Uncovering hidden sources of SARS-CoV-2 viral evolution: A call to action

The COVID-19 pandemic continues to wreak havoc worldwide with a substantial fraction of the population already been infected with SARS-CoV-2 despite the increasing availability of vaccines. This is largely due to the repeated waves of novel variants (e.g., alpha, beta, gamma, delta, and omicron), with increased transmissibility and more adept immune escape.\(^1,2\) These novel variants appear suddenly with a large collection of mutations that arise unexpectedly without evolutionary intermediates or a documented step-wise accumulation of mutations. This paradox is further compounded by the fact that the coronavirus replication machinery encodes proofreading function that results in fewer errors than other RNA viruses.\(^3\) Together, these findings suggest that a source of cryptic SARS-CoV-2 evolution in the community exists that is not yet readily identified by the current viral surveillance strategies.

In 2020, reports began to surface about the appearance of unusual patterns of SARS-CoV-2 infection and evolution within immunosuppressed patients. One of the first such reports was in a heavily immunosuppressed patient with an autoimmune disease who had 5 months of persistent infection and a prolonged period of SARS-CoV-2 viral evolution, especially within the receptor-binding domain (RBD) of the S gene.\(^4\) A number of the SARS-CoV-2 mutations found in this individual were ultimately found to be signature mutations for subsequent variants of concern or interest (VOC/VOIs), raising the possibility that emergence of new viral variants may have arose in an immunocompromised individual before spilling over to the general population.

In the study by Simons et al. published in this issue of Transplant Infectious Diseases, the authors extend our knowledge of SARS-CoV-2 evolution by reporting two additional cases of immunosuppressed individuals with persistent SARS-CoV-2 infection in whom the viral populations acquired mutations associated with circulating VOCs. There were steady increases in intra-host viral population diversity over the course of infection in both patients. Over 131 days, patient A developed a Spike E484Q mutation (also observed in formerly monitored variant Kappa) and the deletion of residues 241–243 (VOC Beta), while Patient B developed a Spike E484K mutation (VOCs Beta and Gamma as well as formerly monitored variants Zeta, Eta, Theta, and Iota) over 106 days of infection. These mutations have been previously monitored for signs of viral persistence and drug resistance.

While these case reports contribute to our understanding of viral evolution in immunosuppressed patients, it also highlights the need for systematic evaluations of SARS-CoV-2 persistence and optimal treatment strategies in this understudied patient population to answer pressing questions. These fundamental questions include what is the frequency of persistent COVID-19 in the immunosuppressed population.
population, which immunosuppressive conditions or medications confer the greatest risk of suboptimal viral clearance, and should combinations of antiviral treatments be used for the treatment of immunosuppressed patients with COVID-19? Given the broad spectrum of immunosuppressive conditions and the challenges of identifying sufficient numbers of patients at any one clinical center, filling these knowledge gaps will likely require a coordinated effort among a network of committed investigators and funders. The answers to these questions will not only allow us to better care for our immunosuppressed patients with COVID-19 but will provide crucial insights into the immune correlates of viral clearance and may uncover the keys to prevent the emergence of future SARS-CoV-2 variants that serve to fuel the ongoing pandemic.

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CONFLICT OF INTEREST
Dr. Li has consulted for Recovery Therapeutics.

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