Novel strategy stymies SARS: Versatile inhibitor prevents viral replication

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Broad-spectrum antibiotics, which are active against a whole range of bacterial pathogens, have been on the market for a long time. Comparably versatile drugs to treat viral diseases, on the other hand, have remained elusive. Using a new approach, research teams led by Dr. Albrecht von Brunn of LMU Munich and Professor Christian Drosten from the University of Bonn have identified a compound that inhibits the replication of several different viruses, including the highly aggressive SARS virus that is responsible for severe acute respiratory syndrome.

The new method exploits the fact that interactions between certain host proteins and specific viral proteins are essential for viral replication. One of these host proteins is part of a signaling relay in the cell. The broad-spectrum antiviral compound used by the researchers blocks this signal pathway without having a deleterious effect on the host. "We have shown in this study that a broadly based search for new cellular targets can uncover new functional principles that have a demonstrable impact on virus replication," says von Brunn. "We have confirmed that the approach works in cell culture. We now hope that these laboratory results can be translated into clinically effective therapies. At the very least, our high-throughput procedure can be utilized to systematically screen various protein-virus interactions as potential targets for inhibitory compounds." The new study was carried out under the auspices of the SARS Research Network, which is supported by the Federal Ministry for Education and Research (BMBF).

Broad-spectrum antibiotics that inhibit the growth of various species of bacterial pathogens are well known. Virologists, unfortunately, have no comparably versatile weapons in their armory. Individual drugs that are active against different types of viral pathogens are simply not available. "All of the antiviral agents we have are directed specifically at the virus itself," explains Professor Christian Drosten, Director of the Institute of Virology at Bonn University Hospital. "And since viral pathogens are highly diverse, each of these agents can attack only certain viruses." Moreover, viruses are also highly mutable, making the weaponry they can deploy against us even more powerful. What works against one viral strain may be essentially useless against another.

The SARS virus, a previously unknown pathogen which threatened to cause a worldwide pandemic in 2003, has spurred on the search for new antiviral substances. Only recently, it was shown that not only Chinese, but also European, bats carry the SARS virus. "But in contrast to the situation with bird influenza, one cannot simply kill these free-living animals in order to eradicate the pathogen," says Drosten. "That would have catastrophic ecological consequences and, apart from that, bats are retiring and secretive in their habits." If one wishes to develop drugs against viruses that can "hide" in animal species, one must explore other alternatives.

The research teams assembled by von Brunn and Drosten have now discovered a way to prevent the replication of a whole family of viruses by depriving them of an essential host factor. They first identified host proteins with which SARS viral proteins interact. This strategy led to the finding that a cellular signaling pathway is essential for the replication not only of the SARS virus, but also of a whole set of related viruses that are pathogenic to humans and animals.

"This signal pathway is normally involved in regulating the immune system," says Drosten. "We used a substance that inhibits the function of

one of the proteins in the pathway, and found that it suppresses viral replication." In other words, drugs that block this pathway inhibit the replication of many different viruses, and therefore act as broad-spectrum antivirals. This opens a route to the treatment of conditions caused by the SARS virus, but also a whole variety of human coronaviruses, and pathogens that infect the internal organs of chickens, pigs and cats. Inhibition of this pathway does not damage the host, because parallel pathways can compensate for its normal role in the cell.

The successful inhibition of virus replication was not a result of serendipity. The researchers in Munich have developed a technique that allows them to systematically probe different proteins for the ability to interact with defined targets. "In order to replicate in the body of its host, a virus must first gain entry to a suitable cell type by binding to a specific receptor protein on its surface," says von Brunn, who works in the Max von Pettenkofer Institute at LMU Munich. "We have used an automated, high-throughput process to systematically test various protein-virus combinations as potential targets for possible inhibitors. The success of this strategy proves that a broadly based search for cellular targets can uncover new functional principles that have a demonstrable impact on virus replication," says von Brunn.

The investigators have shown in cell cultures that their approach actually works. "However, it will be years before we know whether or not these results can be translated into effective treatments," Drosten says. The study also underlines the importance of research collaborations. Drosten is convinced that "neither group could have done this on its own". The SARS Research Network, which is coordinated by Drosten, brings together virological expertise from six university institutes, two veterinary and four medical, located in Hannover, Gießen, Marburg, Bonn, Munich and St. Gallen (Switzerland). (University of Bonn)

More information: The SARS-Coronavirus-Host Interactome:

Identification of Cyclophilins as Target for Pan-Coronavirus Inhibitors, Susanne Pfefferle, Julia Schöpf, Manfred Kögl, Caroline C. Friedel, Marcel A. Müller, Javier Carbajo-Lozoya, Thorsten Stellberger, Ekatarina von Dall'Armi, Petra Herzog, Stefan Kallies, Daniela Niemeyer, Vanessa Ditt, Thomas Kuri, Roland Züst, Ksenia Pumpor, Rolf Hilgenfeld, Frank Schwarz, Ralf Zimmer, Imke Steffen, Friedemann Weber, Volker Thiel, Georg Herrler, Heinz-Jürgen Thiel, Christel Schwegmann-Weßels, Stefan Pöhlmann, Jürgen Haas, Christian Drosten, Albrecht von Brunn, *PLoS Pathogens*, Oct 27 2011. doi:10.1371/journal.ppat.1002331