Global Genomic Analysis of SARS-CoV-2 RNA Dependent RNA Polymerase Evolution and Antiviral Drug Resistance

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4620851
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Year 2021

Title Global Genomic Analysis of SARS-CoV-2 RNA Dependent RNA Polymerase Evolution and Antiviral Drug Resistance

Journal Microorganisms

Volume 9

Number 5

Pages / **Article-Number** 1094

Keywords RNA dependent RNA polymerase; SARS-CoV-2; diagnostics; evolution; genome analysis; remdesivir; resistance; surveillance

A variety of antiviral treatments for COVID-19 have been investigated, involving many repurposed drugs. Currently, the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp, encoded by; nsp12-nsp7-nsp8;) has been targeted by numerous inhibitors, e.g., remdesivir, the only provisionally approved treatment to-date, although the clinical impact of these interventions remains inconclusive. However, the potential emergence of antiviral resistance poses a threat to the efficacy of any successful therapies on a wide scale. Here, we propose a framework to monitor the emergence of antiviral resistance, and as a proof of concept, we address the interaction between RdRp and remdesivir. We show that SARS-CoV-2 RdRp is under purifying selection, that potential escape mutations are rare in circulating lineages, and that those mutations, where present, do not destabilise RdRp. In more than 56,000 viral genomes from 105 countries from the first pandemic wave, we found negative selective pressure affecting; nsp12; (Tajima's D = -2.62), with potential antiviral escape mutations in only 0.3% of sequenced genomes. Potential escape mutations included known key residues, such as Nsp12:Val473 and Nsp12:Arg555. Of the potential escape mutations involved globally, in silico structural models found that they were unlikely to be associated with loss of stability in RdRp. No potential escape mutation was found in a local cohort of remdesivir treated patients. Collectively, these findings indicate that RdRp is a suitable drug target, and that remdesivir does not seem to exert high selective pressure. We anticipate our framework to be the starting point of a larger effort for a global monitoring of drug resistance throughout the COVID-19 pandemic.

Publisher MDPI

ISSN/ISBN 2076-2607

Full Text on edoc No;
Digital Object Identifier DOI 10.3390/microorganisms9051094
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/34069681
ISI-Number WOS:000662407200001
Document type (ISI) Journal Article