New strategy for inhibiting virus replication

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Viruses need living cells for replication and production of virus progeny. Thus far, antiviral therapy primarily targets viral factors but often induces therapy resistance. New improved therapies attempt to targets cellular factors that are essential for viral replication.

The team led by Professor Dr. Ralf Bartenschlager, Director of the Department of Molecular Virology at the Hygiene Institute of Heidelberg University Hospital, has identified a protein in infected liver cells that is essential for hepatitis C virus replication. Inhibiting this protein is highly efficient in blocking virus replication. The study is to be published in the prestigious journal *Public Library of Science Pathogens.*

Viruses need cellular proteins for replication

More than 170 million people worldwide are affected by chronic hepatitis C. In up to 80 percent of infections, the virus can not be eliminated but persists in the infected individual. These chronically infected persons have a high risk of developing serious liver inflammation, liver cirrhosis and even a liver cell tumor.

Viruses contain only a minimum of genetic material and therefore need a host cell for replication. An essential cell factor required for hepatitis C virus replication is cyclophilin, which promotes the proper folding of proteins and the formation of large protein assemblies. Cyclophilin can be inhibited very efficiently by a drug used primarily in the context of organ transplantation - the immunosuppressant cyclosporin. In search for better tolerated drugs to trea chronic hepatitis C, derivatives of

cyclosporin were developed that no longer suppress the immune system, but still effectively inhibit cyclophilin. One of these derivatives is DEBIO-025. Although the exact antiviral mechanism by which DEBIO-025 inhibits hepatitis C virus replication is not yet known, clinical studies are already being conducted.

The critical protein is cyclophilin A

A cell contains numerous variants of cyclophilins that are inhibited by cyclosporin and cyclosporin derivatives. The research team from Heidelberg analyzed liver cells to determine which cyclophilin is critical for hepatitis C virus replication. They found that only blocking cyclophilin A leads complete inhibition of virus replication and this cyclophilin is also the target of DEBIO-025.

Two complementary effects are responsible for the inhibition of hepatitis C virus replication: cyclophilin A is required both for the formation of the viral replication machinery and for the activity of a viral enzyme that is essential for the assembly of infectious virus particles. Inhibiting cyclophilin A with DEBIO-025 thus blocks hepatitis C virus replication from two different sides. By contrast, blocking cyclophilin B had no effect.

"The therapeutic potential of inhibiting cellular factors essential for virus replication has thus far hardly been tapped," explains Professor Bartenschlager. "But this approach has the major advantage that resistance arises less frequently and to a lesser extent in comparison to therapies directly targeting viral factors."

More information: Essential role of cyclophilin A for hepatitis C virus replication and virus production and possible link to polyprotein cleavage kinetics. Artur Kaul, Sarah Stauffer, Carola Berger, Thomas Pertel, Jennifer Schmitt, Stephanie Kallis, Margarita Zayas Lopez,

Volker Lohmann, Jeremy Luban, Ralf Bartenschlager. *PLoS Pathogens*, 2009.

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