**Single-cell analyses and host genetics highlight the role of innate immune cells in COVID-19 severity**

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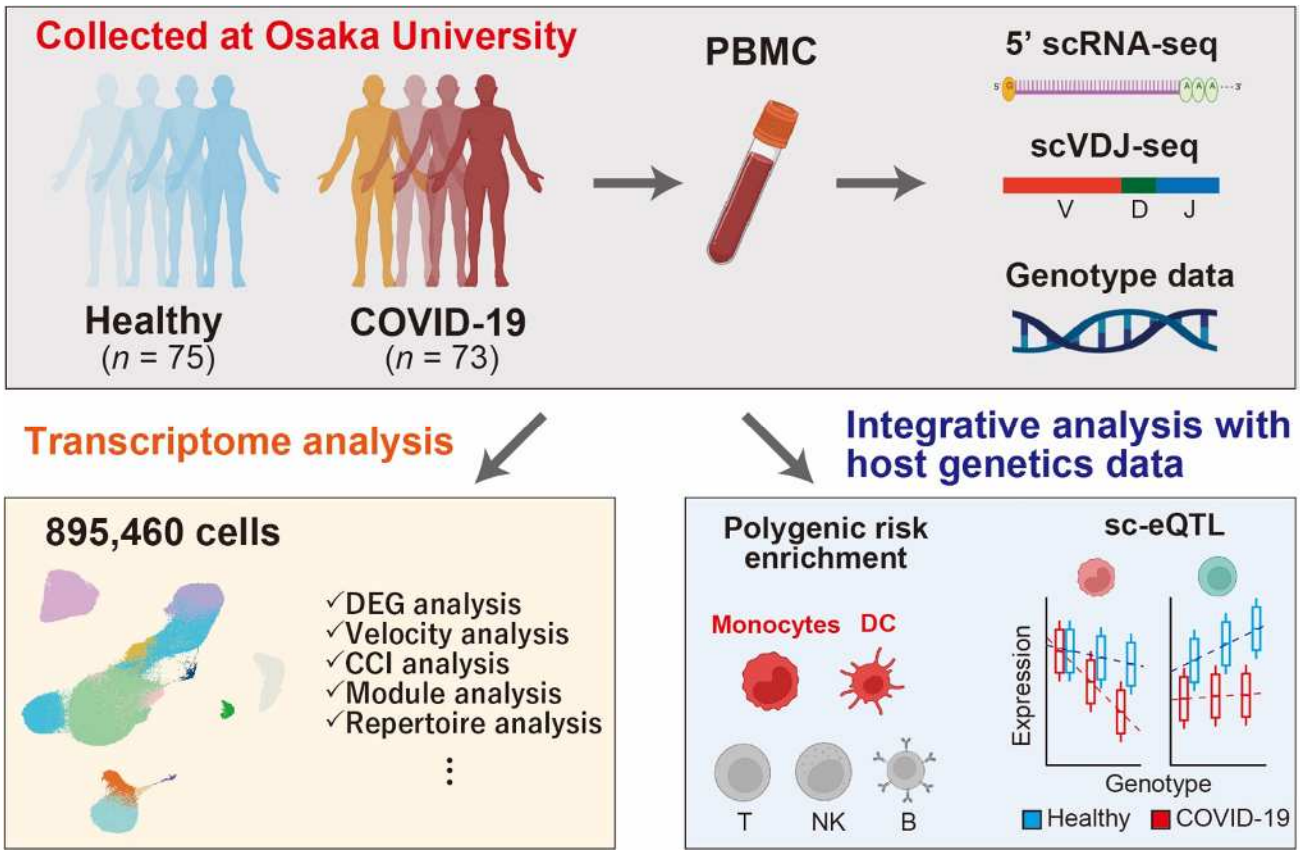
Mechanisms underpinning the dysfunctional immune response in SARS-CoV-2 infection are elusive. We analyzed single-cell transcriptomes and T and B cell receptors of > 895,000 peripheral blood mononuclear cells from 73 Coronavirus disease 2019 (COVID-19) patients and 75 healthy controls of Japanese ancestry with host genetic data. COVID-19 patients showed a low fraction of non-classical monocytes (ncMono). We report downregulated cell transitions from classical monocytes to ncMono in COVID-19 with reduced *CXCL10* expression in ncMono in severe disease. Cell-cell communication analysis inferred decreased cellular interactions involving ncMono in severe COVID-19. Putative disease genes identified by COVID-19 GWAS showed cell type-specific expressions in monocytes and dendritic cells. A COVID-19-associated risk variant at the *IFNAR2* locus (rs13050728) had context-specific and monocyte-specific expression quantitative trait loci effects. Our 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, suggesting a potential new drug target. This study also clearly demonstrated cell-type-specific and context-specific eQTL effects of COVID-19-associated gene variants, implying that such analysis could aid in the understanding of its pathogenesis and the potential for personalized therapy.


Collected at Osaka University
Healthy
(n = 75)
COVID-19
(n = 73)
PBMC
5' scRNA-seq
scVDJ-seq
V D J
Genotype data
Transcriptome analysis
895,460 cells
✓DEG analysis
✓Velocity analysis
✓CCI analysis
✓Module analysis
✓Repertoire analysis
Integrative analysis with host genetics data
Polygenic risk enrichment
Monocytes DC
T NK B
sc-eQTL
Expression
Genotype
Healthy COVID-19