SOUTHWESTERN NEWS

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Studies reveal methods viruses use to sidestep immune system

DALLAS – Feb. 14, 2005 – A series of studies by researchers at UT Southwestern Medical Center sheds light on the mechanisms used by viruses to thwart a host's immune defenses and may aid in the development of more effective drugs to fight hepatitis C and West Nile viruses, as well as the flu and the common cold.

In a study to appear in a March issue of the *Journal of Virology* and currently available online, UT Southwestern researchers describe how an essential gene, called *RIG-I*, turns on a cascade of host immune defenses when the hepatitis C virus (HCV) replicates in cultured human cells.

Those immune defenses should fight off the virus, but in a separate study, scheduled to appear online this week and in an upcoming issue of the *Proceedings of the National Academy of Sciences*, the researchers show how HCV sidesteps the immune response, allowing the virus to replicate unchecked.

Dr. Michael Gale, associate professor of microbiology at UT Southwestern and senior author of the two studies, said the tactics employed by HCV to infect a host are likely to be similar to those employed by other RNA viruses such as West Nile, influenza and the common cold.

"This work has broad implications that go beyond just the hepatitis C virus, and that's what we're most excited about," said Dr. Gale. "It's a battle between viruses and humans. Viruses have co-evolved with their hosts, so every time we have evolved a gene with a new function that allows us to fight off a virus, the virus adapts and comes up with a new function of its own to counteract our defenses."

Further defining how RNA viruses target and control host immune defenses will aid in drug development to combat disease, he said.

In the *Virology* paper, Dr. Gale and his research group found that a specific mutation in the gene *RIG-I* conferred permissiveness to HCV, allowing it to replicate "like gangbusters" in those cells with the mutation, Dr. Gale said. He and his group determined that the protein made by the gene is essential to turning on signals that tell the cell to mount an immune response. Cells with the mutated RIG-I protein were unable to initiate immune signals, abolishing the host cells' defenses to HCV.

When HCV infects a cell, the RIG-I protein physically binds the virus genetic material. RIG-I then changes its shape, which sends a cascade of signals to other proteins to activate a transcription

factor called interferon regulatory factor 3 (IRF-3). This protein turns on the genes responsible for producing interferon, which neutralizes viruses by suppressing their replication.

The researchers also investigated why cells with functioning RIG-I protein still had persistent HCV infection. In a study to appear in *PNAS*, Dr. Gale and his group found an explanation for HCV's tenaciousness. Once HCV infects the cell, it launches a counterattack against RIG-I, producing a protein called a protease to disrupt the cell's immune response that is otherwise turned on through RIG-I by the virus infection. The viral protease, NS3/4A, chops up essential signaling proteins involved in carrying RIG-I's message to IRF-3. Without those signals, IRF-3 can't turn on the genes to make interferon, and the virus continues to replicate unimpeded.

"Having identified RIG-I, now we can spend our time completely defining the signaling pathway that goes from RIG-I all the way down to IRF-3," Dr. Gale said. "Once we've done that, we hope to identify parts of the pathway to target with drugs to try to limit infection."

Drugs called protease inhibitors currently are used to treat patients infected with HIV and have also shown promise in treating hepatitis C patients in experimental trials.

"We now know that treating patients with a protease inhibitor will prevent the viral protease from cutting up the signaling proteins," Dr. Gale said. "We're currently working to identify exactly what proteins the viral protease is attacking, which could help toward further developing the protease inhibitors and more effective therapies for hepatitis C and possibly other viral infections."

A third paper, also appearing in *PNAS,* describes collaborative research with a group at UT Medical Branch in Galveston. The findings shed light on how HCV disrupts a separate immune pathway in infected liver cells, again by unleashing the NS3/4A protease to cleave another protein essential to triggering immune defenses. Again they found that protease inhibitors could reverse the effects of NS3/4A, allowing this immune pathway to be restored to shut down HCV replication.

Hepatitis C is a chronic disease that affects 4 million people in the United States, making it the nation's most common blood-borne infection. It is transmitted primarily through intravenous drug use, blood transfusions or blood products, as well as through sexual contact and is the leading cause of cirrhosis and liver cancer.

UT Southwestern Medical Scientist Training Program (MSTP) student Eileen Foy was an author on all three papers. MSTP student Rhea Sumpter and postdoctoral researcher Dr. Yueh-Ming Loo were authors on two of the papers. Postdoctoral researcher Dr. Chunfu Wang, MSTP student Cynthia Johnson and research associate Penny Mar-Fish also contributed, as did researchers in Japan.

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