Cell barrier shows why bird flu not so easily spread among humans

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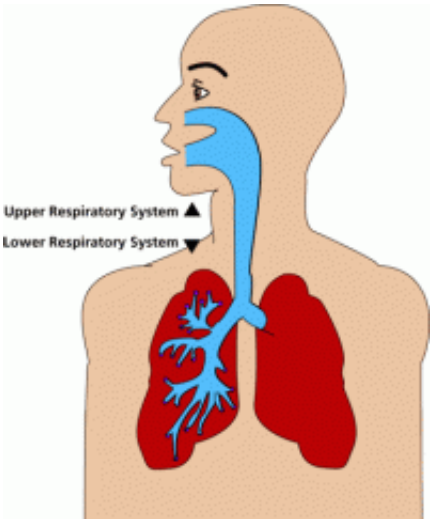

Writing in the journal Nature, a team of scientists led by UW-Madison virologist Yoshihiro Kawaoka reports differences in the receptors on cells in the lower and upper parts of the human respiratory system that avian flu viruses use to gain access to cells. The work shows why the avian influenza virus does not yet transmit easily from human to human. Illustration: Jeff Jerred /University of Wisconsin

Although more than 100 people have been infected with the H5N1 avian influenza virus, mostly from close contact with infected poultry, the fact that the virus does not spread easily from its pioneering human hosts to other humans has been a biomedical puzzle.

Now, a study of cells in the human respiratory tract reveals a simple anatomical difference in the cells of the system that makes it difficult for the virus to jump from human to human.

The finding, reported today in the journal *Nature*, is important because it demonstrates a requisite characteristic for the virus to equip itself to easily infect humans, the key development required for the virus to assume pandemic proportions.

The new report, by a research group led by University of Wisconsin-Madison virologist Yoshihiro Kawaoka, describes experiments using tissue from humans that showed that only cells deep within the respiratory system have the surface molecule or receptor that is the key that permits the avian flu virus to enter a cell.

Flu viruses, like many other types of viruses, require access to the cells of their hosts to effectively reproduce. If they cannot enter a cell, they are unable to make infectious particles that infect other cells - or other hosts.

"Our findings provide a rational explanation for why H5N1 viruses rarely infect and spread from human to human, although they can replicate efficiently in the lungs," the authors of the study write in the Nature report.

By looking at human tissues, Kawaoka's group noted that the cells in the upper portions of the respiratory system lacked the surface receptors that enable avian H5N1 virus to dock with the cell. Receptors are molecules on the surface of cells that act like a lock. A virus with a complementary binding molecule - the key - can use the surface receptor to gain access to the cell. Once inside, it can multiply and infect other cells.

"Deep in the respiratory system, (cell) receptors for avian viruses,

including avian H5N1 viruses, are present," explains Kawaoka, who also holds an appointment at the University of Tokyo. "But these receptors are rare in the upper portion of the respiratory system. For the viruses to be transmitted efficiently, they have to multiply in the upper portion of the respiratory system so that they can be transmitted by coughing and sneezing."

The upshot of the new finding, says Kawaoka, a professor of pathobiological sciences at the UW-Madison School of Veterinary Medicine, is that existing strains of bird flu must undergo key genetic changes to become the type of flu pathogen most feared by biomedical scientists.

"No one knows whether the virus will evolve into a pandemic strain, but flu viruses constantly change," Kawaoka says. "Certainly, multiple mutations need to be accumulated for the H5N1 virus to become a pandemic strain."

The finding suggests that scientists and public health agencies worldwide may have more time to prepare for an eventual pandemic of avian influenza. Periodically, animal forms of influenza such as bird flu evolve to become highly contagious human pathogens.

Most scientists agree a pandemic of avian influenza will occur at some time. The worst-case scenario would be a form of influenza similar to the strain of 1918 that killed between 30 million and 50 million people globally.

The new work may also help scientists keep track of evolving strains of influenza and provide earlier warning of potential pandemics. For the H5N1 strain of flu virus to evolve to a pathogen easily transmissible from one human to another, changes need to occur in the virus' hemagglutinin surface protein - a molecule embedded in the virus

membrane - to recognize human receptors, Kawaoka says.

"Mutations in the hemagglutinin for avian H5N1 viruses to recognize human receptors are needed for the virus to become a pandemic strain," Kawaoka explains.

Viruses isolated from humans infected with avian flu can thus be monitored in a way to provide more advance warning of a potential pandemic.

"Identification of H5N1 viruses with the ability to recognize human receptors would bring us one step closer to a pandemic strain," says Kawaoka. "Recognition of human receptors can serve as molecular markers for the pandemic potential of the isolates."

The new study was conducted in collaboration with Kyoko Shinya and Shinya Yamada of the University of Tokyo; Masahito Ebina of the Institute of Development, Aging and Cancer; Masao Ono of Tohoku University; and Noriyuki Kasai of the Institute for Animal Experimentation in Japan.

Source: University of Wisconsin