

JULY 09, 2008

Fruit Fly Gene Study Could Yield New Flu Treatments

As they design new drugs to fight off influenza, scientists may not need to attack the virus directly. Instead, they may be able to stave off infection by targeting one of more than 100 proteins inside host cells on which the virus depends.

These potential drug targets are the result of a study in which scientists, led by Howard Hughes Medical Institute investigator Paul Ahlquist and colleague Yoshihiro Kawaoka at the University of Wisconsin-Madison, tested the ability of a modified influenza virus to infect fruit fly cells. “Our findings give us considerable hope that—with a large number of host targets to choose from—we could develop drugs to more stably suppress the virus and not allow the virus to evolve nearly as quickly to generate resistance,” Ahlquist said. The team described their findings in a July 9, 2008, advance online publication of the journal *Nature*.

Viruses possess only a limited number of genes, so they must hijack a host cell's own protein machinery to enter the cell and replicate their genes. Relatively few of influenza's interactions with host proteins are understood, according to Ahlquist, and this has limited drug development.

"Our findings give us considerable hope that—with a large number of host targets to choose from—we could develop drugs to more stably suppress the virus and not allow the virus to evolve nearly as quickly to generate resistance."

- Paul Ahlquist

“So far, antiviral treatments against influenza have targeted specific viral enzymes or functions,” he said. “The problem has been that the virus can mutate itself to develop resistance to these drugs. Our hope is that by

identifying host functions on which the influenza virus depends, we can develop drugs that target these functions. And since those functions are encoded by the host, the virus cannot use simple mutations to develop resistance to such drugs.”

Although fruit flies are not naturally infected by the influenza virus, Ahlquist and his colleagues knew the fly would be a powerful tool in identifying the genes and proteins that facilitate infection. A great many fly genes have counterparts in humans, and the researchers could analyze the function of individual fly genes using a technique known as RNA interference. So the researchers genetically altered influenza virus so that it could infect cultured fruit fly cells grown in the laboratory. They also added a gene that would produce a telltale fluorescence when the virus successfully replicated in fly cells.

They next used RNA interference -- treating fly cells with small snippets of RNA -- to individually suppress the function of each of 13,071 genes, representing 90 percent of all fly genes. If a gene is important for allowing the virus to replicate, fly cells in which that gene had been shut off would not emit the fluorescent signal signifying infection. Using this screen, the researchers identified more than 100 host cell genes that the virus depended on for infection.

“We found that the virus depends on the function of fly genes in a wide range of cellular processes,” said Ahlquist. “This tells us that quite a variety of host functions are important to the virus and that there could be a broad range of options for antiviral drugs.”

The researchers wanted to be sure that their findings were relevant for influenza infections that occur outside of the laboratory. So, as an initial check, they tested the ability of natural strains of the virus to infect mammalian cells lacking three of the genes they had identified in the fruit fly cells. The genes they chose participate in three different cellular processes known to be involved in the life cycle of the virus. They found that suppressing the function of any of the three diverse genes—called *ATP6V0D1*, *COX6A1* and *NXF1*—thwarted viral replication.

The researchers also tested how blocking these genes might affect infection with other viruses, and found that all three genes were influenza-specific. Suppressing them did not affect replication of two other viruses they tested. Thus, said Ahlquist, the influenza virus functions in a way that is distinct from the other viruses and that may offer a prime target for influenza-specific antiviral drugs.