UNIQUE DIFFERENTIATION AND HOMING FEATURES OF T CELLS IN INDIVIDUALS WITH LONG COVID

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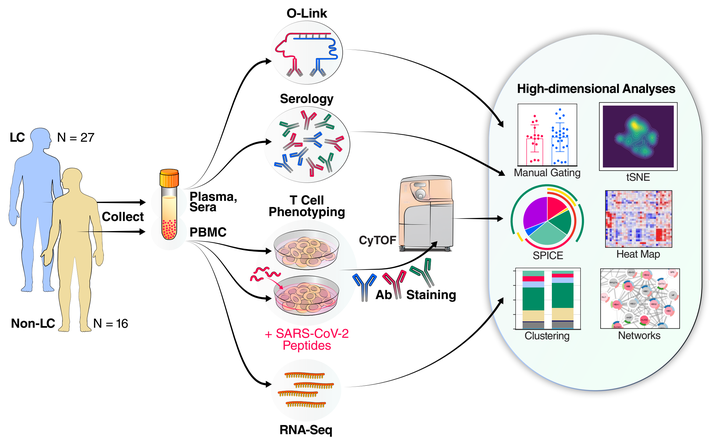
Abstract

Long COVID (LC), a type of post-acute sequelae of SARS-CoV-2 infection (PASC), occurs after at least 10% of SARS-CoV-2 infections, yet its etiology remains poorly understood. Here, we used multiple "omics" assays (CyTOF, RNAseq, Olink) and serology to deeply characterize both global and SARS-CoV-2-specific immunity from blood of individuals with clear LC and non-LC clinical trajectories, 8 months following infection and prior to receipt of any SARS-CoV-2 vaccine. Our analysis focused on deep phenotyping of T cells, which play important roles in immunity against SARS-CoV-2 yet may also contribute to COVID-19 pathogenesis. Our findings demonstrate that individuals with LC exhibit systemic inflammation and immune dysregulation. This is evidenced by global differences in T cell subset distribution in ways that imply ongoing immune responses, as well as by sex-specific perturbations in cytolytic subsets. Individuals with LC harbored increased frequencies of CD4+ T cells poised to migrate to inflamed tissues, and exhausted SARS-CoV-2-specific CD8+ T cells. They also harbored significantly higher levels of SARS-CoV-2 antibodies, and in contrast to non-LC individuals, exhibited a mis-coordination between their SARS-CoV-2-specific T and B cell responses. Collectively, our data suggest that proper crosstalk between the humoral and cellular arms of adaptive immunity has broken down in LC, and that this, perhaps in the context of persistent virus, leads to the immune dysregulation, inflammation, and clinical symptoms associated with this debilitating condition.

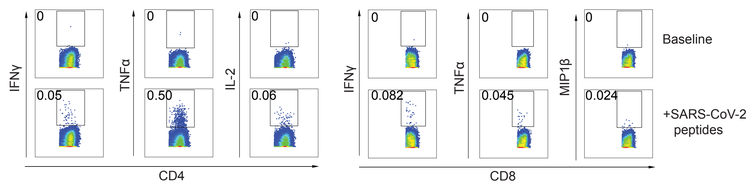
Experimental design



Plasma and sera from 27 individuals with Long COVID (LC) and 16 individuals without LC (Non-LC) were subjected to Olink and serological analyses. PBMCs from the same individuals were subjected to RNAseq analysis, as well as to CyTOF analysis to characterize T cell responses as indicated above.

Results

Identification of SARS-CoV-2-specific T cells in individuals from the LIINC cohort

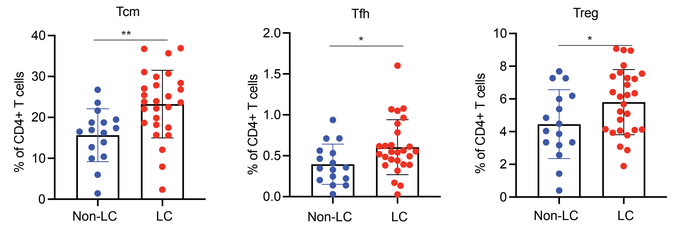


Left: SARS-CoV-2-specific CD4+ T cells are identified as those producing IFNγ, TNFα, or IL2 following SARS-CoV-2 peptide stimulation.

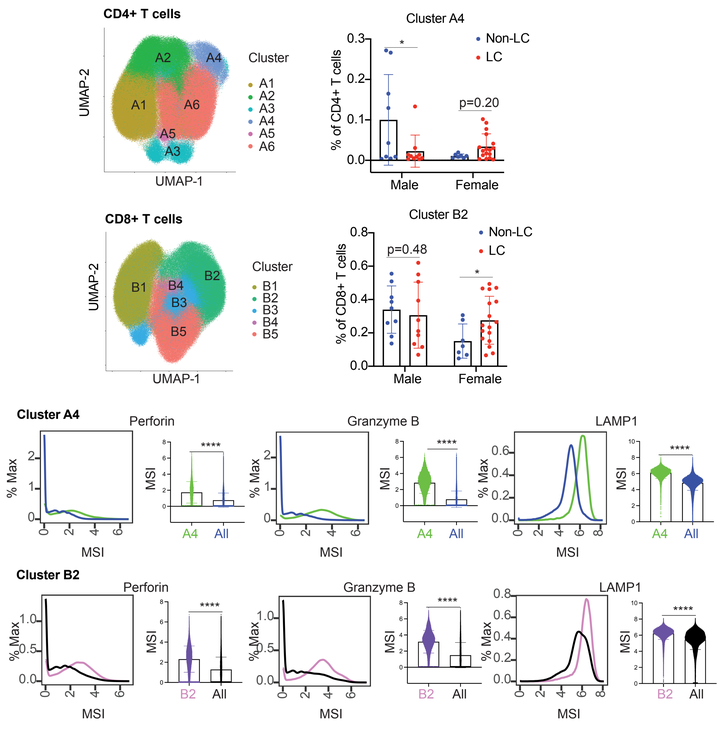
Right: SARS-CoV-2-specific CD8+ T cells are identified as those producing IFN γ, TNFα, or MIP1β following SARS-CoV-2 peptide stimulation.

Results

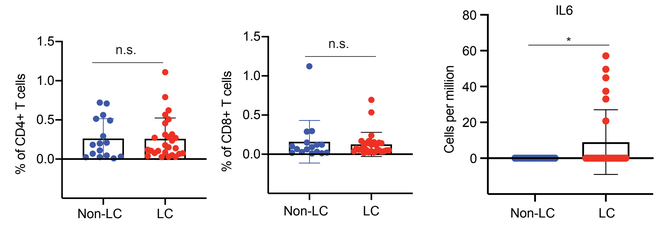
CD4+ T cell subset distribution differs between individuals with vs. without LC



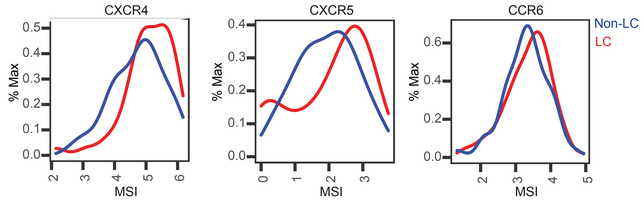
Individuals with LC exhibit different distributions of cytolytic T cell subsets in a sex-dimorphic fashion



No significant differences were observed in frequencies of total SARS-CoV-2 specific T cells between LC vs non-LC, but IL6+ SARS-CoV-2-specific CD4+ T cells were exclusively observed in individuals with LC

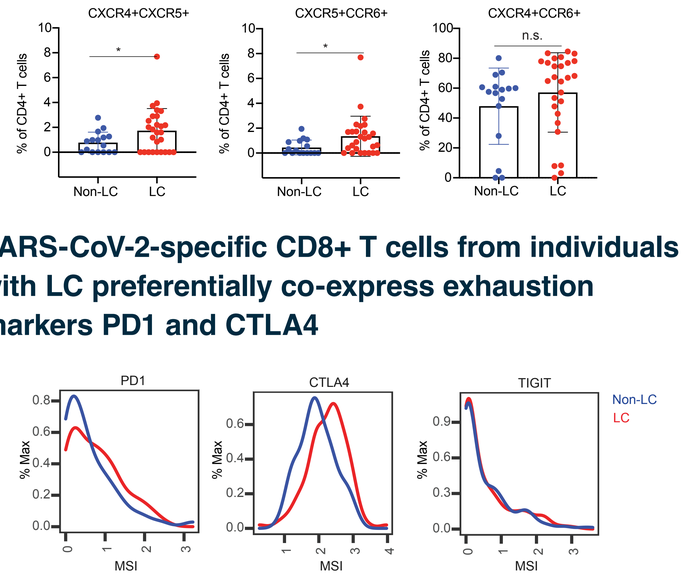


SARS-CoV-2-specific CD4+ T cells from individuals with LC preferentially express tissue homing receptors

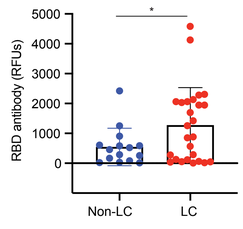


Results (Continued)

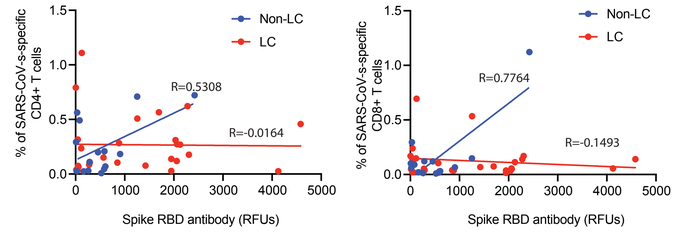
SARS-CoV-2-specific CD8+ T cells from individuals with LC preferentially co-express exhaustion markers PD1 and CTLA4



SARS-CoV-2 antibody levels are elevated in individuals with LC as compared to those without



SARS-CoV-2 antibody levels positively correlate with magnitude of SARS-CoV-2-specific T cell response in individuals without LC, but not in those with LC



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LIINC Long-term Impact of Infection with Novel Coronavirus

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