HEPATITIS

NPC1L1 identified as a novel HCV entry factor

The cholesterol-uptake receptor Niemann-Pick C1-like 1 (NPC1L1) has been identified as a novel factor that is crucial to entry of HCV into host cells in a study published in *Nature Medicine*. Not only is NPC1L1 a potential new target for antiviral therapy, but these novel findings show that the NPC1L1 antagonist ezetimibe—already available in the clinic and FDA-approved for lowering cholesterol—inhibits or delays establishment of HCV infection and could be a new HCV therapy.

An estimated 170 million people worldwide are chronically infected with HCV. As such, “more effective, less toxic HCV antiviral therapeutics are desperately needed to treat the millions of people chronically infected with HCV,” say study authors Bruno Sainz and Susan Uprichard.

The HCV entry process involves multiple cellular and viral factors, and remains an untapped potential target for new antiviral agents. As HCV infectivity is dependent on cholesterol, Sainz *et al.* reasoned that cholesterol-uptake receptors such as NPC1L1 could be involved in HCV entry.

First, the researchers found that NPC1L1 expression was essential for HCV entry; blocking NPC1L1 expression using a variety of methods (small interfering RNA knockdown, antibody-mediated blocking and pharmacological inhibition with ezetimibe) impaired HCV infection *in vitro*. Crucially, ezetimibe inhibited infection by all major HCV genotypes (1–7).

The inhibitive effects of ezetimibe were then utilized to decipher exactly how NPC1L1 participates in viral entry. Ezetimibe was found to inhibit a late phase of HCV entry—the postbinding, pre-fusion stage—a step that is dependent on the cholesterol content of the virion.

Finally, the researchers were able to confirm that ezetimibe could inhibit HCV infection *in vivo*; treatment with ezetimibe 2 weeks before challenge

HCV entry into liver hepatocytes is a dynamic multistep process that includes interaction with surface receptors (including CD81 and SR-BI), followed by clathrin-mediated endocytosis, fusion and release of the viral genome into the host cell. NPC1L1 participates at a late step in viral entry via a virion cholesterol-dependent mechanism, a process that can be specifically blocked by the NPC1L1 antagonist, ezetimibe. Image created in consultation with B. Sainz Jr and S. L. Uprichard.

with HCV genotype 1b delayed the establishment of infection in a humanized chimeric mouse model.

Sainz and Uprichard are excited about taking their discovery to the next stage of research. “One of the first things we have done is initiate clinical trials to determine if adding ezetimibe to the current HCV standard of care will synergistically enhance HCV inhibition as we have seen in cell cultures and chimeric mice.”

They also hope to expand their clinical studies into the context of HCV-related liver transplantation—NPC1L1 inhibitors could help slow or prevent infection of newly transplanted livers—and to further investigate the complex biology behind HCV entry.

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Original article Sainz Jr, B. *et al.* Identification of the Niemann-Pick C1-like 1 cholesterol absorption receptor as a new hepatitis C virus entry factor. *Nat. Med.* doi:10.1038/nm.2581