Antibodies triggered by avian influenza virus vaccine illuminate a new path toward a universal flu vaccine

8 June 2016

Credit: National Cancer Institute

Diverse antibodies induced in humans by vaccination with an avian influenza virus vaccine may offer broader, more durable protection against multiple strains of influenza than today's vaccines typically provide, according to a study led by Florian Krammer, PhD, Assistant Professor in the Department of Microbiology at the Icahn School of Medicine at Mount Sinai, and Patrick Wilson, PhD, Associate Professor in the Department of Medicine at the University of Chicago. The research, published today in the journal *Cell Host & Microbe*, suggests new pathways toward the long-cherished goal of a "universal vaccine" that would be effective against all strains of influenza virus.

Influenza epidemics lead to as many as half a million deaths annually around the world, according to the World Health Organization. While generally effective, vaccines against seasonal influenza must be reformulated every year at great cost based on educated guesses as to which strains of influenza virus will dominate. This dilemma is caused by "antigenic drift"—a phenomenon in which gene mutations constantly alter sites on the virus that can be targeted by antibodies of a vaccinated individual. A true universal influenza vaccine would defeat antigenic drift, improve vaccine efficacy, and eliminate the constant need to reformulate vaccines and revaccinate populations at risk.

"The research in this study provides insights into how we can generate broadly protective immune responses against influenza viruses," Dr. Krammer said. "It shows us mechanisms of protection we didn't understand, or appreciate, or even know of before. I believe it will have huge implications for the development of a universal influenza virus vaccine."

A key objective of the study was to understand and assess the protective antibodies that are induced when individuals are vaccinated against pathogenic H7N9 avian influenza viruses, and to characterize the sites on the virus, called epitopes, to which antibodies bind. Mount Sinai scientists, in collaboration with a University of Chicago team led by Dr. Wilson, characterized the binding and functional properties of 12 monoclonal antibodies induced by an experimental vaccine based on live-attenuated avian influenza virus (H7N9).

One important result was the identification of unique epitopes on the head and stalk of the virus, which could be important antibody binding sites for future vaccines. But perhaps the most significant result was an enhanced understanding of the protective power of "non-neutralizing" antibodies, a class of monoclonal antibodies whose activity is not currently recognized or utilized in the development of commercial influenza vaccines.

Today's influenza vaccines are designed to induce

so-called neutralizing antibodies that target the glycoprotein hemagglutinin (HA), which carries many epitopes on the surface of the virus. Assays used to test the effectiveness of seasonal influenza vaccines—a step required by regulatory bodies such as the U.S. Food and Drug Administration before the vaccines can be licensed—only measure antibody activity targeting the highly variable head region of the virus. The new study indicates this approach to developing, testing, and deploying vaccines may not be optimal.

"We have showed that the assay used every year to prove influenza vaccines are effective can only detect one portion of the antibodies you get after vaccination with avian influenza virus," Dr. Krammer said. "There are a number of other neutralizing and non-neutralizing antibodies, some of which target previously unrecognized epitopes on the HA protein, and which provide protection against lethal infection in mouse models."

"Our results suggest that non-neutralizing antibodies, a class of antibodies typically not examined in assessments of vaccine efficacy, may contribute to protection," said Dr. Wilson of the University of Chicago.

"The antibodies we characterized in this study are very broad," Dr. Krammer said. "They bind not only to the H7 strain but to H3 and other strains. These results show us that we see only a small part of a bigger picture when we assess vaccine efficacy using today's most widely accepted assays." The new study suggests tantalizing opportunities for optimizing influenza vaccines and, importantly, also supports the hypothesis behind the universal influenza virus vaccine candidate that the team at Mount Sinai is currently developing.

"Assessing which non-neutralizing antibodies contribute to protection and how to measure their significant contribution in vaccinees remains a difficult challenge," said Mount Sinai's Dr. Krammer. Dr. Krammer expressed optimism that further research into the protective mechanism of broadly-reactive neutralizing and non-neutralizing antibodies could provide significant insights into human immunology that could ultimately lead to universal influenza virus vaccines that protect against all types of influenza viruses.

Provided by The Mount Sinai Hospital