Newly discovered antibody recognizes many strains of flu virus

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Some vaccines are once-in-a-lifetime; others need a booster shot or two to maintain their potency. And then there's the flu vaccine, which only lasts a year. Strains of influenza virus change so much from year-to-year that new vaccines must be developed annually to target the strains of virus that are most likely to cause illness. But Howard Hughes Medical Institute (HHMI) scientists have now discovered a human antibody that recognizes many different flu strains. Understanding more about this antibody may help scientists design a longer-lasting vaccine against the influenza virus.

To find the new antibody, Stephen C. Harrison, an HHMI investigator at Harvard Medical School and Children's Hospital, Boston, took advantage of the diversity of the human immune system.

When given the flu vaccine, every person's body will produce slightly different antibodies, which are immune system molecules that recognize and remember pathogens, such as viruses. Antibodies are small compared to the flu virus, but they need only recognize one piece of the virus's outer shell to be effective. This means that within the human population, there's great diversity when it comes to antibodies that recognize flu. For example, some people will produce an antibody against one bit of the virus, while others have antibodies that recognize a different viral snippet, and so on.

Strains of flu virus differ from one another largely in the genes that code for surface molecules called glycoproteins, which are the primary targets

of the body's immune system in defending against flu viruses. Like a coat of armor, the hemagglutinin and neuraminidase surface proteins stud the tiny influenza virus particle. When the virus mutates, it essentially "changes coats," altering the shape of its exterior surface and becoming unrecognizable to the human (or animal) immune system. This is the essence of immune evasion, a hallmark of influenza.

To study how the immune system determines which antibodies to produce, Harrison and collaborators at Duke University, turned to a new technology that lets scientists quickly scan the molecules in a person's immune cells.

"What this allows us to do is get a snapshot of the different kinds of antibodies being made in a person in response to a vaccine," says Harrison.

While the research team was taking such snapshots of immune cells, they found an antibody they weren't expecting—one that recognized multiple strains of the flu virus.

There's one part of the influenza virus that doesn't mutate—the binding area that recognizes receptors on human cells. If this receptor pocket mutates, the virus is no longer infectious. Scientists had previously believed that antibodies couldn't target this small area with such specificity.

"It has been assumed that because antibodies have a larger contact area than most virus receptors," says Harrison, "an antibody might target that receptor binding area, but it would still also recognize surrounding, changeable areas." This means if that surrounding area mutated, the antibodies wouldn't bind.

But the new antibody that the researchers isolated—dubbed

CH65—binds so tightly to the receptor pocket that it appears not to be strongly affected if the surrounding area mutates. When collaborators at the U.S. Food and Drug Administration tested the new antibody against 36 flu strains that have arisen between 1988 to 2007, they found that the antibody recognized and blocked 30 of those strains.

While this knowledge could theoretically be used to develop a vaccine that stimulates production of the CH65 antibody, this could just push viruses to mutate in the area around the binding pocket. If this occurs, the vaccine would eventually become obsolete. Instead, Harrison would like to use CH65 to probe how the immune system chooses which antibodies to produce. If one person can make the broad CH65 antibody, why can't everyone? Can scientists learn to coax the human immune system to produce CH65?

"Our goal," he says, "is to understand how the immune system selects for antibodies and use that information to get better at making a vaccine that will take you in a direction that favors breadth over specificity."

Harrison is now collaborating with HHMI investigator Nikolaus Grigorieff at Brandeis University to get structural information on antibodies as they evolve in the immune system after vaccine administration. By taking structural snapshots of antibodies over time, they may be able to deduce a pattern in how the immune system selects which antibody structures to favor.

Others, however, may use CH65 in a more direct clinical setting. "Some scientists are thinking about therapeutic antibodies, which can be administered to patients with severe flu cases, or compromised immune systems, as a way of fighting the virus," says Harrison. "And this antibody is a very interesting molecule to consider for that."

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