

Study builds understanding of hepatitis C virus replication

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Hepatitis C virus infection is a common cause of liver disease and of liver cancer in the United States. Through a new study that explores one aspect of how the virus hijacks host cell machinery to replicate itself, UNC Lineberger Comprehensive Cancer Center researchers have gained insight into the workings of a potential drug target for hepatitis C.

The study, published online Feb. 5 in the journal *Cell Host & Microbe*, explains the role of one small, but critical molecule called miR-122 in helping the virus replicate itself.

"This small host molecule is essential for [hepatitis C](#) replication in the liver, but we have never fully understood how or why," said Stanley M. Lemon, MD, a UNC Lineberger member, a professor in the UNC School of Medicine Division of Infectious Diseases, and the principal investigator of the study. "This study gives us a pretty clear idea of what miR-122 is doing to promote the viral life cycle."

Made specifically by liver cells, miR-122 is a type of molecule called a microRNA. MicroRNAs are short RNA molecules that do not code for specific proteins, but rather regulate the production of proteins that are coded by much longer "messenger" RNAs made by the cell. Specifically, microRNAs down-regulate the translation of cellular messenger RNAs into proteins.

While the normal function of miR-122 is to down-regulate the expression of numerous proteins in the liver, the hepatitis C virus uses

the molecule to promote its own reproduction. Specifically, the UNC Lineberger-led study found that miR-122 helps promote viral reproduction by directing the viral genome away from viral protein production and toward synthesis of more of the virus' own RNA.

The code carried by the viral RNA genome is used to make virus proteins as well as to make more RNA, Lemon said. And both proteins and RNA are needed for viral growth, but the hepatitis C genome can't do both at the same time.

"What we show in this study is that miR-122 shifts the genome from making viral protein to making more viral RNA," he said. "RNA synthesis is critical, and miR-122 optimizes it so production of new virus is maximized."

The finding builds on the previous understanding of the importance of miR-122 to hepatitis C, Lemon said. It was already known that miR-122 helps to protect the viral genome from being degraded by the host cell, but the molecule's full role in promoting viral replication wasn't appreciated.

"This research builds on about 10 years of understanding that miR-122 is critical for the ability of hepatitis C to grow in the liver, and more recently, on the finding that miR-122 makes the viral RNA more stable by protecting it against degradation," Lemon said.

There is an effort to develop a new hepatitis C treatment that would block viral growth by inhibiting miR-122, and Lemon said the study's findings could help explain how those potential treatments could work.

And in general, he said it helps build a greater understanding of the virus' life cycle in the cell. Such research has helped bring other treatments into the clinic, such as several new hepatitis C drugs approved

last year, on the heels of two others approved in 2011. All of the approved drugs block the actions of specific proteins needed by the hepatitis C virus to replicate.

"Such knowledge has contributed immeasurably to the development of new therapies that have recently entered the clinic," Lemon said of basic science research into the viral life cycle. "However, we have much to learn still about how this [virus](#) causes cancer, and how this can be prevented."

More information: "miR-122 Stimulates Hepatitis C Virus RNA Synthesis by Altering the Balance of Viral RNAs Engaged in Replication versus Translation." [DOI: 10.1016/j.chom.2014.12.014](https://doi.org/10.1016/j.chom.2014.12.014)

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