Infection Warning System Contains Targets for Antiviral & Vaccine Strategies

University of Washington

Two new targets have been discovered for antiviral therapies and vaccines strategies that could enhance the body's defenses against such infectious diseases as West Nile and hepatitis C. The targets are within the infection warning system inside living cells.

No vaccines exist for the viruses that cause West Nile or hepatitis C. New therapies are urgently needed to prevent and treat serious infections by these and related viruses.

The University of Washington is engaged in a major, multipronged effort to design therapeutics that harness the warning signals the body produces when viruses attack. Such therapies would prod people's cells into launching a stronger counterattack to control infections by elusive viruses.

UW specialists in how the body fends off viral diseases are studying pattern recognition molecules, called RIG-I-like receptors, found inside living cells. When these receptors detect virus invasions, they call in the immune system to fight infection.

Scientists in the laboratory of Dr. Michael Gale, Jr., UW professor of immunology, observed an interaction between these molecular dispatchers and a protein called 14-3-3 epsilon This protein acts a docking station where other proteins can gather. There they can more efficiently send out signals in response to threats.

The researchers noticed that the interaction between the alert trigger (RIG-I) and the docking station (14-3-3 epsilon) steps up when cells were infected with virus. The agitation prompts RIG-I to work with other proteins, such as TRIM25. Those proteins are essential for RIG-I to warn the immune system to respond to a virus intruder.

"Our work also demonstrated that RIG-I binding to 14-3-3 epsilon is important for RIG-I to move from within the cell where it detects viral RNA to a location on the cell's membrane where the cell's antiviral defenses can be activated," said Dr. Helene Liu, a postdoctoral fellow who led the study. The move is somewhat like running from the inner corridors of a building to a window to call for help.

"By understanding the molecular partners and location changes that RIG-I requires to convey its signal that virus is present in a cell, we can start to design therapeutics that can trigger this process to kick-off an antiviral immune response and fight virus infection," Liu said.

The scientists reported these initial findings in the May 17 issue of Cell Host & Microbe. The Gale laboratory reports additional observations on the RIG-I-like receptors in the August issue of Immunity, published online July 26.

Postdoctoral fellows Dr. Mehul Suthar and Dr. Hilario Ramos found that, during West Nile virus infection, an RIG-I like receptor called LGP2 promotes the survival and activity of CD8+ T white blood cells, commonly called killer T cells. These disease-fighters eliminate virus-infected cells from the body.

"By increasing the ability and length of time CD8+T cells can work within the body when West Nile virus is present, the immune system is strengthened and has a better chance of eliminating the virus," Suthar commented. Ramos added, "Based on this work, we can consider new ways to boost vaccine effectiveness through design of adjuvants or immune-stimulants. These might be applied within a vaccine approach to regulate LGP2 to enhance immunity to infection."

Gale directed the research effort for both projects. He heads the Center for Study of Innate Immunity to Hepatitis C Virus and the Center for Immune Mechanisms of Flavivirus Control, as well as two National Institutes of Health-funded multi-million dollar programs to develop new antiviral therapies and vaccine adjuvants.

"These two new discoveries," Gale said, "greatly advance our knowledge of how the body senses and responds to virus infection and provide us with new avenues to explore when designing antiviral therapies and new vaccines.

"West Nile virus is an emerging virus that has spread across the United States, and hepatitis C virus infects over 170 million people globally. Both viruses are devastating to the health of the individuals they infect. That is why the development of new clinical resources such as vaccines and antivirals for each is so critical."

West Nile virus is spreading throughout North America through infected mosquitoes. It can cause paralysis and death in people. Hepatitis C virus is transmitted through contact with blood or blood products containing the virus. It causes swelling and inflammation of the liver.

Most hepatitis C infections are persistent because the virus evades the immune defenses that normally limit the course of disease. The virus generates a chronic liver inflammation which scars the organ's tissues. The scarring can lead to liver failure and increases the risk of liver cancer. While therapies are available to treat hepatitis C infections, these treatments have harsh side-effects and are not effective in all people. No antiviral therapies are available to treat people infected with West Nile virus.

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Nile virus infections.

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