

Multitasking may be Achilles heel for hepatitis C

November 23 2009

(PhysOrg.com) -- Hepatitis C, a formidable virus that affects 130 million people worldwide, is nursing some pretty impressive bruises. By knocking out sections and subsections of one of its proteins, scientists reveal weak spots in the virus's armor and gain new momentum for developing drug targets for sufferers of the disease.

Despite its tiny genome, the [hepatitis C](#) virus packs a mean punch. The virus is a microcosm of efficiency, and each of its amino acids plays multiple roles in its survival and ability to sidestep attack. But new research from Rockefeller University suggests that this fancy footwork and multitasking could be the key to bringing down the virus. The work, which focuses on a once-ignored protein, provides insights on how drug therapy for sufferers of the disease might be improved.

The protein, NS2, which is one of the 10 proteins that make up the hepatitis C virus, gained momentum as a plausible drug target in 2006, when Charles M. Rice, head of the Laboratory of [Virology](#) and Infectious Disease, and his team solved the structure of its protease domain. The domain spans the second half of NS2 and acts like a molecular scissor, cleaving itself from its neighbor, NS3. (At first, the 10 proteins that make up the virus are strung together in a continuous chain, which is later cleaved by various enzymes.) By that time, it's also known to aid in the production of infectious virus particles.

Now Rice and his team have dissected the nooks and crannies of this protease domain down to the amino acids that make them up, and have

mapped which [amino acids](#) are responsible for churning out infectious particles, and distinguished them from those involved in the cleaving process. During the researchers' meticulous poking and prodding, deleting and replacing, one amino acid in particular caught their attention: the protein's very last one.

“When we changed or deleted the terminal leucine — leucine 217 — infectious virus production shut down,” says graduate student Thomas Dentzer, who led the research. “But what really intrigued us was leucine 217’s position.”

After the protease makes its cut, leucine 217 remains in a protein fold that makes up the protease’s active site. Although the active site isn’t involved in making infectious virus particles, Dentzer and Rice — who is also Maurice R. and Corinne P. Greenberg Professor in Virology and scientific director of the Center for the Study of Hepatitis C at Rockefeller — showed that it is essential for the protease’s cleaving activity. With both functions mapping to this tiny region of NS2, the researchers suggest that drugs targeting this area might be able to pack a double punch against the virus.

Since the [hepatitis C virus](#) has an uncanny ability to mutate and evade detection just when the body’s immune forces are closing in, punching several phases of the virus’s life cycle simultaneously may be a better approach than dealing one phase a forceful blow. “A double punch may give the immune system time to attack the virus before it mutates,” says Dentzer. “So this is a good therapeutic target to explore.”

The fact that this amino acid is exposed on the virus’s surface makes the finding all the more exciting and suggests that it is involved in protein-protein interactions during the life cycle of the virus. “We not only have a target that can weaken the [virus](#), but a target that is also accessible,” says Rice. “It is a lead that can really help us move forward.”

More information: *Journal of Virology* online: October 7, 2009;
[Determinants of hepatitis C virus nonstructural protein 2 protease domain required for production of infectious virus](#); Thomas G. Dentzer, Ivo C. Lorenz, Matthew J. Evans and Charles M. Rice

Provided by Rockefeller University ([news](#) : [web](#))

Citation: Multitasking may be Achilles heel for hepatitis C (2009, November 23) retrieved 2 May 2024 from <https://medicalxpress.com/news/2009-11-multitasking-achilles-heel-hepatitis.html>

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