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Innate immune cell genetic risk factors are linked to COVID-19 severity

Single-cell RNA-sequencing analysis combined with host genetic data for a Japanese population reveals the dysfunction of innate immune cells, particularly non-classical monocytes, in individuals with severe COVID-19, as well as enrichment of host genetic risk factors for severe COVID-19 in monocytes and dendritic cells.

The project

Coronavirus disease 2019 (COVID-19) represents a serious global public health issue. Although effective vaccines have successfully reduced both viral transmission and disease burden, an urgent need remains to elucidate the mechanisms that lead to severe COVID-19, predict its severity and develop new treatments. Although multiple single-cell RNA-sequencing (scRNA-seq) studies of peripheral blood samples have highlighted dysregulated immune responses in patients with COVID-19 (Ref. 1), the mechanisms that underly the dysfunctional immune response in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are not yet fully understood. In addition, genome-wide association studies (GWASs) of patients with COVID-19 have demonstrated that the host's genetic background influences their susceptibility to and/or the severity of COVID-19 (Refs. 2,3). However, the functional roles of the genetic variants that have been identified by these GWASs remain elusive, especially in non-European populations.
Our goal was to elucidate the immune responses in COVID-19 from both a pathophysiological and host genetic perspective in the Japanese population.

The discovery

We used a multi-omics approach including scRNA-seq, T cell receptor and immunoglobulin heavy chain (VDJ) sequencing to analyze 895,460 peripheral blood mononuclear cells (PBMCs) from 73 patients with COVID-19 and 75 healthy controls, all of Japanese ancestry, to investigate the systemic immune response in COVID-19 (Fig. 1a). Next, we integrated our scRNA-seq data with polygenic signals from the largest COVID-19 GWAS[2] using a single-cell disease-relevance score (scDRS)[4] to evaluate the contribution of genome-wide host genetics to risk of COVID-19 and identify subpopulations of disease-associated PBMCs. Finally, to understand how transcriptional dynamics are regulated by COVID-19-associated variants, we examined single-cell expression quantitative trait loci (eQTL) effects of the COVID-19 risk variants that were replicated in a GWAS of a Japanese population[3,5].

We found that the decreased fraction of non-classical monocytes (ncMono), a known COVID-19-specific feature[1], is partially due to downregulation of the cellular transition from classical monocytes (cMono) to ncMono. Differential expression analysis revealed reduced *CXCL10* expression in ncMono in individuals with severe COVID-19. Cell–cell communication analysis inferred that cellular interactions involving ncMono are decreased in severe disease, which suggests that their dysfunction might be closely involved in the immunopathology of COVID-19 severity.
We also observed enriched expression of the putative disease genes that were identified by the GWAS of patients who were hospitalized and those with very severe COVID-19 in the monocytes and dendritic cells, whereas no cell type showed enriched expression of these genes in the GWAS of people with self-reported infection (Fig. 1b,c). The single-cell eQTL analysis revealed that COVID-19-associated variants (such as the *IFNAR2* variant rs13050728) had context (COVID-19)-specific and cell-type (monocyte)-specific eQTL effects.
These multimodal and integrative data analyses consistently indicated an enrichment of host genetic factors that confer an increased risk of severe COVID-19 in innate immune cells.

The implications

This study highlights the essential role of innate immune cells in determining COVID-19 severity. We revealed that ncMono are involved in the pathogenesis of COVID-19 severity, which suggests a potential new drug target. We also clearly demonstrated cell-type-specific and context-specific eQTL effects of COVID-19-associated gene variants, which implies that such analysis could aid in the understanding of its pathogenesis and the potential for personalized therapy.

Comprehensive evaluation of the latest GWAS-identified COVID-19 risk variants is desirable. We adopted a pseudo-bulk approach for our eQTL analysis that was restricted to coarse cell states that imperfectly partition a continuous transcriptional landscape. Therefore, conducting a genome-wide and dynamic eQTL analysis at single-cell resolution would provide a more comprehensive understanding of dynamic gene regulation in the context of COVID-19.

To this end, we aim to further expand our single-cell dataset via an international collaboration network to cover the global diversity of host genetic data and perform genome-wide single-cell eQTL analysis. In parallel, we want to explore the immunological mechanisms that underpin the dysfunction of ncMono using other single-cell modalities such as assay for transposase-accessible chromatin (ATAC)-seq and in vivo experiments.

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EXPERT OPINION

"The researchers conducted a scRNA-seq study of peripheral blood cells from 73 patients with COVID-19 and a genetic association analysis in which these patients were compared with 75 healthy control individuals. The data included in this study form a rich resource for deep mining the immunological changes caused by COVID-19 and the associated genetic background." **Xianwen Ren, Changping Laboratory, Beijing, China.**

FIGURE

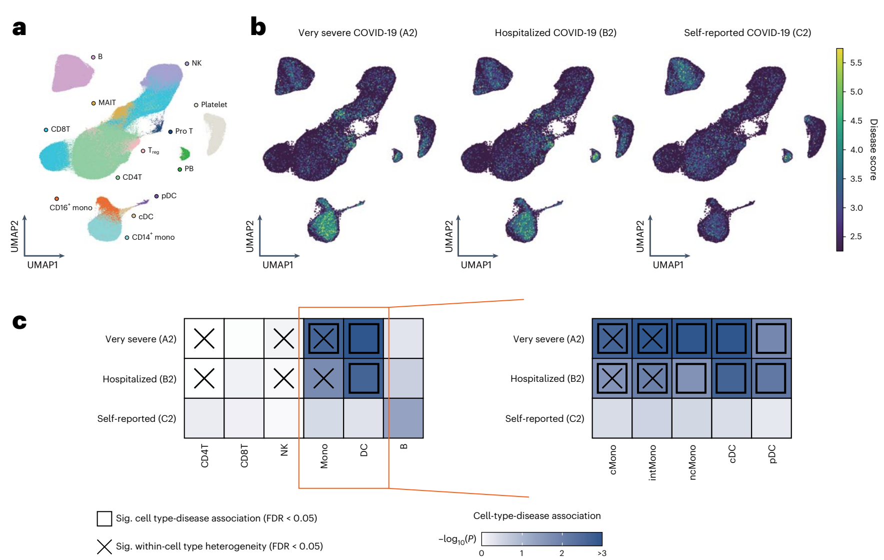

Fig. 1 | Associations of cell types with host genetic risk of COVID-19. **a**, Uniform manifold approximation and projection (UMAP) of 895,460 PBMCs, colored by 13 cell types. **b**, COVID-19 PBMCs colored by scDRS[4] calculated from GWAS summary statistics of three phenotypes[2]. **c**, Heatmaps depicting each cell type–disease association for three disease phenotypes. Colors denote uncorrected *P* values for cell type–disease associations evaluated using a scDRS[4]. False discovery rates (FDRs) were calculated via the Benjamini–Hochberg method across all pairwise comparisons. cDC, conventional dendritic cells; DC, dendritic cells; int, intermediate; MAIT, mucosal-associated invariant T cells; NK, natural killer cells; PB, plasmablasts; pDC, plasmacytoid dendritic cells; pro, proliferative; sig, significant; T_{reg}, regulatory T cells. © 2023, Edahiro, R. et al. CCBY 4.0.

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BEHIND THE PAPER

In early 2020, the Japan COVID-19 Task Force was established as a nationwide multi-center consortium and conducted a COVID-19 GWAS and eQTL analysis in the Japanese population[3,5]. In parallel, we conducted PBMC scRNA-seq analysis of Japanese patients with COVID-19 and healthy controls, supported by the Team Osaka University Research Project and the Nippon Foundation. The COVID-19 GWAS by the Japan COVID-19 Task Force reported the COVID-19-specific eQTL effect of identified risk alleles in a cell-type-specific manner[3]. Motivated by these findings, we chose to focus on ncMono in our study. The 2022 report from the COMBAT Consortium[1], a comprehensive multi-omics study that compared patients with COVID-19 and individuals who had influenza or sepsis with healthy controls, convinced us that ncMono have an important role in the pathogenesis of COVID-19. **R.E & Y.O.**

FROM THE EDITOR

"This study provides an invaluable resource for those interested in studying the role of the innate immune system in COVID-19 at single-cell resolution. By integrating these data with host genetic data, the authors provide much-needed insight into the factors that govern disease severity." **Safia Danovi, Senior Editor, *Nature Genetics*.**