

Elusive HIV Shape Change Revealed; Key Clue to How Virus Infects Cells

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Crystal Images Could Yield New Strategies for AIDS Vaccine and Drug Development

Structural biologists at Children's Hospital Boston and Harvard Medical School have shown how a key part of the human immunodeficiency virus (HIV) changes shape, triggering other changes that allow the AIDS virus to enter and infect cells. Their findings, published in the Feb. 24 issue of the journal *Nature*, offer clues that will help guide vaccine and treatment approaches.

Researchers led by Howard Hughes Medical Institute Investigator Stephen Harrison, PhD, and Bing Chen, PhD, focused on the gp120 protein, part of HIV's outer membrane, or envelope. gp120's job is to recognize and bind to the so-called CD4 receptor on the surface of the cell HIV wants to infect. Once it binds, gp120 undergoes a shape change, which signals a companion protein, gp41, to begin a set of actions that enable HIV's membrane to fuse with the target cell's membrane. This fusion of membranes allows HIV to enter the cell and begin replicating.

The structure of gp120 after it binds to the CD4 receptor and changes its shape was solved several years ago by another group. Harrison and Chen have now described gp120's structure before the shape change, yielding vital before-and-after information on how the molecule rearranges itself when it encounters the CD4 receptor.

"Knowing how gp120 changes shape is a new route to inhibiting HIV -

by using compounds that inhibit the shape change," says Harrison. He notes that some HIV inhibitors already in development seem to inhibit the shape change; the new findings may help pin down how these compounds work and hasten their development into drugs. "The findings also will help us understand why it's so hard to make an HIV vaccine, and will help us start strategizing about new approaches to vaccine development."

The studies, performed in the Children's Hospital Boston Laboratory of Molecular Medicine, used the closely related simian immunodeficiency virus (SIV) as a stand-in for HIV. By aiming an X-ray beam through a crystallized form of gp120, they obtained the first high-resolution three-dimensional images of the protein in its unbound form. They surmounted considerable technical challenges, including difficulty in getting gp120 to form good crystals.

"Without very well-ordered crystals you get a very blurry picture," explains Harrison. "It took a very long time, and lots of computational work, to get that picture to sharpen up enough to get an answer."

One of the lab's first steps will be to determine which shape of gp120 - bound to the CD4 receptor, or unbound - is recognized by a person's antibodies. gp120's shape change is an important "escape mechanism" for HIV, allowing the virus to bind to and enter a cell before the immune system can "see" it, notes Harrison.

"We can now compare the bound and unbound forms and try to understand whether there are any immunologic properties that differ and that might provide a route to new vaccine or drug strategies," Harrison says.

Source: Children's Hospital Boston

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