Potential Drug Resistance in SARS-CoV-2: Importance of Mutational Surveillance in Pandemics

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Abstract

Repurposed antiviral drugs such as remdesivir and favipiravir will likely continue before clinical trials are completed. Both drugs are inhibitors of viral RNA-dependent RNA polymerase (RdRp). Accumulation of mutations in SARS-CoV-2 RdRp may facilitate antigenic drift, generating resistance against these drugs. Due to the lengthening pandemic and evolving nature of the virus, predicting potential residues prone to mutation is crucial for the management of drug resistance. We used a rational high-throughput ligand-based protein design strategy to generate more than 100,000 designs each for the remdesivir- and favipiravir-binding site of RdRp to identify mutational hotspots. After designing 46 and 41 residues in the remdesivir- and favipiravir-binding sites of nsp12, respectively, the designs retained 97-98% sequence identity, suggesting very few mutations in nsp12 are required for SARS-CoV-2 to attain drug resistance. Several mutants displayed decreased binding affinity to these drugs, suggesting drug resistance. These hotspot residues had a higher probability of undergoing selective mutation, thus conferring drug resistance. For favipiravir, out of 134 mutations documented in the CoV-GLUE database, 63 specific mutations were already predicted as resistant in our calculations, thus attaining ~47% correlation with the clinical data. The data indicate that SARS-CoV-2 may develop resistance to these drugs within a short time and after very few mutations. Identifying potential residues prone to mutation is critical for understanding COVID-19 pathogenesis and may guide developing strategies for antiviral design and discovery. Also, the findings improve our understanding of the potential signatures of adaptation in SARS-CoV-2 against these antivirals.

Keywords: Drug resistance; protein design; mutation; directed evolution; viral fitness; evolutionary pressure.