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## PERSPECTIVE

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# Divergent immunological characteristics of COVID-19, influenza, and other community-acquired pneumonia are shown by integrated single-cell analysis

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### ABSTRACT

Methodological variability and a dearth of pertinent disease controls continue to cast doubt on the precise immunopathophysiology of Community-Acquired Pneumonia (CAP) brought on by SARS-CoV-2 (COVID-19). It is challenging to differentiate between immunological signs specific to COVID-19 and the typical features of a dysregulated

host response to pneumonia since single-cell examinations in the larger population of patients with CAP are not routinely performed. Expanding our understanding of the peripheral immune response in various pneumonia etiologies, we describe shared and diverging transcriptional and phenotypic patterns using this balanced, multi-omics approach, such as in COVID-19, there were higher concentrations of type I interferon-stimulated NK cells, cytotoxic CD8 T EMRA cells in both COVID-19 and influenza, and different monocyte compositions in each group.

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### INTRODUCTION

The predicted global caseload and mortality for the Coronavirus Disease of 2019 (COVID-19) as of June 11<sup>th</sup>, 2022, are over 535 million cases and over 6.3 million fatalities, respectively. The seriousness of this global crisis has fuelled COVID-19 research. In recent memory, nothing has ever had such a devastating effect on both the global and interpersonal levels as COVID-19. Patients with severe COVID-19, which is brought on by the SARS-CoV-2 virus, experience organ failure resembling sepsis, bilateral pneumonia, and severe systemic inflammation. Thousands of thousands of unnecessary fatalities have occurred worldwide in the year since its discovery. A defective and overwhelming host immune response to SARS-CoV-2 mediates illness progression into a life-threatening condition. Lymphopenia, a role for activated and worn-out T cells, hyper inflammatory monocytes with reduced antigen presenting capacity, delayed or dysfunctional interferon responses, expansion of plasma blasts, and suppressive immature neutrophils in severe disease are some of the distinct patterns that are starting to emerge in this immune response in hospitalised patients. Importantly, most studies lack disease controls despite early indications that similar immunological abnormalities, clinical signs, and organ dysfunctions in COVID-19 can also occur in other infections. It is critically necessary to directly compare COVID-19 with another infectious disease state that is well matched in order to separate the actually

unique immunological features from the common traits of a dysregulated host response to infection. Nevertheless, despite the fact that numerous studies examined the immune response during COVID-19 pneumonia at the single cell level, such research is currently absent for the larger population of people who have contracted Community-Acquired Pneumonia (CAP). Peripheral Blood Mononuclear Cells (PBMCs) from patients with CAP caused by either SARS-CoV-2, Influenza A, or other pathogens admitted to a non-intensive care ward were used for CITE-Seq (Cellular Indexing of Transcriptomes and Epitopes by Sequencing<sup>19</sup>). Patients were matched based on their age, gender, and disease severity. We create a high-resolution snapshot of cellular phenotypes and functional states by combining single cell RNA-sequencing with highly multiplexed surface protein marker detection, similar to classical flow cytometry. This provides insight into the peripheral immune features of various pneumonia etiologies. Most reports on the deep immunophenotyping of COVID-19 patients to date have varied (both within and between studies) in key aspects of the immune response, such as disease severity, timing of sampling, and participants' age and sex. Mechanical ventilation and vasopressors, two crucial therapies in intensive care units, aggravate this issue by quick and significant immunomodulatory effects. Due to these factors, it is challenging to distinguish the true COVID-19 immunopathophysiology signal from methodological heterogeneity noise and potential bias and

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confounding distortions. Covid-19 Immune Repertoire Single-Cell Analysis

By identifying and removing antigens derived from infection and illness, T cells and B cells mediate antigen-specific adaptive immunity. Antigen specificity describes a T cell's or B cell's capacity to recognise the antigen epitope in a particular way. Specific antigen recognition depends on the surface of each T cell or B cell expressing a distinct T Cell Receptor (TCR) or B Cell Receptor (BCR; membrane-bound Immunoglobulin (Ig)). A wide range of antigens can be recognised thanks to the tremendous diversity of TCRs and BCRs expressed on a huge number of T cells and B cells. The TCRs and BCRs (or T cell and B cell clonotypes) present in an individual are collectively referred to as the immunological repertoire.

The great diversity of TCRs and BCRs is mostly produced by the somatic recombination process known as V (D) J recombination in growing T cells and B cells. By assembling the variable region of TCR or BCR genes from component V, D, and J gene segments through V(D)J recombination, a potential diversity of over 10<sup>13</sup> distinct TCR and BCR sequences (or T cell and B cell

clonotypes, respectively) is produced. Single-cell VDJ sequencing is a method that is similar to scRNA-seq for sequencing transcripts with VDJ regions in single T or B cells by targeted enrichment (scVDJ-seq).

#### CONCLUSION

We started by examining the peripheral blood immune response in COVID-19 pneumonia patients and healthy controls. Thirteen clusters of myeloid and lymphoid immune cells were found using Uniform Manifold Approximation and Projection (UMAP) to reduce the dimensionality of the transcriptome of all individual cells from these participants. The Supplementary section lists the top Differentially Expressed Genes (DEGs) between these clusters. The transcriptome-based clusters were consistent with the cell surface protein expression levels of traditional lineage-defining markers (such as CD3, CD4, CD8, CD14, and CD19). Patients with COVID-19 showed marked differences in the proportional composition of cell clusters when compared to age- and sex-matched non-infectious control subjects, including a decrease in monocytes and memory B cells and an increase in naive B cell.