Mutations in spike protein of SARS-CoV-2 pirola variant found to augment infection of lung cells

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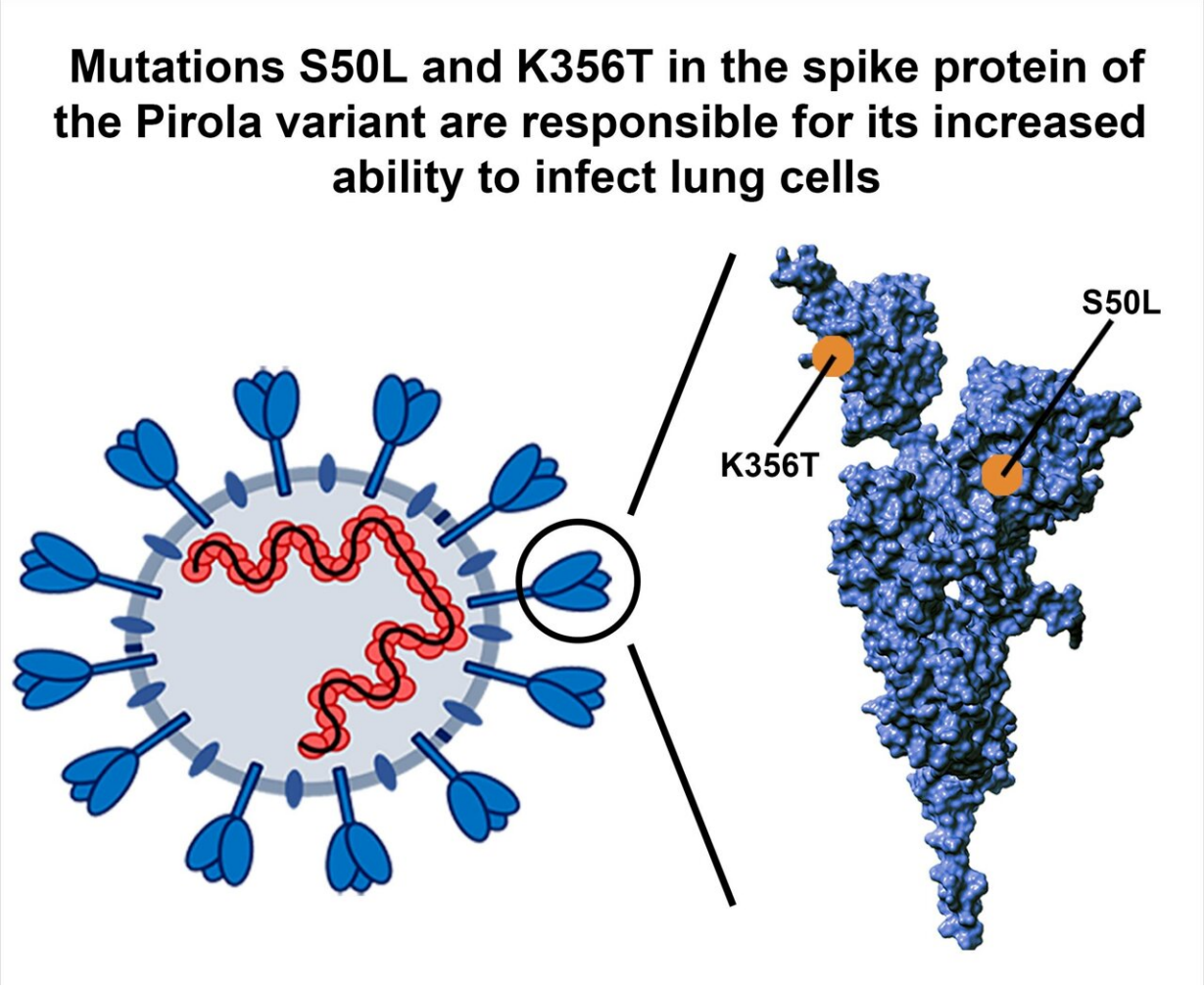

The spike protein of the heavily mutated Pirola variant harbors two mutations, S50L and K356T, which increase infectious entry into lung cells. Credit: Markus

Hoffmann/DPZ

Despite the end of the pandemic, COVID-19 continues to pose a serious health threat. Most individuals have established robust immune protection and do not develop severe disease but the infection can still lead to marked and sometimes long-lasting disease symptoms.

In the late summer of 2023 a new SARS-CoV-2 variant emerged, BA.2.86 (pirola), which, based on genetics, differs markedly from all previously circulating variants. A team of researchers from the German Primate Center (DPZ, Göttingen), jointly with partners at Charité (Berlin), Hannover Medical School, Helmholtz Center for Infection Research (Braunschweig) and Friedrich-Alexander-University Erlangen-Nuremberg has now investigated the biological properties of the new variant.

The researchers discovered that the pirola variant, in contrast the all previously circulating omicron variants, enters lung cells with high efficiency and uses the cellular enzyme TMPRss2 for entry, thereby exhibiting surprising parallels to variants alpha, beta, gamma and delta that circulated during the first years of the pandemic. The improved entry into lung cells might indicate that the virus is more aggressive but production of new, infectious viral particles in infected cells was reduced, which may limit spread and pathogenic potential.

The researchers report in the journal *Cell* that the pirola variant is resistant against all therapeutic antibodies and efficiently evades antibody responses in vaccinated individuals with and without breakthrough infection. However, the virus was appreciably inhibited by antibodies elicited by the new, XBB.1.5-adpated mRNA vaccine.

In summary, the results show that four years after the start of the pandemic the virus is still capable of profound changes and can reacquire properties that may promote the development of severe disease .

The spread of SARS-CoV-2 is associated with the constant emergence of new viral variants. These variants have acquired mutations in the spike protein, which allow evasion of neutralizing antibodies in vaccinated and convalescent individuals. The emergence of viral variants started with the alpha variant followed by the beta, gamma and delta variants.

At the end of the year 2021 the omicron variant became globally dominant, which, based on genome sequence, differed markedly from previously circulating variants. However, the virus had to pay a price for this massive change. Thus, the omicron variant evades neutralizing antibodies and is transmitted with high efficiency but has lost the ability to efficiently use a host cell enzyme, the protease TMPRSS2, for lung cell entry. As a consequence, the omicron variant induces pneumonia less frequently.

Pirola: A quantum leap in SARS-CoV-2 evolution

Descendants of the omicron variant dominated globally until the end of the year 2023. New variants frequently differed only by few mutations from their predecessors and there was evidence that viruses circulating in 2023 had only limited options to evade antibody pressure in the human population. Therefore, the discovery of a new SARS-CoV-2 omicron subvariant, pirola (BA.2.86), which, based on genome sequence, strongly differed from other circulating viruses drew a lot of attention.

The pirola variant, analogous to the omicron variant, likely arose in

immunocompromised patients and presents a quantum leap in SARS-CoV-2 evolution. The spike protein of the pirola variant harbors more than 30 mutations relative to its precursor variant, BA.2, and it is largely unknown how these mutations affect the biological properties of the virus.

A team of researchers from the German Primate Center (DPZ) led by Markus Hoffmann and Stefan Pöhlmann addressed this question jointly with the research groups of Christian Drosten (Charité, Berlin), Georg Behrens (Hannover Medical School), Luka Cicin-Sain (Helmholtz Center for Infection Research, Braunschweig) and Hans-Martin Jäck (Friedrich-Alexander-University Erlangen Nuremberg).

Pirola can infect lung cells more efficiently

The researchers discovered that the pirola variant, in contrast to all previously circulating omicron subvariants, enters lung cells with high efficiency and in a TMPRSS2-dependent manner. Further, they could demonstrate that mutations S50L and K356T in the spike protein of the pirola variant are important for the highly efficient lung cell entry.

"It is noteworthy that two years after the global dominance of the omicron variant, which fails to robustly enter lung cells, now a quite different virus is spreading and that this virus is able to again enter lung cells with high efficiency. If the augmented lung cell entry translates into more severe disease upon infection with the pirola variant remains to be investigated in animal models," says Pöhlmann, head of the Infection Biology Unity of the German Primate Center.

Pirola replicates less well than its predecessors

SARS-CoV-2 infected cells produce new virus particles many of which,

but not all, are able to infect new cells. The researchers provided evidence that cells infected by the pirola variant are less well able than cells infected with previous variants to produce intact viral particles. "The relatively inefficient production of infectious particles by cells infected with the pirola variant was surprising," says Hoffmann, the lead contact of the study.

"It will be interesting to analyze which mechanism is responsible. Maybe the infected cells produce defective interfering particles, which regulate spread of the pirola variant and contribute to antibody evasion."

Therapeutic antibodies are ineffective against pirola

Recombinantly produced neutralizing antibodies were successfully used for COVID-19 prophylaxis and therapy. However, due to the emergence of viral variants with mutations in the antibody binding sites most of those antibodies are not active against currently circulating variants. The present study shows that the pirola variant is no exception—none of the tested antibodies was able to neutralize the virus.

"These results show that the development of new, broad spectrum antibodies is an important task," says Hoffmann.

New, adapted vaccine protects against pirola

The pirola variant was also able to evade antibodies induced by vaccination or infection but with less efficiency than the contemporaneously circulating Eris variant (EG.5.1). However, antibodies induced by vaccination with the new XBB.1.5-adapted vaccine were able to appreciably inhibit both the pirola and the Eris variant.

"These results suggest that the XBB.1.5-adpated vaccine might induce a robust, although likely short-lived, protection against infection with the pirola variant," says Hoffmann.

"In this context it is interesting that subvariants of pirola are currently globally on the rise that harbor an additional mutation in the spike protein, which may increase antibody evasion. The virus is in the process of optimizing itself and the consequences of this optimization should be studied," adds Lu Zhang, first author of the study.

More information: Lu Zhang et al, SARS-CoV-2 BA.2.86 enters lung cells and evades neutralizing antibodies with high efficiency, *Cell* (2024). DOI: 10.1016/j.cell.2023.12.025

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