Some flu viruses potentially more dangerous than others

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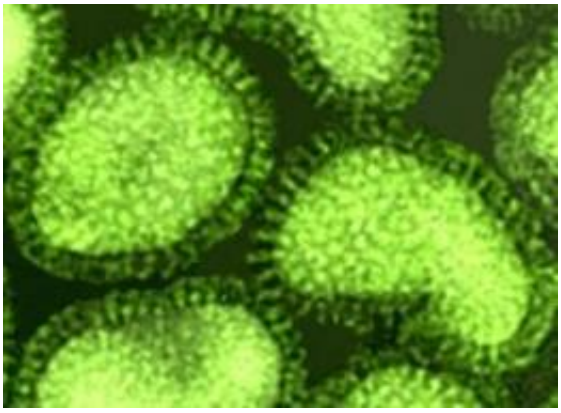

Flu virus

Certain subtypes of avian influenza viruses have the potential to cause more severe disease in humans than other avian influenza subtypes and should be monitored carefully to prevent spread of disease, according to a study published this week in *mBio*, the online open-access journal of the American Society for Microbiology.

The work, directed by researchers at the National Institute of Allergy and Infectious Diseases in Bethesda, Md., found that flu viruses expressing the low pathogenicity avian H1, H6, H7, H10 or H15 hemagglutinins (genes that encode the major surface protein for the virus) led to fatal infections in mice and caused more cell damage in normal human lung cells grown in culture as compared to avian influenza

viruses with other subtypes. The 1918 H1 subtype hemagglutinin has been already identified as a key virulence factor in the pandemic influenza virus of 1918. That virus, which caused the so-called "Spanish flu," spread rapidly around the world, resulting in approximately 50 million deaths.

"Viruses with these avian hemagglutinins have some type of inherent virulence motif to them, in that they induce a marked inflammatory response in mammals including human cells in culture," said senior study author Jeffery K. Taubenberger, MD, PhD, chief of the Viral Pathogenesis and Evolution Section of NIAID's Laboratory of Infectious Diseases. In 2013-2014 there have been close to 400 cases of avian influenza H7N9 infections in people in China, many severe, along with small numbers of severe human infections with H10N8 and H6N1 subtypes. "From a public health and epidemiology standpoint, it's useful to know that avian viruses of these subtypes (for example, H6, H7, or H10) might lead to more severe infections in humans and is something to look out for."

In a specialized laboratory , Taubenberger and colleagues developed a series of viruses mimicking 13 subtypes of contemporary low pathogenicity avian influenza A viruses. Each avian influenza virus tested was genetically identical to each other except that they expressed different hemagglutinin subtypes. After growing the viruses in culture, the researchers inoculated them into mice and watched to see what would happen. This approach allowed a direct comparison of the role of different hemagglutinins in virulence.

The viruses expressing the H1, H6, H7, H10 and H15 subtypes all caused rapid weight loss and fatal pneumonia infections within a week. By contrast, the H2, H3, H5, H9, H11, H13, H14 and H16-expressing viruses caused only mild weight loss but no significant disease.

The research team performed a similar test using hemagglutinins from two 2013 H7N9 flu viruses from outbreaks in Anhui and Shanghai, China, with similar results in mice. They also took a subset of these viruses and put them in culture with normal human lung cells that line the airways. The cells had developed into a thick layer called an epithelium. The disease-causing viruses like H1 and H7 caused mature cells to rapidly die over a couple of days, leaving just a thin lining behind.

These results suggest that hemagglutinins may not require immune cells to trigger cell damage but instead may cause programmed cell death or other molecular processes that could ultimately lead to enhanced disease or fatalities, Taubenberger said. In the future it will be important to tease out the differences in the hemagglutinins' structural features and investigate the molecular processes involved as the viruses infect mammalian cells, he said.

Meanwhile, until more is understood about how flu viruses cross from animals to humans and spread, more research is needed into producing a more broadly protective "universal" flu vaccine that may ultimately offer the best protection against future pandemics, he said.

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