Researchers discover how hepatitis C virus reprograms human liver cells

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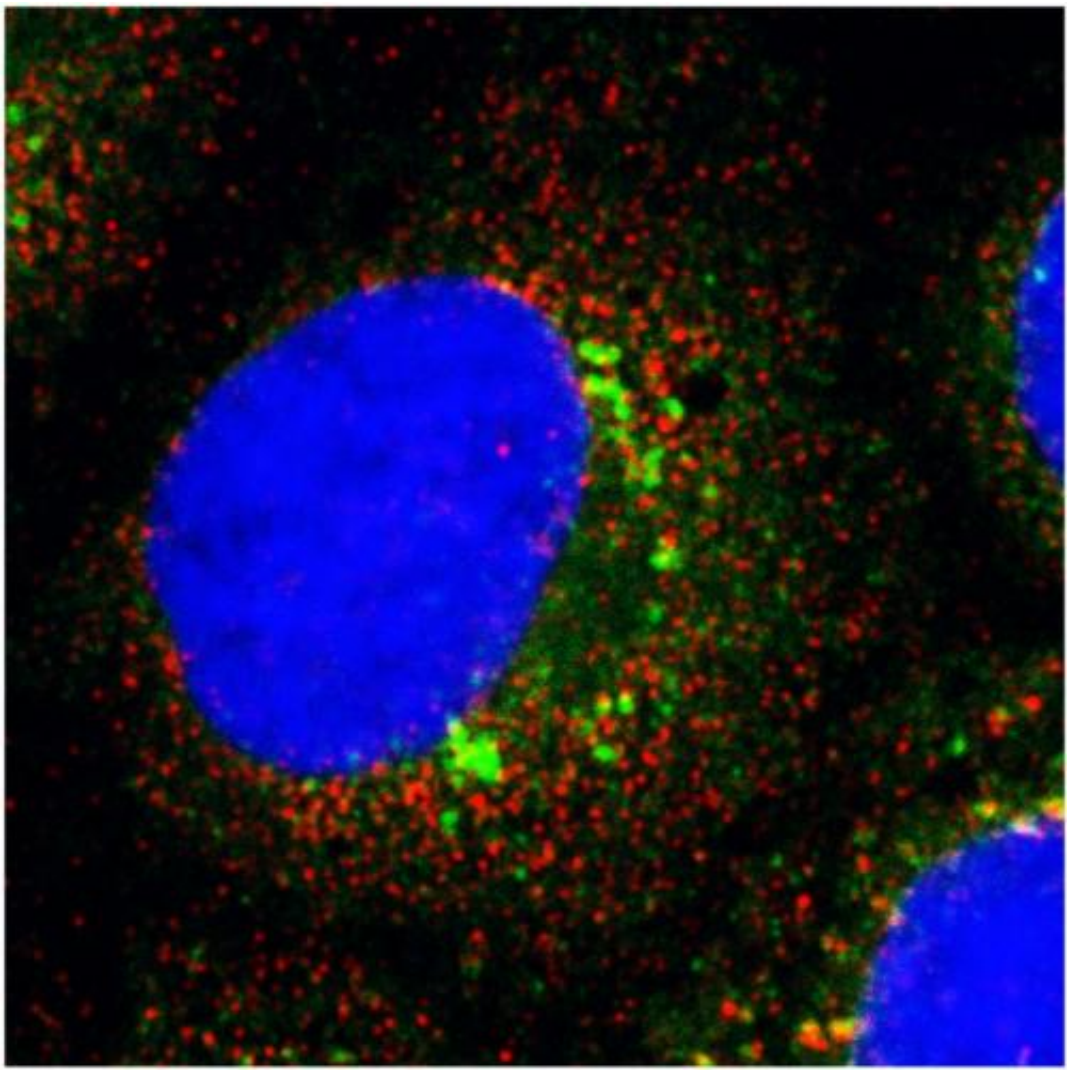

This image shows a cultured liver cancer cell infected with hepatitis C. The virus, stained red, surrounds the blue-stained nucleus and is in the process of being reproduced by virus within the cytoplasm. Credit: Photo courtesy of Takahiro Masaki/UNC Lemon Lab

Hepatitis C virus has evolved to invade and hijack the basic machinery of the human liver cell to ensure its survival and spread. Researchers at the University of North have discovered how hepatitis C binds with and repurposes a basic component of cellular metabolism known as a microRNA to help protect and replicate the virus.

In a paper published online in the *Proceedings of the National Academy of Sciences* Dec. 17, researchers in the laboratory of Stanley M. Lemon, MD, professor of medicine and microbiology and immunology and member of UNC Lineberger Comprehensive Cancer Center, the Center for Translational Immunology, and the UNC Center for Infectious Disease, outline the critical role the microRNA known as miR-122 plays in the life cycle of the hepatitis C virus.

A chronic blood-borne virus that attacks the liver, hepatitis C infects more than four million in the United States and more than 130 million worldwide. Deaths from the infection surpass those due to HIV/AIDS in the U.S. The virus is currently the leading factor in liver transplantation and a major cause of liver cancer, the third most fatal cancer worldwide and the ninth most deadly in the United States. Chronic hepatitis virus infections factor into more than two-thirds of liver cancer deaths.

"There is no cancer in the United States that is increasing in incidence as fast as liver cancer, and that is because of hepatitis C," said Dr. Lemon.

One question has been why hepatitis C virus specifically targets the liver. The research of Dr. Lemon and his colleagues points to the interaction between the hepatitis virus and miR-122 as the explanation.

The human genome contains around 1,000 microRNAs, strands of cellular material that play a diverse role in regulating gene expression

and cellular metabolism. In a healthy liver cell, the microRNA miR-122 regulates the activity and decay of numerous cellular RNAs responsible for the production of proteins. It normally functions to block protein expression or to promote degradation of RNAs in the cell. The hepatitis C virus genome is entirely RNA, but miR-122 acts on it in a completely different manner - stabilizing it and enhancing its ability to produce viral proteins. In effect, it promotes and protects the invader.

"MicroRNAs almost always promote the degradation of cellular RNAs. This is actually stabilizing the viral RNA," said Dr. Lemon.

While Dr. Lemon's team has explored the manner in which hepatitis C exploits miR-122 to protect the viral RNA in previous publications, the new research suggests a much deeper bond between the microRNA and virus. Hepatitis C RNA contains a site that binds directly to the microRNA, and the team has shown that the presence of miR122 is actually crucial for functioning of the virus. Dr. Lemon believes the virus has evolved a unique dependency and that it requires the host's microRNA to reproduce.

"It is a relationship that is unique to hepatitis C and not seen, as far as we know, with any other virus," said Dr. Lemon.

Because of the importance of miR-122 to the replication of hepatitis C, the microRNA presents a promising target for new drugs. The pharmaceutical industry has already begun developing therapies that target miR-122. Dr. Lemon said that his research will help explain the underlying biology behind why these drugs work and suggest new possibilities for treatment by targeting other enzymes and proteins that play a role in the interactions between the virus and miR-122.

"If you target miR-122 with a therapeutic that blocks its function or sequesters it so it is no longer accessible to the virus, the replication of

the virus is severely impaired," said Dr. Lemon.

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