

SARS-COV-2 GENOME-WIDE SINGLE-CHAIN-TRIMER PEPTIDE-MHCS REVEAL CD8+ T CELL LANDSCAPE IN COVID-19 PATIENTS AND DISTINCT TCR REPERTOIRE DYNAMICS

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Background Post-acute sequelae of COVID-19 (PASC), or long COVID, is the emergence of persistent symptoms following acute COVID-19. Detailed characterization of the immunological underpinnings of PASC remain elusive. This may be due to the difficulty in identifying and analyzing the antigen-specific cells that play key roles in the acute and long-term antiviral immune responses. Prominent T cell epitopes have been reported to elicited CD8 T cell response during acute Sars-Cov-2 infection. However, the full spectrum of antigen-specific T cell response with in-depth multi-omics analysis is still unclear given the limited number of antigens being tested.

Methods To reveal the scale and full spectrum of SARS-Cov-2 specific CD8 T cell response in COVID-19, we experimentally scanned the complete SARS-CoV-2 genome sequence to generate mammalian expressed, single chain trimer peptide-MHC (pMHC) libraries presenting >500 predicted epitopes for HLA A*02:01.

Sars-Cov-2 Antigen specific CD8 T cells identified from individual patients from various disease severity comprised with contributions from multiple phenotypes lead us to integrate with the electronic healthy records (EHRs) to guide the interpretation of the molecular signatures of CD8 T cell response with clinical features including sex, age, disease severity, and lab measurements.

We longitudinally characterized CD8 T cells, including those specific for the full SARS-CoV-2-proteome, from 309 COVID-19 patients using single-cell proteomics, transcriptomics, epigenomics, and T cell receptor/antigen pairings.

Results High-throughput profiling of proteome-wide SARS-CoV-2-specific CD8+ T cells. We observed heterogeneity of SARS-CoV-2+ T cells across the virus genome in different patient.

Clonal tracking of Sars-CoV-2 CD8 T cells reveal phenotypic signatures of subset of long-lived T cell clones and their association with decreased PASC risk (figure 1).

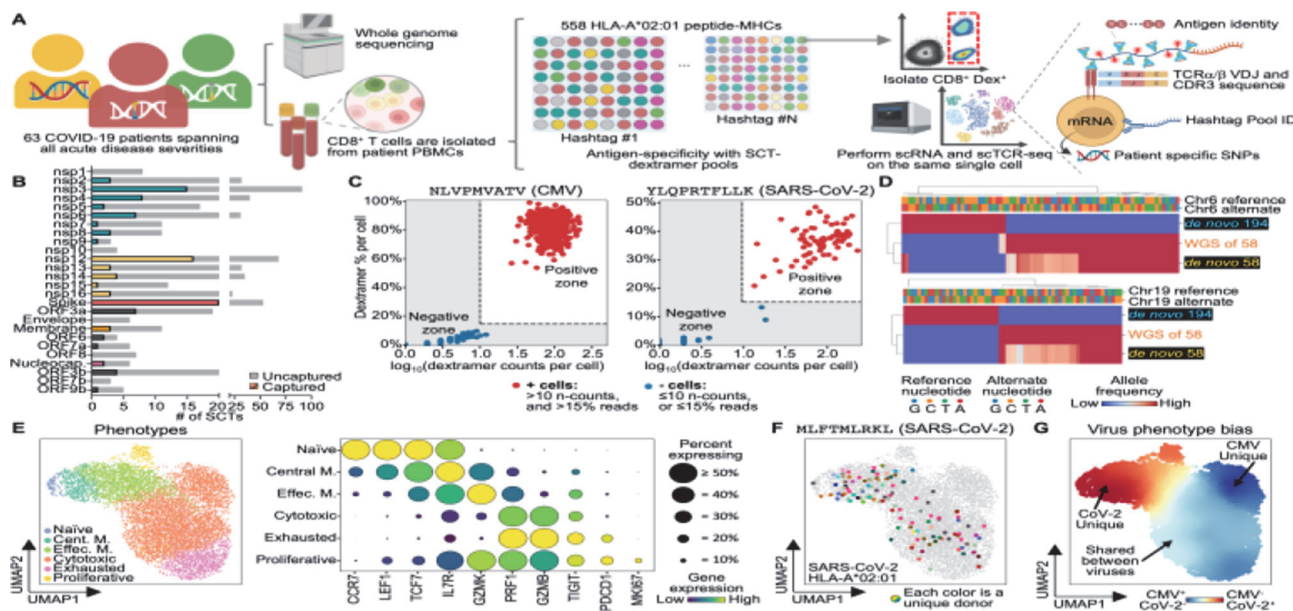
Our multi-omics analyses suggest that SARS-CoV-2 specific CD8+ T cell clonotypes with regulated characteristics play an important role throughout the disease journey.

Conclusions We explore the large-scale application of soluble SCT peptide-MHC reagents expressed by mammalian cells, which enable the high-throughput analysis of antigen-specific CD8 T cells in a large cohort of clinical samples. In addition to the advanced biotechnology, we utilized single-cell multi-omics to study the dynamics of viral-antigen specific CD8+ cytotoxic T cell responses from the time point of initial COVID-19 diagnosis to convalescence 2–3 months later. We defined the spectrum of immunogenic epitopes from the entire genome of SARS-CoV-2 virus using SCT technology. We identified the regulated characteristics of SARS-CoV-2 specific CD8+ T cell clonotypes that protect patients against long COVID. This strategy can be adapted for vaccine design and evaluation, cancer neoantigen identification, and immunotherapy.

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