Mutation altering stability of surface molecule in acid enables H5N1 infection of mammals

February 28 2013

A single mutation in the H5N1 avian influenza virus that affects the pH at which the hemagglutinin surface protein is activated simultaneously reduces its capacity to infect ducks and enhances its capacity to grow in mice according to research published ahead of print today in the *Journal of Virology*.

"Knowing the factors and markers that govern the efficient growth of a virus in one host species, tissue, or cell culture versus another is of fundamental importance in viral infectious disease," says Charles J. Russell of St. Jude Children's Research Hospital, Memphis, TN, an author on the study. "It is essential for us to identify influenza viruses that have increased potential to jump species, to help us make decisions to cull animals, or quarantine humans." The same knowledge "will help us identify targets to make new drugs that stop the virus… [and] engineer vaccines."

Various influenza viruses are spreading around the globe among wild birds, but fortunately, few gain the ability to jump to humans. However, those that do, and are able to then spread efficiently from person to person, cause global epidemics, such as the infamous pandemic of 1918, which infected one fifth and killed an estimated 2.7 percent of the world's population. Occasionally, one of these viruses is exceptionally lethal. For example, H5N1 has killed more than half of the humans it has infected. The specter of such a virus becoming easily transmissible

among humans truly frightens public health officials. But understanding the mechanisms of transmission could help microbiologists find ways to mitigate major epidemics.

When influenza viruses infect birds, the hemagglutinin surface protein of the virus is activated by acid in the entry pathway inside the host cell, enabling it to invade that cell. In earlier work, Russell and collaborators showed that a mutant version of the influenza H5N1 virus called K58I that resists acid activation, loses its capacity to infect ducks. Noting that the upper airways of mammals are more acidic than infected tissues of birds, they hypothesized, correctly, that a mutation rendering the hemagglutinin protein resistant to acid might render the virus more infective in mammals.

In this study the investigators found that K58I grows 100-fold better than the wild-type in the nasal cavities of mice, and is 50 percent more lethal. Conversely, the mutant K58I virus failed completely to kill ducks the investigators infected, while the wild-type killed 66 percent of ducks, says Russell. "A single mutation that eliminates H5N1 growth in ducks simultaneously enhances the capacity of H5N1 to grow in mice. We conclude that enhanced resistance to acid inactivation helps adapt H5N1 influenza virus from an avian to a mammalian host."

"These data contribute new information about viral determinants of influenza virus virulence and provide additional evidence to support the idea that H5N1 influenza virus pathogenesis in birds and mammals is linked to the pH of [hemagglutinin] activation in an opposing fashion," Terence S. Dermody of Vanderbilt University et al. write in an editorial in the journal accompanying the paper. "A higher pH optimum of [hemagglutinin] activation favors virulence in birds, whereas a lower pH optimum… favors virulence in mammals."

Based on this and another study, "…surveillance should include

phenotypic assessment of the [hemagglutinin] activation pH in addition to sequence analysis," Dermody writes.

The journal carefully considered whether to publish the paper, because it raised issues of "dual use research of concern" (DURC), writes Dermody. DURC is defined as "Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security," according to a US government policy document. However, both the National Institute of Allergy and Infectious Diseases and the St. Jude Institutional Biosafety Committee concluded that the study failed to meet the definition of DURC. Clinching the case, "the addition of the key mutation in the Russell paper to other previously reported mutations would not result in an even more virulent H5N1 influenza virus," says Dermody.

More information: H. Zaraket, O.A. Bridges, and C.J. Russell, 2013. The pH of activation of the hemagglutinin protein regulates H5N1 influenza virus replication and pathogenesis in mice. J. Virol. online ahead of print February 28, 2013, doi:10.1128/JVI.03110-12

Provided by American Society for Microbiology