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Hepatitis C's Interferon Resistance Mechanism Discovered

Though interferon, the body's naturally occurring antiviral agent, is the mainstay treatment for hepatitis C virus (HCV), it cures only 20 percent of infected patients. The reason, according to new research, may be that HCV can mimic one of the molecular targets of interferon and may block its ability to kill viruses.

"Not only have we solved a major clinical problem relating to the treatment of HCV, but researchers may be able to use this information to develop more effective HCV therapies," said Michael Lai, the leader of the scientific team that made the discovery and an HHMI investigator at the University of Southern California School of Medicine.

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— **Michael Lai**

Nearly four million people in the United States alone suffer from HCV infection, which results in 10,000 deaths a year from cirrhosis, liver failure or liver cancer. The virus is spread through intimate sexual contact, needle sharing, and blood products.

Chronic HCV infection, which develops in 80 percent of patients, progresses slowly. Indeed, patients can remain symptom-free for 20 years or more following infection, but the virus eventually attacks the liver. A large percentage of patients who are currently waiting for liver transplants are infected with HCV. In the United States, treatment of chronic HCV infection costs an estimated \$600 million annually.

During the initial stages of HCV infection, interferon produced by certain fibroblast and immune system cells does its job by binding to receptors on the surface of HCV-infected liver cells. This triggers the infected cell to produce protein kinase (PKR), an enzyme that adds a chemical entity known as a phosphate group (a process called phosphorylation) to a variety of proteins, including itself.

Among PKR's targets is a protein called eukaryotic initiation factor 2 (eIF2 α). Adding a phosphate group to eIF2 α turns off protein synthesis within the infected cell. Though the cell dies, so too does the virus. Without protein synthesis, HCV cannot replicate and cannot establish a successful liver cell infection.

Lai's team's studies of interferon resistance focused on E2, a protein component of HCV's outer sheath, or envelope. The investigators found that E2 from all genotype 1 HCV (the most common form of HCV in the United States), which is essentially resistant to interferon, contains a 12 amino acid sequence that is identical to the site that PKR phosphorylates, both on itself and on eIF2 α .

Further experiments by Lai and his colleagues confirmed that the E2 protein not only blocks PKR phosphorylation in cells, but blocks PKR's ability to inhibit protein synthesis, too. The results of these studies appeared in the July 2, 1999, issue of the journal *Science*.

"Our findings show that E2 inhibits interferon by targeting PKR and eIF2 α ," explained Lai. "It does so by providing a site that PKR will bind to instead of its normal targets for phosphorylation."

By identifying E2's target, Lai believes that pharmaceutical researchers will now be able to develop strategies to overcome the virus' ability to neutralize interferon. This will not be an easy task since HCV's genome is highly heterogeneous, or varied. To make matters worse, the *E2* gene of HCV is probably the most heterogeneous gene of all. "The consequence of the genetic diversity of HCV is a virus that has the ability to escape the immune surveillance of its host, leading to a high rate of chronic infections and a lack of protective immunity in individuals exposed repeatedly to the virus," said Robert Purcell, an HCV researcher at the National Institutes of Health. Fortunately, the region of E2 that bears resemblance to PKR is a relatively invariable sequence, said Lai.

Lai believes that this extensive genetic diversity, besides creating clinical complications, offers one more proof that HCV and other viruses are alive. "After studying viruses for 25 years, I believe strongly that the popular belief that viruses are not alive is wrong," he stated. "Viruses do things that we don't expect. They adapt to the environment. They change themselves to survive. They can pick up pieces of cellular genes or incorporate their genes into the cell's genome. That means that evolution occurs all the time in viruses.

"Just look at HCV," he continued. "It's developed a very clever strategy to counteract interferon."