Knowing origin of broadly neutralizing antibodies could aid universal flu vaccine design

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National Institutes of Health scientists have identified how a kind of immature immune cell responds to a part of influenza virus and have traced the path those cells take to generate antibodies that can neutralize a wide range of influenza virus strains. Study researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH, were led by Gary Nabel, M.D., Ph.D., director of NIAID's Vaccine Research Center. Their findings appear online in advance of print in *Nature*.

"This new understanding of how an immature immune cell transforms into a mature B cell capable of producing antibodies that neutralize a wide variety of influenza viruses could speed progress toward a universal flu vaccine—one that would provide protection against most or all influenza virus strains," said NIAID Director Anthony S. Fauci, M.D.

Universal flu vaccines, which are in development at NIAID and elsewhere, differ significantly from standard influenza vaccines. Unlike standard vaccines, which prompt the immune system to make antibodies aimed at the variable head of a lollipop-shaped influenza protein called hemagglutinin (HA), a universal flu vaccine would elicit antibodies that target HA's stem. Because the stem varies relatively little from strain to strain and does not change substantially from year to year, a vaccine that can elicit HA stem-targeted antibodies would, in theory, provide recipients with broad protection from the flu. The neutralizing antibodies generated would recognize any strain of flu virus.

Finding ways to elicit these broadly neutralizing antibodies (bnAbs) is thus a key challenge for universal flu vaccine developers. However, there is a snag. Researchers knew what the end products (mature bnAbs) look like, but they did not have a clear picture of the initial steps that stimulate their development. Specifically, they lacked an understanding of how the precursor immune cell—called a naive B cell—first recognizes the HA stem and starts down a path that ends in mature bnAb-producing B cells.

In the new research, Dr. Nabel and his colleagues demonstrated that the immature antibodies can only recognize and bind to HA's stem when the antibodies are attached to the membrane of a naive B cell. The investigators showed that this initial contact delivers a signal that triggers the maturation of these naive B cell into countless daughter cells, some of which acquire the specific genetic changes that give rise to HA-stem-binding antibodies. "We have repeated the first critical steps in the route leading to broadly neutralizing influenza antibodies," said Dr. Nabel. "Understanding how such antibodies originate could allow for rational design of vaccine candidates that would prompt the correct naive B cells to go on to mature into bnAb-producing cells."

The findings could also be relevant to HIV vaccine design, noted Dr. Nabel. There, too, eliciting bnAbs to relatively constant portions of HIV is a key goal. The insights into how naive B cells recognize constant components of a virus and mature into bnAb-producing cells could guide efforts to design an HIV vaccine capable of reproducing this effect.

More information: D Lingwood et al. Structural and genetic basis for development of broadly neutralizing influenza antibodies. *Nature* DOI 10.1038/nature11371 (2012).

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