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A single-cell atlas reveals shared and distinct immune responses and metabolic pro les in SARS-CoV-2 and HIV-1 infections

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Introduction: Within the in ammatory immune response to viral infection, the distribution and cell type-specific profiles of immune cell populations and the immune-mediated viral clearance pathways vary according to the specific virus. Uncovering the immunological similarities and differences between viral infections is critical to understanding disease progression and developing effective vaccines and therapies. Insight into COVID-19 disease progression has been bolstered by the integration of single-cell sc)RNA-seq data from COVID-19 patients with data from related viruses to compare immune responses. Expanding this concept, we propose that a high-resolution, systematic comparison between immune cells from SARS-CoV-2 infection and an in ammatory infectious disease with a different pathophysiology will provide a more comprehensive picture of the viral clearance pathways that underscore immunological and clinical differences between infections.

Methods: Using a novel consensus single-cell annotation method, we integrate previously published scRNA-seq data from 111,566 single PBMCs from 7 COVID-19, 10 HIV-1$^+$, and 3 healthy patients into a unified cellular atlas. We compare in detail the phenotypic features and regulatory pathways in the major immune cell clusters.

Results: While immune cells in both COVID-19 and HIV-1$^+$ cohorts show shared in ammation and disrupted mitochondrial function, COVID-19 patients exhibit stronger humoral immunity, broader IFN-I signaling, elevated Rho GTPase and mTOR pathway activity, and downregulated mitophagy.

Discussion: Our results indicate that differential IFN-I signaling regulates the distinct immune responses in the two diseases, revealing insight into fundamental disease biology and potential therapeutic candidates.

KEYWORDS

HIV, Single-cell RNA sequencing, SARS-CoV-2, type 1 interferon, in ammation, metabolic signaling

Introduction

Viral infection in humans initiates a coordinated response between the innate and adaptive immune systems. This defense response involves: recruitment and activation of in ammatory cell populations, such as macrophages and monocytes (Koyama et al., 2008); IFN-I signaling, which drives transcription of multifunctional IFN-stimulated effector

molecules (Koyama et al., 2008; McNab et al., 2015); and significant metabolic shifts in immune cells, attributed to increased cytokine signaling (Chandler et al., 2016; Sumbria et al., 2020). Cytotoxic T cells clear infected cells *via* cytokine-mediated destruction or direct killing, while helper T cells prime B cells to produce antibodies, which neutralize viral replication. However, the distribution and cell type-specific profiles of the different immune cell populations vary across different viruses/diseases, conditions, and stages of disease progression (MacParland et al., 2018; Travaglini et al., 2020; Delorey et al., 2021). Within what seems like a common in ammatory program, the immune-mediated pathways are virus-specific.

Single-cell RNA sequencing (scRNA-seq), which can accurately annotate individual cells, is widely used to characterize heterogeneity within immune cell subsets (Tang et al., 2009; Treutlein et al., 2014; Gawad et al., 2016; Reyfman et al., 2019; Chow et al., 2021). Integration of scRNA-seq data to compare immune responses across different viral diseases (typically with similar pathophysiologies) can reveal similarities and differences in the in ammatory immune response. This strategy has drawn increased interest since the onset of the COVID-19 pandemic as it can facilitate translation of insights from one disease to another. For example, Lee et al., used scRNA-seq to examine peripheral blood mononuclear cells (PBMCs) from patients with in uenza or severe COVID-19, reporting a common enrichment of in ammatory monocytes upregulating TNF- , IL-1β, and IFN-I, alongside in uenza-specific expression of *STAT1* and *TLR4* and COVID-19-specific expression of *NFKB1/2* and *STAT4* (Lee et al., 2020). Schuurman, Reijnders, et al. found that monocytes and NK cells from patients with SARS-CoV-2-derived community-acquired pneumonia (CAP) expressed higher levels of interferon-stimulated genes (ISGs) compared to monocytes and NK cells from patients with non-SARS-CoV-2-derived CAP (Schuurman et al., 2021). The COMBAT Consortium generated an integrated blood atlas of COVID-19, in uenza, and sepsis which revealed a shared neutrophil signature, alongside elevated plasmablast frequencies, type-2 T cell responses, and plasma concentrations of in ammatory cytokines (such as IL-6 and IL-8) in patients with COVID-19 (COvid-19 Multi-omics Blood ATlas (COMBAT) Consortium, 2022). Altogether, these studies point to a common theme of in ammation regulated by specific genes and cytokines, particularly IFN-I. However, the myriad virus-specific pathways activated by the immune system cannot be revealed by comparing only related diseases. We propose that a high-resolution, systematic comparison between immune cells from SARS-CoV-2 infection and an in ammatory infectious disease with a different pathophysiology will provide a more comprehensive picture of viral clearance pathways.

SARS-CoV-2 and HIV-1 are RNA viruses and thus exhibit high mutation rates relative to DNA viruses. SARS-CoV-2 and HIV-1 are both highly virulent, but disease progression differs substantially. Immune cell subsets such as macrophages and monocytes have been implicated in driving in ammatory cytokine signaling during both SARS-CoV-2 and HIV-1 infection. (Deeks et al., 2013; Campbell et al., 2014; Schulte-Schrepping et al., 2020; Knoll et al., 2021). However, most of the mortality and morbidity observed with SARS-CoV-2 infection occurs within days of infection, compared to months or years with HIV-1 infection. Furthermore, neutralizing antibody responses are rapidly generated following SARS-CoV-2 infection, but these take many years to develop in people living with HIV-1 (Stamatatos et al., 2009; Cotugno et al., 2021; Dangi et al., 2021). These clinical and immunological differences are driven in part by how the host responds to distinct viral infections.

Here, we sought to identify the disease-specific drivers and mediators of in ammation, IFN-I signaling, and metabolism pathways of immune-mediated viral clearance in patients with COVID-19 and HIV-1. We present a comprehensive strategy to integrate scRNA-seq data of 111,566 single PBMCs from 7 COVID-19, 10 HIV-1^{+}, and 3 healthy patients from previously published datasets (Wilk et al., 2020; Kazer et al., 2020; Wang et al., 2020; 10xGenomics, 2020). Our strategy combines the advantages of manual annotation, correlation-based label transfer and deep-learning-based classification to generate a high-quality unified cellular atlas of the immune landscape. We compare in detail the phenotypic features and regulatory pathways in each of the major immune compartments (T cells, B cells, natural killer cells, dendritic cells, and monocytes). We find common signatures of in ammation and disrupted mitochondrial function in both COVID-19 and HIV-1. Moreover, we identify important differences in cell signaling, antibody diversity, IFN-I signaling, and metabolic function, including differential IFN-I signaling that likely regulates the distinct immune responses against the two diseases.

Materials and methods

Preprocessing, integration, and clustering

Raw single-cell count matrices were collected from publicly available sources (Tables 1–3) (Kazer et al., 2020; Wang et al., 2020; Wilk et al., 2020; 10xGenomics, 2020) and merged. We performed quality control and downstream analysis using the Seurat package (v4.0.4) (Stuart et al., 2019). We removed cells with greater than 15,000 unique molecular modifiers (UMIs) or fewer than 500 UMIs, as well as greater than 20% mitochondrial reads per cell. We performed log-based normalization with the "NormalizeData" function with the "LogNormalize" parameter and selected the top 10,000 variable features with the "vst" parameter using "FindVariableFeatures". We scaled and centered the count matrix using the "ScaleData" function and supplied "percent.mito" as a latent variable to regress out the effect of percentage mitochondrial reads. We performed principal component analysis (PCA) on the top 100 PCs using the "RunPCA" function. To remove study-specific batch effects, we performed integration across each patient using the Harmony algorithm (v0.1.0) (Korsunsky et al., 2019) on the top 50 principal components (PCs) with the "RunHarmony" function. We then performed Uniform Manifold Approximation and Projection (UMAP) reduction using the "RunUMAP" function on the top 50 PCs with "min.dist" = 0.1 and "n.neighbors" = 20. We ran the "FindNeighbors" function on the top 50 Harmony dimensions, then performed Louvain clustering using the "FindClusters" function with a resolution of 0.3. We removed doublets using the scDblFinder package (v1.10.0) (McGinnis et al., 2019) by supplying sample source, 50 Harmony dimensions, 10,000 variable features, and 100 PCs as parameters.