Designing more effective anti-HIV antibodies

November 19 2010

Although people infected with HIV produce many antibodies against the protein encapsulating the virus, most of these antibodies are strangely ineffective at fighting the disease. A new study suggests why some of the most common of these antibodies don't work: they target the protein in a form it takes after the virus has already invaded the cell, when it's too late, report researchers at Children's Hospital Boston and their colleagues.

The findings, published online Nov. 14 in the journal *Nature Structural & Molecular Biology*, refocus attention on the rare group of neutralizing antibodies that do work, described by the team in an earlier study. These antibodies home in on the protein at an earlier moment when the virus latches onto a healthy cell. Many people believe an effective HIV vaccine will need to greatly expand this rare antibody immune response to block infection. Children's has filed for patents on two new proteins designed to expand this rare antibody response.

"The key finding of this paper is that we can distinguish the shape of the protein targeted by useful antibodies," said senior author Bing Chen, PhD, of the Department of Molecular Medicine at Children's. "That means we can think about designing immunogens trapped in this defined structure and ways to prevent the protein from forming into an irrelevant conformation."

The same HIV protein, known as gp41, takes two such dramatically different configurations that it reacts with two different kinds of antibodies, Chen's group shows. In HIV, the protein travels under wraps

on the surface of virus particles. When the virus locks onto a healthy cell, the protein briefly unfolds and stretches out to its full length, extending out like a person reaching high overhead. This is the shape that generates rare but useful neutralizing antibodies in some people.

Then comes another shape change. After taking hold of the cell membrane, the protein folds over, like a person touching his toes, to fuse the cell to the virus membrane. That final calisthenic to fuse the membranes also creates an opening that allows the viral contents to invade the cell. At this stage, the protein functions as a decoy, serving only to bring on fruitless antibody responses and to distract the immune system, the authors wrote in the paper.

"We now believe that the neutralizing antibodies bind to the intermediate state, which prevents further structural rearrangements and blocks membrane fusion," said Chen, who is also affiliated with Harvard Medical School. "The key is that we can now separate which antibody recognizes which state, so that we can move forward to design an immunogen to induce an effective antibody response."

The findings suggest a new way of generating more useful anti-HIV antibodies. The intermediate stage of the protein normally lasts only about 15 minutes, too quickly to mount a successful immune response. For earlier work, the team leveraged the power of the first fusion-inhibiting antiviral drug, T20 (enfuviritide), approved for late-stage disease when other treatment options are failing. The drug traps the protein in the shape that spurs useful antibodies, the researchers reported in an earlier paper. In the latest study, the team further refined the protein for this study in a variation that does not require the drug. Additional biochemical experiments confirmed that two rare neutralizing antibodies from patients tackled the fleeting intermediate state of the experimental protein.

"This paper helps to resolve key questions plaguing the field: Why do certain forms of the protein interact with certain antibodies, and why aren't these antibodies in general more effective?" said virologist Dan Barouch, professor of medicine at Harvard Medical School and Beth Israel Deaconess Medical Center, who was not involved in the study. "This paper shows how particular antibodies react with different conformation states of gp41, but the implications are well beyond that. The results also offer a new way of thinking about envelope immunogen design." Barouch is collaborating with Chen to test the immunogenicity of the protein in animal models.

Chen's team discovered the immune-evasion power of the decoy protein shape in studies led by Gary Frey, PhD, and Jia Chen, PhD. Frey and Chen solved the atomic structure of a useless antibody bond to the final form of the protein. "The postfusion state is very stable," said Chen, allowing plenty of time for the body to churn out worthless antibodies.

A companion paper from a Duke University group published simultaneously online shows another non-neutralizing antibody binding to a slightly different region of the protein in the postfusion form, further confirming the findings reported by Chen's group.

Provided by Children's Hospital Boston