Long-lasting and profound reprogramming of immune cells after COVID-19
Novel study published on innate immunity in SARS

SARS-CoV-2 infection causes severe inflammation of the lungs and other vital organs. Why some infected individuals respond with an exaggerated immune response to the virus remains not well understood. In a new study, researchers at the University Hospital of Cologne are focusing on a surface protein of SARS-CoV-2, the spike protein. This protein is primarily known for its stimulatory activity of the so-called acquired immunity and antibody generation. The spike protein is the basic building block for most vaccines targeting SARS-CoV-2.

For the first time, the work of the Cologne researchers investigates the effect of the spike protein on the innate immune system, which is strongly associated with severity of disease. The results have now been published in the renowned scientific journal "EMBO Molecular Medicine".

SARS-CoV-2 infection can lead to a massive release of pro-inflammatory signalling molecules, so-called cytokines, which in some patients leads to severe organ damage and, in a chain reaction, attracts activated immune cells into the tissue. How the virus triggers the release of cytokines is not well understood. Researchers in Cologne have now been able to show that certain white blood cells (macrophages, also known as phagocytes) are massively stimulated by the viral spike protein to produce the pro-inflammatory signalling molecule interleukin-1. However, this was only observed when macrophages from COVID-19 patients were examined in the experiments. Macrophages from people who had not yet been infected with SARS-CoV-2 did not react to the spike protein. "This selective immune response of a classical signalling pathway of the innate immune system is very unusual and has not yet been described in this way. There are now many starting points here to better understand why some people react with an exaggerated response of the immune system" explains Dr. Jan Rybniker (MD-PhD), head of the Infectious Diseases Research Laboratory at the University Hospital of Cologne (www.tru-id.de) and lead author of the study. The signalling pathway of the so-called inflammasome, which was investigated in this study, is also considered as a possible therapeutic target for immunomodulatory therapies in severe COVID-19 infections. A scientific basis for this approach, was identified in this work.

Interestingly, macrophages were still highly reactive towards the spike protein several weeks to months after SARS-CoV-2 infection. "Since macrophages have a very short lifespan of only a few days, this argues for changes in the genetic material of macrophage progenitor cells. We were able to detect these so-called epigenetic changes through elaborate sequencing experiments," reports Dr. Sebastian Theobald (PhD), postdoctoral researcher at the University Hospital of Cologne and first author of the study. These profound changes found in macrophages from otherwise healthy individuals after infection with SARS-CoV-2 can now be used for a better understanding of long-term consequences of COVID-19, for example within post-COVID syndromes.

The findings are also relevant for vaccination approaches against the disease. "Our work extensively examines the immune response towards the spike protein. Almost all currently available vaccinations are based on this protein," reports Dr. Alexander Simonis (MD), assistant physician at the University Hospital of Cologne and second author of the study. It is certainly beneficial for the success of the various vaccine constructs, that the spike protein leads to a strong
activation of the innate immune system. However, some side effects we observe after vaccination may also result from potent immune activation of macrophages exposed to the spike protein, Rybniker adds. These multifaceted and in-depth investigations were only possible with the help of several collaborating partners. A total of eight research groups from the University of Cologne and the Max Planck Institute for the Biology of Aging were involved in the study, according to Dr. Jan Rybniker. The study was funded by the German Research Foundation (DFG), the German Center for Infection Research (DZIF) and the Netzwerk Universitätsmedizin (NUM).

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For further communication and requests:
Christoph Wanko
Stellvertretender Pressesprecher
Stabsabteilung Unternehmenskommunikation und Marketing
Telefon: 0221 478-5548
E-Mail: presse@uk-koeln.de

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Dr. Alexander Simonis, Dr. Sebastian Theobald and Priv. Doz. Dr. Jan Rybniker (f. l. t. r.)
Christoph Wanko
Figure
Rybniker