Characterization of SARS-CoV-2 evolution in the light of chronic infections

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The evolution of SARS-CoV-2 within chronically infected individuals (CIIs) has likely played a critical role in the emergence of Variants of Concern (VOCs), defined as variants with altered transmissibility, immune escape, or disease severity. CIIs are characterized by prolonged infections and occur most often in individuals with compromised immune systems leading to an environment conducive to the accumulation of adaptive mutations. This is due to the combination of large viral population sizes, weak selection pressure from the host immune system, multiple niches available for the virus, and prolonged time. Importantly, we surmise that all of the above may enable the occurrence of rare evolutionary events that potentially spawn large novelty, as described herein. This research focuses on understanding the evolutionary dynamics of SARS-CoV-2 within CIIs through three core objectives. The first aim is to detect positive correlations between pairs of mutations that emerge in CIIs, with the aim of inferring epistatic interactions. By analyzing mutation pairs and their fitness effects, this study seeks to understand how compensatory or synergistic mutations drive viral adaptation. The second objective involves mapping onward transmission events originating from CIIs. Using phylogenetic approaches and temporal analyses of clade composition, this research aims to uncover patterns in mutation acquisition and divergence, shedding light on how CIIs contribute to the broader spread of adaptive mutations. Finally, the third aim investigates the emergence of cheater viruses in SARS-CoV-2 populations, particular in CIIs. Cheater viruses, also known as defective interfering particles, are defective when infecting cells on their own. However, during co-infection with intact viruses, cheaters exploit them and replicate rapidly. This research surmises that point-mutant cheater viruses may emerge readily in CIIs and perhaps serve as stepping-stones towards adaptation. The research will integrate advanced bioinformatics tools with experimental validation through reverse genetics and tissue culture systems. Ultimately this work will provide novel insights into the unique drivers that allow the successive emergence of VOCs in SARS-CoV-2 evolution, while offering a broader understanding of RNA virus dynamics.