Changes in amino acids in the 1918 influenza virus cut transmission

February 5 2007

(Modest changes in the 1918 flu virus's hemagglutinin receptor binding site—a molecular structure critical for the spread of infection—stopped viral transmission in ferrets, according to a new study conducted by researchers at Mount Sinai School of Medicine and at the Centers for Disease Control and Prevention.

The finding, published in the February 5 issue of *Science*, could have significant clinical implications in helping scientists develop ways to break the disease cycle and possibly help reduce the risk for a potential pandemic.

While flu pandemics occur every 10 to 40 years, the factors that lead to the emergence of pandemic viruses are not well understood, explains study co-author Adolfo García-Sastre, PhD, Professor of Microbiology at Mount Sinai School of Medicine. "What's most threatening is the possibility of another pandemic, similar to that of 1918, which was caused by a novel influenza subtype virus capable of causing severe respiratory disease and death," says Dr. García-Sastre. "So if we can understand the molecular mechanisms behind its transmission, perhaps we can do something to block transmission and prevent illness."

To do this, Dr. García-Sastre and his team studied two key molecular structures: hemagglutinin, a protein located in of the surface of the influenza virus, and sialic acid, a cellular molecule that is recognized by hemaglutinins of both human and avian strains of influenza virus. These molecules are key to initiation of infection. There are 16 different

subtypes of hemagglutinin called H1 through H16, present in influenza virus strains circulating in birds. H1 and H3 are found today in human influenza viruses.

Hemaglutinin helps open the door to the cell to allow the virus to infect. The first step is in this process is the binding of the hemagglutinin to sialic acid containing molecules in the cell surface. There are two primary ways sialic acids are associated with molecules in the cell surface—one is through an alpha-2,6 bond and another is through an alpha-2,3 bond. Hemagglutinins from avian influenza virus prefer binding to alpha 2-3 sialic acids, while hemagglutinins from human influenza viruses prefer binding to alpha 2-6 sialic acids, which are highly abundant in the upper respiratory tract of humans. For an avian virus to be able to jump to humans and to start a new pandemic, it has been hypothesized that the hemagglutinin needs to mutate and change its binding preference from alpha2-3 to alpha2-6 sialic acids.

In this study, the researchers used ferrets as an animal model of human influenza virus infection, due to the presence of alpha2-6 sialic acids in the respiratory tract of ferrets, similar to the human scenario. Groups of ferrets were infected with three types of influenza viruses; two from existing viral strains related to the 1918 flu and taken from human tissue, and the third, which was artificially created in a laboratory and made to look like avian flu. One virus bound to only alpha-2,6, the second bound to both, and the artificially-generated virus bound to only alpha-2,3.

The researchers were surprised to discover that the ferrets infected with all three viruses, including the one with preference for binding to alpha2-3 sialic acids, experienced severe disease, with high levels of virus replication in the respiratory tract. However, only the virus with specificity for binding to alpha2-6 silaic acids was able to transmit by aerosols to contact ferrets. "It appears that when the virus only had an alpha-2,3 binding activity, replication and virulence didn't change,"

explains Dr. García-Sastre. "These animals still had symptoms, however transmission was practically abolished." Since the artificially-generated virus featured alpha-2,3 sialic acid binding activity, this finding indicated that alpha-2,6 sialic acid binding activity was more important for optimal viral transmission.

"Our findings indicate that, to become more transmissible in humans, the currently circulating avian influenza H5N1 virus requires a receptor binding change in the hemagglutinin to a predominant alpha-2,6 sialic acid binding preference," Dr. García-Sastre adds. "Although this is likely not to be the only change required by H5N1 viruses to become transmissible in humans, this could help us make more accurate predictions on the ability of an influenza virus to transmit among humans and unravels the existence of molecular determinants of transmission that could be used as targets for the development of novel drugs that will stop influenza virus transmission, and therefore, help to stop epidemics and pandemics of influenza."

Source: The Mount Sinai Hospital