Scientists Propose New Explanation for Flu Virus Antigenic Drift

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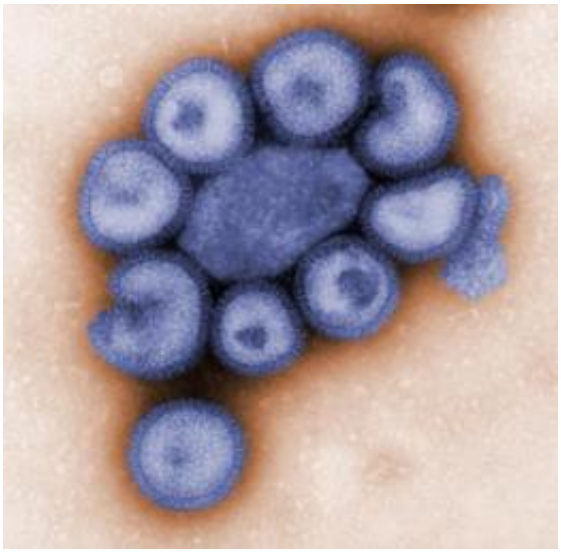

This colorized negative-stained transmission electron micrograph (TEM) depicts the ultrastructural details of a number of influenza virus particles, or “virions." Image: CDC/Dr. F. A. Murphy

(PhysOrg.com) -- Influenza viruses evade infection-fighting antibodies by constantly changing the shape of their major surface protein. This shape-shifting, called antigenic drift, is why influenza vaccines — which are designed to elicit antibodies matched to each year's circulating virus strains — must be reformulated annually.

Now, researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, have

proposed a new explanation for the evolutionary forces that drive antigenic drift. The findings in mice, using a strain of seasonal influenza virus first isolated in 1934, also suggest that antigenic drift might be slowed by increasing the number of children vaccinated against influenza.

Scott Hensley, Ph.D., Jonathan W. Yewdell, M.D., Ph.D., and Jack R. Bennink, Ph.D., led the research team, whose findings appear in the current issue of *Science*.

"This research elegantly combines modern genetic techniques with decades-old approaches to give us new insights into the mechanisms of antigenic drift and how influenza viruses elude the immune system," says NIAID Director Anthony S. Fauci, M.D."

"No one is sure exactly how the antigenic drift of flu viruses happens in people," says Dr. Yewdell. According to the prevailing theory, drift occurs as the virus is passed from person to person and is exposed to differing antibody attacks at each stop. With varying success, antibodies recognize one or more of the four antigenic regions in hemagglutinin, the major outer coat protein of the flu virus. Antibodies in person A, for example, may mount an attack in which antibodies focus on a single antigenic region. Mutant viruses that arise in person A can escape antibodies by replacing one critical amino acid in this antigen region. These mutant viruses survive, multiply and are passed to person B, where the process is repeated.

It is not possible to dissect the mechanism of antigenic drift in people directly, notes Dr. Yewdell. So he and his colleagues turned to a classic mouse model system developed in the mid-1950s at the University of Chicago, but used rarely since. The team infected mice with a strain of seasonal influenza virus that had circulated in Puerto Rico in 1934. Some mice were first vaccinated against this virus strain and developed

antibodies against it, while others were unvaccinated.

After infecting the vaccinated and unvaccinated mice with the 1934 influenza strain, the scientists isolated virus from the lungs of both sets of mice and passed on these viruses to a new set of mice. They did this nine times. After the final passage, the researchers sequenced the gene encoding the virus hemagglutinin protein. Of course, says Dr. Yewdell, gene sequencing was not possible in the mid-1950s, when the nature of the gene was first elucidated, and until very recently, sequencing was expensive and time-consuming. "Now, with automated gene sequencers, sequencing of dozens of isolates is easily done overnight," he says.

Sequencing revealed that the unvaccinated mice — which lacked vaccine-induced antibodies — had no mutated influenza viruses in their lungs. In contrast, the hemagglutinin gene in virus isolated from vaccinated mice had mutated in a way that increased the ability of the virus to adhere to the receptors it uses to enter lung cells. Essentially, says Dr. Yewdell, the virus can shield its hemagglutinin antigenic sites from antibody attack by binding more tightly to its receptor.

"The virus must strike the right balance, however," Dr. Yewdell says. "Excessively sticky viruses may end up binding to cells lining the nose or throat or to blood cells and may not make it into lung cells. Also, newly formed viruses must detach from infected cells before they can spread to the next uninfected cell. Viruses that have mutated to be highly adherent to the lung cell receptors may have difficulty completing this critical step in the infection cycle."

Next, the researchers infected a new set of unvaccinated mice with the high-affinity mutant virus strain that had emerged in the first series of experiments. In the absence of antibody pressure, the virus reverted to a low-affinity form and was once again able to easily infect cells and spread.

"We propose a model for antigenic drift in which high- and low-affinity influenza virus mutants alternate," says Dr. Yewdell. In adults — who have been exposed to many strains of influenza in their lifetime and, correspondingly, have a wide range of antibody responses — the virus is pressured to increase its receptor affinity to escape antibody neutralization. When such high-affinity mutants are passed to people — such as children — who have not been exposed to many influenza strains or who have not been vaccinated against flu, receptor affinity decreases. People who have not been exposed to multiple influenza virus strains or who have never been vaccinated against influenza are said to be immunologically nad′ve.

"Our model predicts that decreasing the immunologically nad′ve population — by increasing the number of children vaccinated against influenza, for example — could slow the rate of antigenic drift and extend the duration of effectiveness of seasonal influenza vaccines," he says.

More information: SE Hensley et al. Hemagglutinin receptor binding avidity drives influenza A virus antigenic drift. *Science*. DOI: 10.1126/science.1178258

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