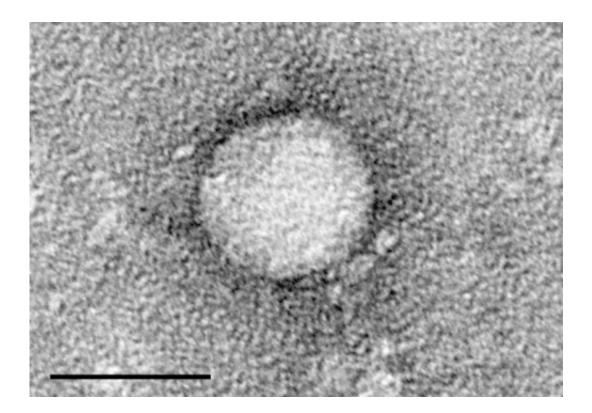


## Inside the hepatitis C virus is a promising antiviral

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Electron micrographs of hepatitis C virus purified from cell culture. Scale bar is 50 nanometers. Credit: Center for the Study of Hepatitis C, The Rockefeller University.

A peptide derived from the hepatitis C virus (HCV) kills a broad range of viruses while leaving host cells unharmed by discriminating between the molecular make-up of their membranes, reveals a study published January 5 in the *Biophysical Journal*. The peptide was potent against a



range of cholesterol-containing viruses, including West Nile, dengue, measles, and HIV.

"Although there are many antiviral drugs on the market, a common problem is that the virus learns how to evade them, becoming resistant to the drug treatment. There is a growing recognition that new classes of <u>antiviral drugs</u> that target multiple <u>viruses</u> are needed," says senior study author Atul Parikh of the University of California, Davis and Nanyang Technological University, Singapore. "Because the HCV-derived peptide appears to meet this need, we reason it targets the Achilles' heel of viruses—a lipid coating or membrane envelope less likely to become resistant to drugs targeting them."

It's been known that the HCV  $\alpha$ -helical (AH) peptide has broad antiviral properties—the same property that allows the peptide to hijack host cell structures for HCV replication also produces ruptures in viral membranes, exposing the viral genome to host enzymes that destroy the pathogens. However, the development of therapies inspired by the actions of the AH peptide has been limited by the lack of knowledge about why it selectively attacks the viral envelope but not host cell membranes.

To address this question, a collaborative research team led by Parikh and Nam-Joon Cho of Nanyang Technological University tested the AH peptide on simplified model lipid membranes that varied in their size and chemical composition. Upon exposure to the peptide, virus-like models with cholesterol-rich membranes showed molecular changes and an increase in openings. But at comparable concentrations, the peptide did not perturb cholesterol-free vesicles.

The researchers believe that the AH peptide probably displays broadspectrum antiviral activity because it targets cholesterol-rich membranes shared by many viruses (this evolutionary conservation is important



because viruses would be slow to develop resistance to it). Additional experiments suggested that the AH peptide also discriminates between viral envelopes and <u>host cell</u> membranes on the basis of their size differences.

"These results are important not only for furthering the membranetargeting strategy for developing antivirals against HCV using viral peptides, but also for identifying other viruses, whose membrane compositions include comparable concentrations of cholesterol, that can be inhibited by the HCV antiviral," Cho says. "Although several compounds that destabilize the viral membrane have been recently proposed, no drug on the market currently targets the lipid membrane."

Before researchers can translate this promising strategy to humans, much work is needed to expand these studies to more realistic model systems. "These simplified model membranes are excellent models to dissect how drugs target lipid components of viral or cell membranes, but we need to remember that they are still models" Cho says. "It will be important to extend the cues drawn from these studies to biological systems, namely human cells and live viruses, to validate the biophysical insights before preclinical translation can occur."

To that end, the researchers plan to continue their biophysical investigations with <u>membrane</u> compositions that more closely match those of viral and cellular membranes. They will also investigate the effects of other viral peptides on these membranes and establish collaborations with virologists to begin to explore translational opportunities.

"Understanding how the drug candidate interacts with these biologically important lipids, we reason, should open the door to deciphering the rich and complex biology of these systems and lead to new opportunities for antiviral strategies," Parikh says. "Studies such as ours provide hope that



replacing the old paradigm of 'one-bug, one-drug' with broadly applicable drugs against which viruses cannot develop resistance may become a reality soon."

**More information:** *Biophysical Journal*, Hanson and Gettel et al.: "Cholesterol-enriched microdomain formation induced by viral-encoded, membrane active amphipathic peptide" <u>dx.doi.org/10.1016/j.bpj.2015.11.032</u>

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