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Study of Sugars on Cell Surface Identifies Key Factor in Flu Infection

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Scientists have identified a key factor that determines the ability of influenza viruses to infect cells of the human upper respiratory tract—a necessary step for sustaining spread between people. The research, described in the January 6 online edition of *Nature Biotechnology* and funded by the National Institutes of Health (NIH), offers new insights into how the H5N1 avian flu virus currently circulating in birds would have to change in order to gain a foothold in human populations.

The H5N1 virus has infected several hundred people, but person-to-person transmission has been limited. To trigger a widespread outbreak, experts agree that the bird flu virus must infect the cells lining our noses and throats. We then would spread the virus to others through coughing or sneezing. The latest study, led by Ram Sasisekharan, Ph.D., of the Massachusetts Institute of Technology in Cambridge, refines this notion: The virus can gain access only through a subset of the sugar molecules coating the cells of our upper airways.

"Using an approach that combines experimentation and database analysis, Sasisekharan's team has changed our view of flu viruses and how they must adapt to infect us," said Jeremy M. Berg, Ph.D., director of the National Institute of General Medical Sciences, the NIH component that supported the research. "The work may improve our ability to monitor the evolution of the H5N1 virus and thwart potential outbreaks."

Chains of sugars called glycans sit on the surface of our cells and control the gates through which different molecules enter. For a virus to gain access to a cell, proteins on the virus's surface must bind to certain glycans.

The binding protein for flu viruses is hemagglutinin. The protein can vary with each flu strain and, as a result, latch on to glycans from different types of cells. While the protein from human-adapted flu viruses favors the sugars dotting the cells of the nose and throat, the one from bird flu viruses opts for glycans on cells deeper in the respiratory tract.

Sasisekharan noted that recent studies have shown that the hemagglutinin protein from bird flu viruses has on occasion attached to glycans of the upper airways. The surprising finding, he explained, is that the virus didn't always spread effectively.

"This was a conundrum," said Sasisekharan.

To solve it, he and his team turned to the Consortium for Functional Glycomics (CFG), an initiative supported by NIGMS to explore the interactions between proteins and different types of sugars.

Mining data from the CFG glycan array, a tool for quickly screening protein-glycan binding preferences, Sasisekharan began to explore the structures of the different sugar chains coating upper respiratory tract cells.

“We found remarkable diversity,” he said. “Even though these glycans are all linked the same way chemically, they have very different shapes.”

According to the results, glycans of upper respiratory tract cells come in two main varieties: short and cone-shaped, and long and umbrella-shaped.

When the researchers combined this information with data from experiments and the glycan array, they found that the hemagglutinin protein from human-adapted flu viruses attached specifically to the long glycans of the upper respiratory tract. They also confirmed that the hemagglutinin from H5N1 viruses bound mainly to the cone-shaped glycans found in the lower respiratory tract.

These findings suggest that for the H5N1 bird flu virus to infect people and sustain its spread in humans, it must adapt so that it can latch onto the umbrella-shaped glycans of the upper respiratory tract.

“Until now, we had an incomplete understanding of avian flu hemagglutinin and how the protein must adapt to humans,” said Sasisekharan.

The new knowledge may unlock strategies for tracking mutations in the avian flu virus that allow it to bind to long glycans, point to new therapeutic targets for both seasonal and pandemic flu, and expand our basic knowledge of glycans and their diversity.

In addition to Sasisekharan, authors of the paper include MIT researchers Aarthi Chandrasekaran (Ph.D. candidate); Aravind Srinivasan, Ph.D.; Rahul Raman, Ph.D.; Karthik Viswanathan, Ph.D.; S. Raguram, Ph.D.; and V. Sasisekharan, Ph.D.; as well as Terrance M. Tumpey, Ph.D., of the U.S. Centers for Disease Control and Prevention.

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To learn more about the CFG, visit <http://www.functionalglycomics.org> or contact the NIGMS Office of Communications and Public Liaison at 301-496-7301.

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