Press Release

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LEIBNIZ INSTITUTE OF VIROLOGY (LIV)

SARS-CoV-2:
Antiviral treatment promotes emergence of new variants

Study published in Cell Reports Medicine

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Hamburg. Do patients with prolonged infections contribute to the emergence of new SARS-CoV-2 variants? A research team from the Leibniz Institute of Virology (LIV) and the University Medical Center Hamburg-Eppendorf (UKE) has investigated this question in more detail and has now been able to show that it is not the prolonged infection per se that leads to the emergence of new variants. Rather, it requires an evolutionary bottleneck such as can be created by antiviral treatment. The results have now appeared in the renowned journal *Cell Reports Medicine* as pre-proof version.

Prolonged SARS-CoV-2 infections occur primarily in immunocompromised patients and have been repeatedly discussed as important contributors in viral evolution: Reduced immune restriction could lead to a broad increase in viral diversity within the host, favoring the emergence of new variants, especially if antiviral treatments such as with *Remdesivir* or convalescent plasma exert selection pressure for the acquisition of escape mutations.

Analysis of genomic diversity in prolonged infections

In the published study, a research team led by Prof. Adam Grundhoff (LIV) and Prof. Nicole Fischer (UKE) has now investigated whether patients with prolonged infections generally exhibit increased viral evolution, which could allow for the more rapid emergence of SARS-CoV-2 variants, or whether certain treatment regimens promote the emergence of new mutations.

For this purpose, the genomic diversity within the host was investigated by whole genome sequencing in longitudinal samples from 14 patients with prolonged viral persistence (30 - 146 days) during severe COVID-19 disease; including immunocompromised and immunocompetent patients with or without antiviral treatment to assess the occurrence of mutations with and without selection pressure.

"Overall, the virus was remarkably stable in the vast majority of individuals studied. However, in one patient treated with *Remdesivir*, we observed that a high number of mutations occurred immediately after the start of treatment - including at least one mutation that was highly likely to confer increased resistance to *Remdesivir*," explains Prof. Adam Grundhoff, head of the LIV Virus Genomics Research Group.

Antiviral treatment promotes evolutionary bottleneck

Patients with prolonged SARS-CoV-2 infection and antiviral *Remdesivir* treatment showed a significant increase in viral intra-host diversity with newly emerging mutations. In contrast, in patients receiving anti-inflammatory treatment alone, the emergence of new variants was observed only sporadically.

"Our work shows that it is not the long duration of the infection per se that leads to the emergence of new variants. Rather, this requires an evolutionary bottleneck, such as can be created by antiviral treatment. This finding is particularly important in view of the recent discussions on the use of *Remdesivir* for the treatment of non-hospitalized high-risk patients, but also for the introduction of potentially new antiviral therapeutics," Prof. Nicole Fischer from UKE adds to the results.

Andreas Heyer, Thomas Günther, Alexis Robitaille, Marc Lütgehetmann, Marylyn M. Addo, Dominik Jarczak, Stefan Kluge, Martin Aepfelbacher, Julian Schulze zur Wiesch, Nicole Fischer and Adam Grundhoff. ***Remdesivir-induced emergence of SARS-CoV-2 variants in patients with prolonged infection.*** Cell Reports Medicine (August 16, 2022). https://doi.org/10.1016/j.xcrm.2022.100735

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Leibniz Institute of Virology, LIV

The Leibniz Institute of Virology (LIV) conducts research into human pathogenic viruses with the aim of understanding virus-related diseases and developing new therapeutic approaches.

Based on basic experimental research, new starting points for improved procedures for the treatment of viral diseases such as AIDS, influenza and hepatitis, but also of emerging viral infections, are to be developed. With its main research areas, the LIV covers the world's most important viral infectious agents.

Founded in 1948, the institute's origins go back to the patron Philipp F. Reemtsma and the neurologist Heinrich Pette. As a foundation under civil law, the LIV is a non-profit and independent research institution that has been a member of the Leibniz Association since 1995. The institute is funded proportionally by the German Federal Ministry of Health

(BMG) and the joint research funding of the federal states, represented by the Ministry of Science, Research, Equality and Districts (BWFGB) of the Free and Hanseatic City of Hamburg.
In addition, a large proportion is obtained through competitive procedures.
LIV is member of the German Center for Infection Research (DZIF).

More information: www.leibniz-liv.de

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