion of T cells in the airway did not differ between COVID-19 patients and controls, COVID-19 patients showed elevated numbers of activated tissue resident (TRM) and tissue effector memory (TEM) T cells, as well as fewer regulatory T cells. In contrast, blood samples from COVID-19 patients showed decreased CD4+ and CD8+ T cell counts and elevated myeloid cell frequencies.

However, T cell activation was low in both COVID-19 and control blood samples. These results suggested that T cell mobilization and activation during severe COVID-19 is localized to the airway.

Accordingly, the researchers also found considerable overlap between airway and blood myeloid cell populations in COVID-19 patients, but not healthy controls, suggesting infiltration. Moreover, airway myeloid cell composition was aberrant in COVID-19 patients, with more dysfunctional or immature phenotypes noted. Airway myeloid cell proportions also increased with patient age. Transcriptomic analysis further indicated that airway myeloid cells propagated major inflammatory pathways, including high-level production of chemokines and cytokines that promote tissue damage *in situ* and recruit other cells.

Airway immune cells work to create a pro-inflammatory environment

The group therefore performed highly multiplexed bulk proteomic analysis to examine whether cellular function matched the phenotypic and transcriptomic information they had acquired. Using a low volume secretome proteomic solution, the researchers simultaneously probed 23 cytokines and chemokines involved in adaptive immunity. The study noted marked differences between the secretomic profiles of airway and blood samples in severe COVID-19 patients at both early and later time points. Specifically, airway samples presented elevated levels of the chemoattractants MCP-1, MIP-1α, and MIP-1β, as well as T cell-associated cytokines granzyme B, IL-7, and TNF-β. All of these, aside from MIP-1β, were undetectable in the blood. Additionally, the presence of the key monocyte chemoattractants MCP-1 and MIP-1α resulted in the recruitment of dysregulated blood monocytes into the lungs, especially around alveolar spaces critical for oxygenation.

In airway samples, protective T cell signatures were associated with younger patient ages and survival from severe COVID-19. In contrast, myeloid cells, mainly macrophages and monocytes, were responsible for driving immune cell recruitment and lung inflammation, which were associated with older patient ages and mortality. These results indicated a highly inflammatory environment in the airways of patients with severe COVID-19 and strongly implicate myeloid cell recruitment as a major mechanism perpetuating this inflammation.

A better understanding leads to more effective therapeutic strategies

The study indicates that airway T cell measurements could be a useful biomarker for monitoring patients and stratifying risk. The researchers also identified a potential role for MCP-1 in recruiting dysregulated monocytes to the airways and lung and believe that disrupting this chemotactic axis may serve to reduce lung inflammation and damage. The results indicate that promoting lung-localized immune responses could be a viable alternative vaccination strategy for individuals, such as the immunocompromised or elderly, who are unable to develop effective systemic antibody responses.

REFERENCE

1. P. Szabo et al., "Longitudinal profiling of respiratory and systemic immune responses reveals myeloid cell-driven lung inflammation in severe COVID-19," *Immunity*, 54(4):797-814.e6, 2021.