Study explores barriers to HIV vaccine response

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Researchers at The Scripps Research Institute (TSRI) discovered that an antibody that binds and neutralizes HIV likely also targets the body's own "self" proteins. This finding could complicate the development of HIV vaccines designed to elicit this protective antibody, called 4E10, and others like it, as doing so might be dangerous or inefficient.

"We developed two new mouse models that allow us to visualize the fate of the rare B cells that can see HIV and we thought could be stimulated by vaccines to produce neutralizing antibodies—the type of antibodies we seek to produce in response to a vaccine," said David Nemazee, PhD, professor in the Department of Immunology and Microbial Science at TSRI and senior author of the study. "We were able to study vaccine responses of b12, an antibody that sees the CD4 binding site of HIV, but, surprisingly to us, not 4E10, an antibody that sees the stem of the HIV envelope protein."

Nemazee and his team went on to discover that cells with the potential to produce 4E10 antibodies trigger several natural safeguards that shut down the production of any antibody that might recognize and destroy the body's own tissues. They concluded that 4E10 cross-reacts with host tissues in this way, prompting its removal before it can do any harm—or good. The study was recently published by *The Journal of Immunology*.

HIV Vaccine Development

4E10 antibodies were originally isolated from a human HIV patient. The antibodies specifically recognize and bind an HIV surface protein called gp41. The virus uses gp41 like a long spike to poke holes in its host's immune cells. But when 4E10 antibodies clog up gp41, the virus is neutralized and host cells are protected.

4E10 especially interests HIV researchers because the antibody recognizes and binds to gp41 on the surface of many different strains of the virus, not just the one strain with which the patient was most recently infected. If a vaccine could be made to specifically and safely stimulate 4E10-like production, recipients would likely be protected against multiple HIV strains.

In humans, HIV slowly destroys the immune system, leading to Acquired Immune Deficiency Syndrome (AIDS). According to the Centers for Disease Control and Prevention, more than 1.1 million people in the U.S. are living with HIV infection. While treatments developed in the past decade can keep the virus in check for many years, there is no vaccine and there is no cure.

Proceeding with Caution

In several ongoing studies, the TSRI team and others are working out how to make a vaccine that stimulates the production of 4E10, b12 and other broadly neutralizing anti-HIV antibodies. However, this latest study indicates that this approach might be complicated by unwanted self-reactivity. Antibodies that cross-react with host tissue—like 4E10 has now been shown to do—are associated with autoimmune diseases such as multiple sclerosis and lupus.

The TSRI study also raises the question of how 4E10 was generated in the first place. According to Nemazee, 4E10 may be a fluke, cropping up in an HIV patient who was also prone to autoimmune diseases.

Alternatively, the autoreactive antibody could have arisen in the patient as a consequence of the disease—perhaps the body's normal mechanism for weeding out such antibodies failed, allowing the serendipitous production of an anti-HIV antibody.

Despite this new concern, there is still hope for 4E10's role in HIV vaccine development. A companion paper published in the same issue of *The Journal of Immunology* found that another potent, broadly neutralizing anti-HIV antibody, b12, was not self-reactive and could respond to a candidate vaccine preparation provided by Richard Wyatt, TSRI Professor of Immunology and Director of Viral Immunology at the International AIDS Vaccine Initiative Neutralizing Antibody Center.

"It's still possible that we could safely elicit the 4E10-like antibody in order to protect against HIV," Nemazee said. "We just have to think about how to generate the best antibodies without causing other problems. We have a lot of questions. And now we have a good model to help us answer them."

More information: "Immune Tolerance Negatively Regulates B Cells in KnockIn Mice Expressing Broadly Neutralizing HIV Antibody 4E10," www.jimmunol.org/content/191/6/3186.abstract

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