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Article | Published: 05 February 2021

SARS-CoV-2 evolution during treatment of chronic infection

Steven A. Kemp, Dami A. Collier, [...] Ravindra K. Gupta

Nature 592, 277–282 (2021) | Cite this article

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Abstract

The spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical for virus infection through the engagement of the human ACE2 protein¹ and is a major antibody target. Here we show that chronic infection with SARS-CoV-2 leads to viral evolution and reduced sensitivity to neutralizing antibodies in an immunosuppressed individual treated with convalescent plasma, by generating whole-genome ultra-deep sequences for 23 time points that span 101 days and using in vitro techniques to characterize the mutations revealed by sequencing. There was little change in the overall structure of the viral population after two courses of remdesivir during the first 57 days. However, after convalescent plasma therapy, we observed large, dynamic shifts in the viral population, with the emergence of a dominant viral strain that contained a substitution (D796H) in the S2 subunit and a deletion (Δ H69/ Δ V70) in the S1 N-terminal domain of the spike protein. As passively transferred serum antibodies diminished, viruses with the escape genotype were reduced in frequency, before returning during a final, unsuccessful course of convalescent plasma treatment. In vitro, the spike double mutant bearing both Δ H69/ Δ V70 and D796H conferred modestly decreased sensitivity to convalescent plasma, while maintaining infectivity levels that were similar to the wild-type virus. The spike substitution mutant D796H appeared to be the main contributor to the decreased susceptibility to neutralizing antibodies, but this mutation resulted in an infectivity defect. The spike deletion mutant Δ H69/ Δ V70 had a twofold higher level of infectivity than wild-type SARS-CoV-2, possibly compensating for the reduced infectivity of the D796H mutation. These data reveal strong selection on SARS-CoV-2 during convalescent plasma therapy, which is associated with the emergence of viral variants that show evidence of reduced susceptibility to neutralizing antibodies in immunosuppressed individuals.

Main

A septuagenarian male was admitted to a tertiary hospital in the summer of 2020 and had tested positive for SARS-CoV-2 using reverse-transcription quantitative PCR (RT-qPCR) 35 days previously in a nasopharyngeal swab (day 1) at a local hospital (Extended Data Figs. 1, 2). His past medical history included marginal B cell lymphoma diagnosed in 2012, with previous chemotherapy including vincristine, prednisolone, cyclophosphamide and anti-CD20 B cell depletion with rituximab. It is likely that both chemotherapy and underlying lymphoma contributed to combined immunodeficiency of B and T cells (Extended Data Figs. 2, 3 and Supplementary Table 1). Computed tomography of the chest showed widespread abnormalities consistent with pneumonia associated with coronavirus disease 2019 (COVID-19) (Supplementary Fig. 1). Treatment included two 10-day courses of remdesivir with a 5-day gap in between (Extended Data Fig. 1). Two units of convalescent plasma were administered on days 63 and 65 (Extended Data Fig. 3). After clinical deterioration, remdesivir and a unit of convalescent plasma were administered on day 95, but the individual died on day 102 (Supplementary Note).

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Spike mutations impair neutralizing antibody pote...

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