



Clues to the Deadly 1918 Flu Revealed

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FOR DECADES, THE CHARACTERISTICS of the virus that caused the largest recorded outbreak of any infectious disease in history have remained mysterious. But now scientists have unveiled important structural properties of a key viral protein that may help explain why the 1918 “Spanish” influenza pandemic was so devastating, killing 20 to 40 million individuals worldwide.

Several researchers have retrieved viral DNA fragments from Alaskan flu victims buried in permafrost, as well as from archived autopsy materials. Historical records show that influenza spread through one village in Alaska in 5 days, killing about 85% of the adult population; the dead were buried in a mass grave in permafrost.

The researchers used the DNA fragments to recreate the genetic code of H1 hemagglutinin, a protein necessary for influenza virus to bind and fuse with a host cell. With the synthesized gene in hand, they were then able to produce the protein and obtain its crystal structure.

Two new reports suggest the unique structure of the 1918 virus’s hemagglutinin protein may be the reason for the rapid and deadly spread of the disease (*Science*. 2004. Feb 5; Epub ahead of print). One study looked at the structural elements involved with binding to receptors on host cells; the other probed the fusion of viral hemagglutinin with host cells. The results, researchers hope, could aid in the identification of other potentially dangerous influenza viruses and in vaccine development.

FROM FOWL TO FOLKS

All known human influenza pandemics in humans, which are caused by type A influenza viruses, have come from viruses that originated in birds. (Type B viruses, which infect only humans, cause more localized outbreaks.) Most avian viruses cannot infect humans because they have surface proteins that recognize and

bind to receptors on avian cells but not human cells. Because pigs can be infected with both avian and human viruses at the same time, they can act as a mixing pot for avian and human strains and sometimes pass recombined viruses back to birds and humans.

The researchers have found that hemagglutinin gene of the virus that caused the 1918 pandemic contained mostly avianlike sequences, yet it could also spread to humans. Therefore, in some cases, it may take just a few adaptive mutational steps for a virus to jump from poultry to individuals.

“It is quite clear [from these findings] that there were some mutations in the receptor binding site [of the 1918 virus’s hemagglutinin] that seemed to allow it to adapt to the human receptor,” said one of the studies’ authors, Ian Wilson, PhD, of the Scripps Research Institute, in La Jolla, Calif. Wilson’s findings included novel structural features in the hemagglutinin protein that may have contributed to enhanced membrane fusion with host cells.

In the second *Science* article, Sir John Skehel of the Medical Research Council’s National Institute for Medicinal Research, in London, and coauthors describe the particular amino acid residues

of the viral hemagglutinin that they believe allowed it to bind to human cells. They speculated that the 1918 pandemic influenza strain was so deadly because its hemagglutinin enabled the virus to readily invade human cells, and its antigenic properties differed enough from those of other influenza strains that the human population had no cross-immunity from previous influenza infections.

MAKING PREDICTIONS

The findings from both studies may help researchers pinpoint the key components in the hemagglutinin protein that could allow an avian virus to leap into humans. Once these components are better understood, researchers could screen bird populations to examine the influenza strains they harbor. It may someday be possible, said Wilson, to predict which avian strains could make the leap into humans by looking for hemagglutinins with mutations that would aid binding to human receptors.

While the new findings may provide insight into the 1918 virus’s virulence, many questions remain. “Our work answers some questions and it raises some questions—but that’s what science is about,” said Wilson. □

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Gymnasiums and other facilities were used as emergency hospitals for patients during the 1918 influenza epidemic that killed more than 20 million individuals worldwide. The epidemic was the largest recorded outbreak of any infectious disease in history.