Portrait of a Virus: Crafty, Expertly Outsmarting the Liver

Three new studies have identified ways that the hepatitis C virus enters and hijacks liver cells, manipulating them to serve its own aim: reproduction on a massive scale.

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In its essence, hepatitis C is a relatively simple virus, carrying far less genetic information than the liver cells it attacks. But thanks to the fact that the virus rather sloppily replicates itself about a trillion times a day, the wonders of natural selection have led to the evolution of its strikingly symbiotic, complex and ultimately destructive relationship with the human liver.

Three new studies, each published within weeks of each other in December, have helped sharpen the picture of just how the hepatitis C virus (HCV) manages to further its aim of mass reproduction within the human body. Focusing on different key points in the viral life cycle—from the virus's entry into liver cells, to its manufacturing of viral proteins, to the method by which it works to prevent its own decay—each research finding may one day lead to new antiviral therapies.

"A virus, when it infects a cell," says Jeffrey S. Kieft, PhD, an associate professor of biochemistry and molecular genetics at the University of Colorado School of Medicine (UCSM) and the leader of one of the new studies, "it basically has to hijack the cellular machinery in order to make more copies of the virus. And so we really want to understand on a basic molecular level, what are the molecules that allow that to occur and how do they actually take over the cellular machinery."

According to research conducted at the University of Southern California's (USC) Keck School of Medicine, after hep C binds to the surface of liver cells, the virus activates two proteins known as PI3K and AKT that ordinarily aid in cell growth and metabolism. These proteins then cause changes in liver cell physiology that provide the virus the opportunity to enter the cells.

James Ou, PhD, a professor of molecular microbiology and immunology at USC and the lead author of that study, which was published in the Journal of Biological Chemistry, says that the snowballing effects of cellular changes instigated by PI3K and AKT's interaction with the virus may eventually lead those cells to become malignant.

The study by Kieft and his UCSM team, published online in Nature Structural and Molecular Biology, looked at HCV's machinations once the virus has made its way inside the liver cell. In

addition to conducting a variety of biochemical experiments, the researchers used a high-powered electron microscope to record images of hep C's RNA molecules interacting with rabbit liver cell ribosomes, which manufacture proteins. (HCV's genome is made up of RNA rather than DNA.) While scientists have known for some two decades that HCV targets ribosomes, this new research was able to fill in gaps of the overall knowledge, providing greater clarity as to how the viral RNA manipulated these ribosomes into manufacturing viral proteins.

Giving hope for a future therapeutic target, the UCSM researchers found that even very small changes that affected the viral RNA's interaction with this liver cell machinery had a major effect on the RNA's ability to produce the proteins necessary to replicate HCV.

"It's a long pathway from what we've discovered to actually having a drug," Kieft says, "but hopefully it points that this is an Achilles' heel, or this is something that we could target specifically that could have a very real effect."

The third study, coming from the University of North Carolina (UNC) at Chapel Hill, showed how hep C, once inside the liver, helps counteract the threat of decay.

Published online in the Proceedings of the National Academy of Sciences, the UNC study identifies how hep C binds to a part of the liver's cellular metabolism called microRNA in order to co-op the metabolic system.

There are some 1,000 mircoRNAs in the human genome. These small cellular RNA strands play a key role in regulating the expression of hundreds of genes as well as in cellular metabolism. Over half of the microRNA present in the liver is microRNA-122, or miR-122 (pronounced "meer-122"), with more than 70,000 copies in each cell. In a healthy liver, mirR-122 largely acts instigate the decay of cellular RNA by blocking the expression of certain proteins.

But HCV has evolved to hijack this process and force mirR-122 to work in the exact opposite manner when it interacts with the virus: making viral RNA more stable and thus promoting viral replication.

In their new study, the UNC researchers found that an enzyme known as XRN1 is responsible for the viral RNA's degradation. By binding onto a key point of the viral RNA, miR-122 prevents XRN1 from degrading the virus's genetic material.

The UNC team's research further suggests that miR-122 plays an additional, but still undefined, role in viral replication outside of this process of preventing viral genome decay, a mystery they are currently trying to crack.

Stanley M. Lemon, MD, a professor of medicine, microbiology and immunology at UNC and the study's senior author, cautions that miR-122 is fundamentally important to liver function and that it regulates several hundred genes. As such, administering what's known as an "antagonizing molecule" against it could in theory raise the risk of significant side effects. A past study in

chimpanzees of such an antagonist led to a 50 percent drop in total cholesterol. There is also some evidence that miR-122 is protective the development of the very sort of liver cancer hepatitis C can cause.

“Whether short term—a few weeks or months—suppression of miR-122 would make a [harmful] difference is anybody’s guess,” Lemon says.

Taking that guess is the Danish biotech company Santaris, which is currently investigating the miR-122 antagonist miravirsen. In November 2011, Santaris released promising data from a Phase IIb clinical trial of a four-week monotherapy course of treatment in a small cohort of hepatitis C patients. The drug proved safe and well-tolerated. At the time, Santaris representatives expressed hope that the drug would one day lead to a cure through monotherapy.

Reflecting on the similarities between these three studies, Ou notes that “there’s a common feature: The virus goes inside the cells, modifies the cells and creates an environment that’s optimal for viral replication.”

Kieft adds that each paper “starts to suggest that if we could disrupt or alter any one of these steps or hurt the virus’s ability to get over any one of these barriers, each one could be a potential drug target.”

Such therapies wouldn’t target the virus itself, but would seek to foil its interaction with these various components of liver cells. Consequently, such therapies would likely provide a very high barrier to drug resistance when compared with those antivirals available today as well as the drugs making their way out of the antiviral pipeline.

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