Health

COVID-19 research: double-acting antiviral strategy

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news

Frankfurt scientists identify possible weaknesses of the SARS-CoV-2 virus

by Adolf Albus

(30.07.2020) When the SARS-CoV-2 virus penetrates human cells, it has its own proteins made by the human host cell. One of these virus proteins called PLpro is essential for the virus to multiply and spread quickly.

An international team of scientists led by the Goethe University Frankfurt and the University Hospital Frankfurt has now found that the pharmacological inhibition of this viral enzyme not only blocks the virus multiplication, but also strengthens the antiviral immune response (Nature, DOI 10.1038 / s41586-020 -2601-5).

When infected, the SARS-CoV-2 virus has to overcome various defense mechanisms in the human body. This includes the unspecific or innate immune defense. Affected body cells release messenger substances, so-called type I interferons. These attract natural killer cells, which kill the infected cells.

One of the reasons why the SARS-CoV-2 virus is so successful – and therefore dangerous – is because it can suppress the non-specific immune response. For this purpose, the human cell has the virus protein PLpro (papain-like protease) produced. PLpro has two functions: it contributes to the maturation and release of new virus particles, and it suppresses the formation of type I interferons. The German and Dutch scientists have now been able to observe these processes in cell culture experiments. If they also blocked PLpro, virus production was inhibited and at the same time the innate immune response of human cells was strengthened.

Prof. Ivan Đikić, director of the Institute of Biochemistry II at the University Clinic Frankfurt and last author of the thesis, explains: "We used the active ingredient GRL-0617, a non-covalent inhibitor of PLpro, and examined its mode of action biochemically, structurally and functionally. We concluded that inhibition of PLpro is a promising "double strike" therapeutic strategy for the treatment of COVID-19. The further development of PLpro-inhibiting substance classes for use in clinical studies is now a central challenge for this therapeutic approach. "

Another important finding of this work is that the PLpro virus protein from SARS-CoV-2 with higher activity cleaves ISG-15 (interferon-stimulated gene-15) from cellular proteins than the SARS equivalent, which leads to a stronger inhibition of Interferon Type I production leads. This is in line with recent clinical observations that show that COVID-19 has a reduced interferon response compared to other respiratory viruses such as influenza and SARS.

In order to understand in detail how PLpro inhibition stops the virus, scientists in Frankfurt, Munich, Mainz, Freiburg and Leiden have combined their biochemical, structural, computer-aided and virological expertise in close cooperation.

Donghyuk Shin, post-doctoral researcher and first author of the manuscript, comments: "Personally, I would like to underline the importance of science and in particular highlight the potential that emerges from a culture of collaboration. When I saw our joint results, I was really grateful to be a scientist. "

Prof. Sandra Ciesek, director of the Institute for Medical Virology at the University Hospital Frankfurt, explains that the papain-like protease is an extremely attractive antiviral target for her as a doctor, since its inhibition would be a "double strike" against SARS-CoV-2. She emphasizes the excellent cooperation between the two institutes: "Especially when researching a new clinical picture, everyone benefits from the interdisciplinary cooperation and the different experiences and perspectives."

Publikation: Donghyuk Shin, Rukmini Mukherjee, Diana Grewe, Denisa Bojkova, Kheewoong Baek, Anshu Bhattacharya, Laura Schulz, Marek Widera, Ahmad Reza Mehdipour, Georg Tascher, Klaus-Peter Knobeloch, Krishnaraj Rajalingam, Huib Ovaa, Brenda Schulman, Jindrich Cinatl, Gerhard Hummer, Sandra Ciesek, Ivan Dikic. Inhibition of papain-like protease PLpro blocks 1 SARS-CoV-2 spread and 2 promotes anti-viral immunity. Nature, DOI