Scientists identify key interaction in hepatitis C virus

December 29 2010

Scientists from the Florida campus of The Scripps Research Institute have identified a molecular interaction between a structural hepatitis C virus protein (HCV) and a protein critical to viral replication. This new finding strongly suggests a novel method of inhibiting the production of the virus and a potential new therapeutic target for hepatitis C drug development.

The study was published in the January 2010 issue (Volume 92, Part 1) of the *Journal of General Virology*.

These new data underline the essential role of the viral protein known as "core" as a primary organizer of the infectious HCV particle assembly and support a new molecular understanding of the formation of the viral particle itself.

"While our finding that the HCV core interacts with the non-structural helicase protein was not totally unexpected, this had not really been confirmed until this study," said Scripps Florida Professor Donny Strosberg, who led the study. "But the most exciting part is that small molecule inhibitors of dimerization [the joining of two identical subunits] of core actually inhibit interaction between core and helicase, thus possibly preventing production of an infectious viral particle."

A Viral Plague

Hepatitis C virus infects between 130 and 170 million people worldwide and is the cause of an epidemic of liver cirrhosis and cancer. Because current HCV treatments are only partially effective, a number of alternative molecular mechanisms are actively being pursued as possible drug targets.

One of the critical problems of finding inhibitors for the hepatitis C virus is that it mutates at such prodigious rates. An RNA virus such as hepatitis C can mutate at a rate estimated as high as one million times that of DNA viruses such as the herpes virus.

With this in mind, Strosberg has been examining the core protein, the most conserved protein among all HCV genotypes. Core plays several essential roles in the viral cycle in the host cell. It is particularly important in the assembly of the hepatitis C nucleocapsid or capsid, an essential step in the formation of infectious viral particles; the nucleocapsid is the virus genome protected by a protein coat. By interacting with various structural and non-structural viral proteins, core plays an essential role in the HCV cycle during assembly and release of the infectious virus as well as disassembly of viral particles upon entering host cells. Core also interacts with a number of cellular proteins, possibly contributing to the disarmament of several host defense mechanisms and to the activation of oncogenic pathways.

Last year, Strosberg developed a novel quantitative test for monitoring these protein-protein interactions with the specific goal of identifying inhibitors of the core dimerization, which would block virus production. Strosberg and his colleagues uncovered peptides derived from the core protein of hepatitis C that inhibit not only dimerization of the core protein, but also production of the actual virus.

That earlier study led to the discovery of non-peptidic small organic molecules that strongly inhibited HCV production, one of which, SL201,

was used in the new study.

In the new study, Strosberg and his colleagues focused on non-structural proteins that provide functions relating to HCV production, in particular NS3 helicase. The scientists' findings support a growing body of evidence that this protein participates in the assembly and production of infectious viral particles. The interaction of the core protein with this non-structural protein also confirms core as a key organizer of virus assembly and suggests it acts to facilitate the packaging and integration of the newly synthesized viral RNA.

More information: vir.sgmjournals.org/cgi/content/abstract/92/1/101

Provided by The Scripps Research Institute