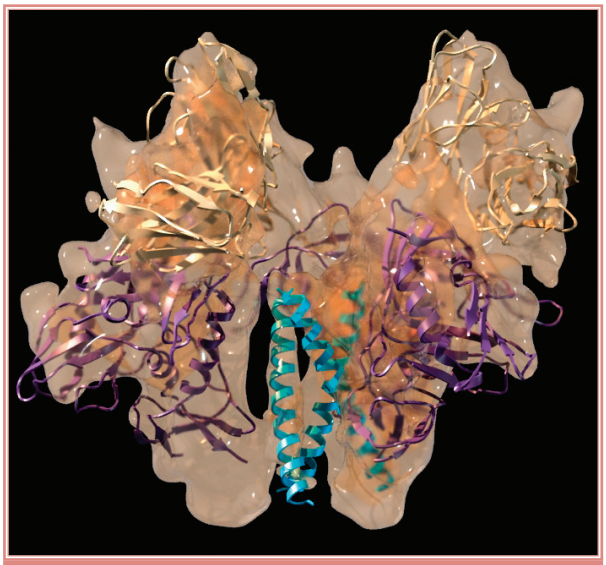
Finding a Chink in the Armor:
Investigating the Structure of HIV

HIV infection depends on two proteins expressed on the virus surface: gp41, which sits in the virus membrane, and gp120, which sits on top of gp41. Three copies, or trimers, of each gp41/gp120 pair make up the protein, Env. Env coats the virus surface and interacts with its receptor, CD4, and a co-receptor on the T cell. Binding to the receptors is thought to cause a structural reorganization of Env, which exposes a fusion peptide that inserts into the T cell membrane and actually forces the virus and host membranes together, initiating an infection. However, the structural details of this process are lacking.



(*Figure: S. Subramaniam, CCR*)

A three-dimensional rendering of the structure of trimeric Env bound to 17b is shown. The map was fitted with three copies of the X-ray structures with gp120 shown in purple and 17b in gold. One copy of the gp41 N-terminal helix, shown in cyan was fitted individually into each of the three densities and occupies the central region of the spike, which is essentially a cavity in the unbound state.

Antibodies directed against different parts of Env may be able to prevent HIV infection, but only if essential structural elements are targeted. Erin Tran, Ph.D., a Postdoctoral Fellow, and Mario Borgnia, Ph.D., a Staff Scientist, working with Sriram Subramaniam, Ph.D., in CCR's Laboratory of Cell Biology, and their colleagues investigated how the structure of Env changes as it binds to its receptor. The conformations of Env in different situations may suggest new regions for antibody targeting that are likely to block HIV infection. Their findings were published July 12, 2012, in *PLoS Pathogens*.

The researchers first examined the structure of Env on intact viruses incubated with a soluble version of CD4 to mimic normal receptor binding or with an antibody called 17b, which simulates co-receptor binding. They rapidly froze the samples to preserve the structures and to prevent ice crystals from forming. The frozen samples were then imaged using electron microscopy and three-dimensional structures were generated. Binding to either soluble CD4 or 17b caused the gp120 molecules to rotate outward, forming an opening in the center of the Env structure. This more open conformation is similar to the structure of Env bound to both CD4 and 17b, indicating that 17b binding alone is capable of inducing a conformational change in Env similar to the change induced by the natural CD4 receptor.

To get an even more detailed picture of Env in the open conformation, the researchers used single particle electron microscopy techniques, which provide higher structural resolution. Incubating soluble Env trimers with 17b again produced the open Env conformation, but this time the researchers were able to detect three helical structures in the center of the Env complex. The researchers attributed these helices to one end of gp41 and suggest that the helices are a part of the HIV fusion peptide, but at a step prior to insertion into a target cell membrane. The researchers also noted that the portion of gp41 that forms each helix is one of the most conserved regions across different HIV strains. This high-resolution structure of Env may provide a new blueprint for building vaccines. Vaccines directed against this structure could stimulate the production of antibodies that will recognize this highly conserved region of Env at a stage where the virus is still poised to infect target cells.

To learn more about Dr. Subramaniam's research, please visit his CCR Web site at http://electron.nci.nih.gov.