Scientists uncover structure of key protein in common HIV subgroup

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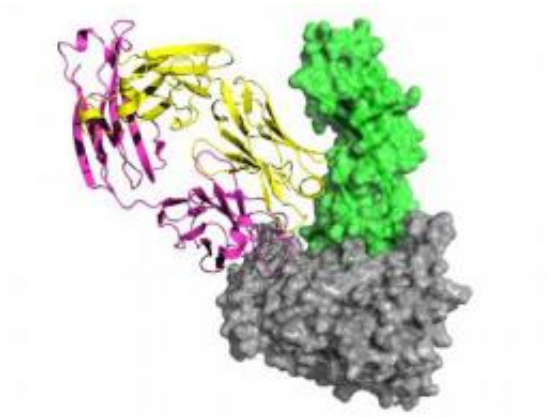

This image of the complex studied by the Caltech team shows gp120 in gray, CD4 in green, the 21c antibody's light chain in yellow, and its heavy chain in magenta. Credit: Caltech/Ron Diskin

Scientists from the California Institute of Technology have provided the first-ever glimpse of the structure of a key protein -- gp120 -- found on the surface of a specific subgroup of the human immunodeficiency virus, HIV-1. In addition, they demonstrated that a particular antibody to gp120 makes contact not only with the protein, but with the CD4 receptor that gp120 uses to gain entrance into the body's T cells.

This three-dimensional understanding of how gp120 is built is more than just a basic scientific advance. "There's a tremendous continuing effort to develop a vaccine for HIV," says Caltech postdoctoral scholar Ron Diskin, "and most of those efforts use gp120. Having more structural information will facilitate better vaccine design."

The findings are detailed in a paper published in the advance online edition of the journal *Nature Structural & Molecular Biology*.

The team looked specifically at gp120 from what is known as clade C HIV-1. To explain what that means, here's a brief HIV family history: Most people who get HIV and proceed to AIDS are infected with a member of the HIV-1 family of viruses. HIV-1 is divided into groups; most AIDS-related strains of the virus come from group M. The groups are further subdivided into what are known as clades.

Clade B is the form of group M HIV-1 most often found in the United States and western Europe, and the one that is probably best-studied to date. Clade C, the clade studied by the Caltech team, is "the one that is devastating Africa and Asia," says Diskin. "It's the one that probably causes the largest number of infections worldwide."

Previous studies had looked at the structure of clade B gp120, and it had been assumed—but not proven—that clade C's version would look much the same.

In order to uncover the structure of clade C gp120—and determine if the hypothesis about its similarities was indeed true—the Caltech team needed to crystallize the protein. That was no easy task. Turns out, says Diskin, the protein itself is not stiff enough for crystallization. And so the researchers created a complex of molecules consisting of a gp120 monomer, a CD4 receptor, and an anti-HIV antibody known as 21c.

This configuration facilitated crystallization, and allowed the scientists to look not only at gp120—which, indeed, "looks pretty much the same in clade C as in clade B," says Diskin—but to visualize the entire binding site and to see how the various components in the complex interact with one another.

That was when they noticed something unusual: Antibody 21c was not only reacting to—and thus making contact with—the gp120 protein sticking out from HIV's envelope, but also was reacting to the

CD4 receptors on the body's own T cells. It is the first time this sort of polyreactivity—a response to more than one antigen—had been visualized in the 3-D structure of an HIV-targeting antibody.

"The most interesting aspect of our structure is the unexpected contact between the antibody and CD4," says Pamela Bjorkman, the Max Delbruck Professor of Biology at Caltech, a Howard Hughes Medical Institute investigator, and the Caltech team's leader. "The binding to CD4 suggests that this class of anti-HIV antibodies has autoreactive properties, which raises many interesting questions about how anti-HIV immune responses affect an HIV-infected individual."

Does this autoreactivity mean that 21c is too dangerous to work with, because clinicians might be courting a potential autoimmune response with a vaccine that elicits 21c-like antibodies?

Not necessarily, says Diskin.

"Other data out there show that some of the best neutralizing antibodies are also autoreactive," he explains.

What it does mean, however, is that there would be additional hurdles to overcome in eliciting such antibody responses, Diskin says. The body tends to eliminate autoreactive antibodies, in an attempt to keep autoimmune diseases at bay. "In order to create a good vaccine to produce 21c-like antibodies, researchers will have to overcome this elimination mechanism."

The next step for the Caltech team is to try to improve on the relatively low-resolution structure worked out in the current paper. In addition, Diskin says, the team would like to try to resolve the structure of a gp120 trimer—a more complex, three-pronged version of the protein.

More information: "Structure of a clade C HIV gp120 bound to CD4 and CD4-induced antibody reveals anti-CD4 polyreactivity," *Nature Structural & Molecular Biology*.

Provided by California Institute of Technology