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Quantitative approaches to understanding immunological heterogeneity in COVID-19

In COVID-19, dysregulated inflammatory responses accompanied by lymphopenia are characteristic of severe disease. Nearly two years into the pandemic, much remains unknown about the mechanisms of immunopathology in patients with COVID-19, including what controls the diversity of responses to SARS-CoV-2 infection. In combination with clinical and experimental efforts, we have deployed a variety of mathematical and computational immunology approaches to help untangle complicated longitudinal immunological data, and to generate new hypotheses about factors influencing disease severity and dynamics.

To begin to answer fundamental questions about immunopathology and heterogeneity in COVID-19, we developed a mechanistic mathematical model of the immunological response to SARS-CoV-2 infection that includes several innate and adaptive immune cell populations and signalling pathways. By expanding a virtual patient cohort, we identified divergent monocyte-to-macrophage differentiation rates between virtual patients with either mild or severe COVID-19. Further, our results suggest that maximum IL-6 concentrations may act as a biomarker for CD8+ T cell depletion. In the same virtual patient cohort, we also studied how viral variants influence immunopathology by merging within-host SARS-CoV-2 evolutionary data and our cohort of realistic virtual patients. We predicted the combined effects of spike protein and interferon-evading mutations on COVID-19 severity, and our results suggest that an individual's immune response and their potential propensity for severe COVID-19 are the key factors distinguishing COVID-19 disease courses and outcomes. Our approaches provide a quantitative basis for exploring the drivers of immunopathology in COVID-19, and a framework for the continued study of heterogeneity during SARS-CoV-2 and other viral infections.