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Surprising diversity of antibody family provides clues for HIV vaccine design

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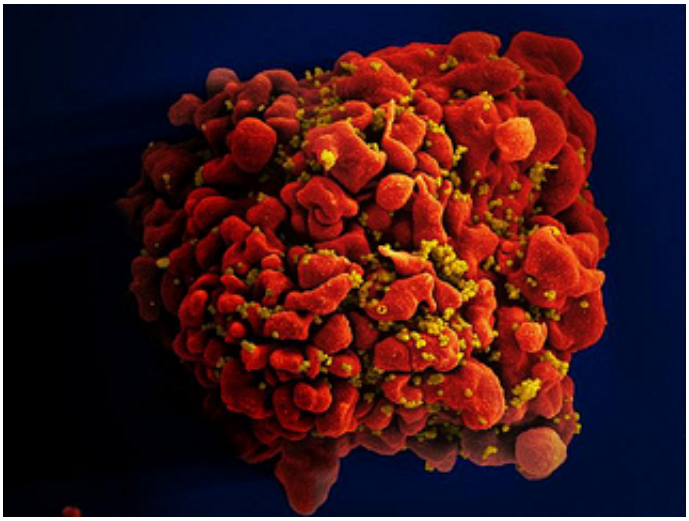

Scanning electron micrograph of an HIV-infected H9 T cell. Credit: NIAID

Scientists at The Scripps Research Institute (TSRI) have described how a single family of antibodies that broadly neutralizes different strains of HIV has evolved remarkably diverse structures to attack a vulnerable site on the virus. The findings provide clues for the design of a future HIV vaccine.

"In a sense, this antibody family takes more than one shot on goal in order to hit divergent forms of HIV," said Ian A. Wilson, the Hansen Professor of Structural Biology and member of the Skaggs Institute for Chemical Biology at TSRI.

"The findings give us new options for vaccine design," added TSRI Professor Dennis R. Burton, who directs the International AIDS Vaccine Initiative's (IAVI) Neutralizing Antibody Consortium and the National Institutes of Health-sponsored Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID) at TSRI.

The new research, reported in the September 25, 2014 issue of the journal *Cell*, is part of a broad effort to "retro design" an effective HIV vaccine, based on an understanding of rare, natural antibodies that effectively hit HIV's most vulnerable sites.

Decoys to the Immune System

Traditional viral vaccine design, which dates back hundreds of years, uses weakened or inactivated virus particles, or large viral subunits, to elicit long-term immune protection. But HIV, like some other viruses, thwarts this approach. It protects its vulnerable sites with a surface envelope protein (Env) that can mutate rapidly from strain to strain and coats its surface with covalently linked sugar molecules (glycans) that are hard for antibodies to grip.

Researchers have found, though that, in some HIV-infected people, the immune system does eventually penetrate the virus's glycan shield. It starts producing antibodies that can grab or at least block the virus's most vulnerable sites—sites that don't change much from strain to strain because they are involved in crucial functions such as docking or fusing with host cells.

These rare, "broadly neutralizing" antibodies are not usually produced in the body in high enough numbers to help already-infected people. But many researchers now are convinced that these antibodies hold the key to a successful preventive vaccine. Indeed, Burton's laboratory and collaborators reported recently that infusions of one such antibody,

PGT121, protected monkeys from new infections with simian HIV and also dramatically lowered virus levels in already-infected monkeys.

Retracing the Immune System's Steps

The big challenge remains the "retro design": taking information about antibodies such as PGT121 and using it to design the main vaccine ingredient—the immunogen molecule—that can elicit high levels of the same antibodies in people. (Active vaccination to elicit a long-term protective response is far more feasible as a public health strategy than infusions of expensive antibodies would be.)

The new study highlights the complexity of that challenge. For the research, Burton's and Wilson's laboratories teamed up to characterize an antibody called PGT124, a recently discovered member of the PGT121 family.

Such families are the products of a powerful diversity-extending process in the immune response called affinity maturation. The B cells of the immune system produce a standard repertoire of millions of "germline" antibodies even in the absence of infection. But when one of those B cells encounters a matching target (such as a specific shape on a virus) and responds by becoming activated and replicating rapidly, its antibody-coding genes mutate slightly with each cell division. A family of not-quite-identical B cells and corresponding antibodies are generated that can potentially hit the same target more strongly and precisely—and also in different ways, hopefully blocking the ability of a virus to escape with mutations of its own.

No one has identified the germline antibody that develops into the PGT121 family. However, by studying its offspring, scientists can infer that original antibody's broad features—and structures a vaccine immunogen could display to stimulate the production of broadly

neutralizing antibodies.

Surprise Findings

Previous studies had found that one branch of the PGT121 antibody family, PGT121-123, attacks a vulnerable site on HIV's envelope protein at the base of a hypervariable structure (called the V3 loop), grabbing relatively non-varying protein components and multiple glycans—with very low affinity for any single glycan.

In contrast, results from this study revealed that another member of the family, PGT124, from a different lineage, maintained its grip on the site by fastening to a small fragment of the viral protein plus a single glycan.

"Affinity maturation is a critical process of directed evolution in mounting an antibody response to all pathogens," said Fernando Garces, a postdoctoral fellow in the Wilson laboratory. "However, molecular details of this process have been unavailable. Now, through structural biology, we have elucidated at the atomic level how antibody maturation can pursue different strategies to recognize HIV-1 gp120, leading to broad neutralization of the virus. Initially, we had assumed that the PGT121 family has a complex epitope involving multiple protein pieces and many glycans.

"So when the crystal structure first popped out on my computer screen and I saw the antibody binding to a single glycan, my first thought was it was wrong," he continued. "Later we confirmed that the PGT124 antibody does indeed require only a single glycan and a few surrounding amino acids on the envelope protein to neutralize up to 70 percent of all HIV-1 strains."

Devin Sok, a research associate in the Burton laboratory, added, "This gives us better detail on how PGT121 family antibodies have diverged

during the affinity maturation process—it's clear that there are multiple pathways, even within a single antibody family, to achieve broad neutralization of HIV. That's important to understand for vaccine design for HIV, as well as other glycan-shielded viruses such as influenza and hepatitis C virus. It's also relevant to the problem of targeting glycan structures on cancers and other diseases."

More information: "Structural Evolution of Glycan Recognition by a Family of Potent HIV Antibodies," *Cell*, 2014.

Provided by The Scripps Research Institute