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Discovery of New Antiviral Mechanism in Mammals May Improve Treatment of Hepatitis C Infections

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A team of researchers led by biologists at the University of California, San Diego has discovered a completely new mechanism that mammalian cells employ to fight infections of the Hepatitis C virus, which affects approximately 2.7 million Americans and 170 million people worldwide.

The achievement, detailed in a paper published in the October 18 issue of the journal *Nature*, could improve current antiviral regimens or result in new treatments that are more effective and possess fewer detrimental side effects for those with the Hepatitis C virus infection, which frequently leads to liver cirrhosis and/or liver cancer.

“Approximately two percent of the human population worldwide is infected with Hepatitis C virus,” said Michael David, an associate professor of biological sciences at UC San Diego who headed the research team. “And about 50 to 80 percent of those people develop persistent infections and are at great risk of developing liver cancer.”

The only approved therapy for Hepatitis C is alpha-interferon, a protein produced by animal cells when invaded by viruses that induces healthy cells to manufacture enzymes that counter the infection. Often alpha-interferon is used in combination with an antiviral drug called ribavirin. However, only 40 to 80 percent of patients respond to this therapy and about half of those who do respond relapse once interferon treatments are stopped. Only about 25 percent of those treated with interferon,

which can also induce flu-like symptoms and kidney damage in some patients, rid themselves of the viral infections. Explaining these varying response rates is difficult, since scientists do not fully understand the mechanisms used by alpha-interferon to fight off Hepatitis C virus infection.

What David and his team discovered is that microRNAs, short strands of RNA that interfere with the expression of specific genes, may also be effective against the Hepatitis C virus, because they are used by mammalian cells to reduce the replication of the virus. Their discovery comes as a surprise because while microRNA interference has been known to occur as a defense mechanism in plants and invertebrates, many scientists doubted it was employed by mammalian cells.

David and his group began by identifying microRNAs whose expression is controlled by alpha-interferon, then used computer prediction to identify potentially affected viral RNAs. Hepatitis C virus emerged as a prime candidate and the UCSD researchers--in collaboration with Hepatitis expert Francis Chisari of The Scripps Research Institute--demonstrated that several alpha-interferon induced microRNAs are able to potently inhibit viral infection and replication.

“This is an entirely new antiviral mechanism in mammalian organisms,” said David. “Use of synthetic microRNAs has become a promising strategy of antiviral treatment. However, selecting the ‘right’ sequence is crucial in order to avoid unwanted and potentially dangerous side effects. The microRNAs used by alpha-interferon have been selected by evolution for efficacy and safety,and might therefore provide a sound basis for the generation of new synthetic antivirals.”

“Now that we have identified this new antiviral pathway or mechanism, pharmaceutical companies may be able to design a more effective therapy against the Hepatitis C virus,” said Irene Pedersen, a project

scientist working in David's laboratory who is the first author of the paper.

Other co-authors of the paper are Francis Chisari, Guofeng Cheng and Stefan Wieland of The Scripps Research Institute and Carlo Croce and Stefano Volinia of Ohio State University. The research was supported by grants from the National Institutes of Health.

Source: University of California, San Diego