

UW scientists unravel mystery of how flu viruses replicate

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Like any other organism, an influenza virus's success in life is measured by its genetic track record, its ability to pass on genes from one generation to the next. But although much is known about the genes and inner workings of flu viruses, how the microbe organizes its genetic contents to seed future generations of viruses has remained an enduring mystery of biology.

Now, with the help of a long-studied flu virus, an electron microscope and a novel idea of how the virus aligns segments of RNA as it prepares to make virions, the particles a virus creates and sends forth to infect cells, that puzzle has been resolved.

The new work, which is reported in this week's (Jan. 26, 2006) edition of the journal *Nature*, is important because it presents opportunities to design new antiviral drugs and harness flu viruses for speedier, more efficient vaccine production. The work is especially critical as the biomedical community and governments worldwide develop strategies to cope with the prospect of an avian influenza pandemic.

"We've found that the influenza virus has a specific mechanism that permits it to package its genetic materials" as it creates its infectious particles, says Yoshihiro Kawaoka, a UW-Madison School of Veterinary Medicine professor and a leading influenza researcher. Kawaoka is also a professor at the University of Tokyo.

Viruses, including influenza viruses, depend on the cells of their hosts to

survive. They infect cells and use them to help make more infectious particles, which are released from the cell and go on to infect other cells.

Using a technique known as electron tomography, a method that enables scientists to generate three-dimensional images of microscopic organisms and structures, Kawaoka and his colleagues, in virtual fashion, dissected a virus and its infectious particles to assess how the virus assembles and organizes the strands of RNA that carry its genes so it can exit one cell and go on to infect other cells.

What Kawaoka found was that the viruses were assembling their infectious genetic elements in a systematic fashion. Virologists have long debated whether the RNA segments in flu viruses assembled at random into the virions or were somehow incorporated into the infectious particle in an organized way.

The RNA segments, according to Kawaoka, form in a distinct pattern abutting the membrane of the virus. They are always arranged in a circle of seven surrounding another segment for a total of eight RNA fragments.

"It was not really known whether the fragments were coming as a set," explains Kawaoka, whose team conducted the work using a long-studied influenza A virus, the family responsible for regular influenza outbreaks, including such medical calamities as the 1918 influenza pandemic.

The fact that the virus requires a systematic - as opposed to a random - method of assembly opens the door to the development of new antiviral drugs and the harnessing of benign influenza viruses as gene vectors to optimize vaccine production, Kawaoka says.

"We need to have more antivirals for influenza," according to Kawaoka, "and as these segments get incorporated into the particle as a set, it

suggests these elements could be a target for disruption. There must be a genetic element in each of the eight segments that allows them to interact."

What's more, scientists have been exploring the possibility of using strains of influenza to ferry genes from one virus to another to speed and optimize vaccine production. More efficient methods of vaccine production will be critical should a global outbreak such as the "Spanish " flu pandemic of 1918 recur. That pandemic killed an estimated 30-50 million people.

Knowing how influenza A viruses package their genetic contents, and knowing that they do so systematically, suggests it may be possible, by manipulating key genetic elements, to quickly engineer viruses that can be used to mass produce vaccines. Researchers have been trying to make viral vectors using nine genetic segments, a strategy that has never worked, Kawaoka notes.

"To develop an influenza virus vector, we have to stick to this eight-segment concept," he says.

Such a strategy may be useful for developing vaccines for a range of diseases, including HIV, the virus that causes AIDS, Kawaoka adds.

The new work, according to Kawaoka, benefited from a critical observation made possible by the dissection of the virus and its virions. The virus particles, when observed as a cross section, always displayed the circle of seven RNA fragments surrounding another segment pattern.

"No one has identified this before, perhaps because no one has ever tried to make serial sections of the virus."

Source: University of Wisconsin (by Terry Devitt)

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