AIDS

Investigators Detail HIV's Fatal Handshake

Before a virus can enter a cell, it typically must perform what amounts to a secret handshake at the cell's door. Until recently, AIDS researchers knew only the opening grip that HIV uses to wangle its way into white blood cells, the virus's main target. But during the past year, studies of the complex relationship between HIV and immune-system chemicals known as chemokines have allowed investigators to glimpse a whole series of elbow bumps, pinky pulls, and forearm grabs that HIV and white blood cells exchange when they meet—an understanding that one day may help researchers slam the door on the virus.

The most detailed picture yet of this ritual appears on page 602 of this issue. The study, led by Cheryl Lapham and Hana Golding of the Food and Drug Administration (FDA) and Dimiter Dimitrov of the National Cancer Institute, reveals a multistage interplay between HIV and two receptors found on the surface of white blood cells. The results show that after binding to the receptor known as CD4, the virus fuses with a second one, a molecule recently renamed CXCR4 which normally binds to chemokines. This double clasp may then signal the receptors to spirit the virus into the cell. "It's very exciting, if these are real observations," says Mark Marsh, a cell biologist who has been working on the HIV entry problem at England's Medical Research Council.

Marsh's cautious enthusiasm is echoed by others in the field who have failed to tease out the precise relationship between HIV and chemokine receptors using techniques similar to those used by Golding and coworkers. "The funny thing is, they didn't really seem to do anything special," says Robert Doms of the University of Pennsylvania. Still, says Doms, "the paper looks pretty convincing." And other, unpublished findings are confirming its conclusions.

The FDA researchers' findings grow out of a search that has preoccupied Golding and many other AIDS researchers for several years. Investigators have known for more than a decade that in HIV's initial clasp with the white blood cells known as T lymphocytes, the viral protein gp120 on the virus's surface binds to the cell's CD4 receptor. But studies in 1986 revealed that HIV required an additional factor—most likely a second receptor on the cell surface—to breach the cell membrane.

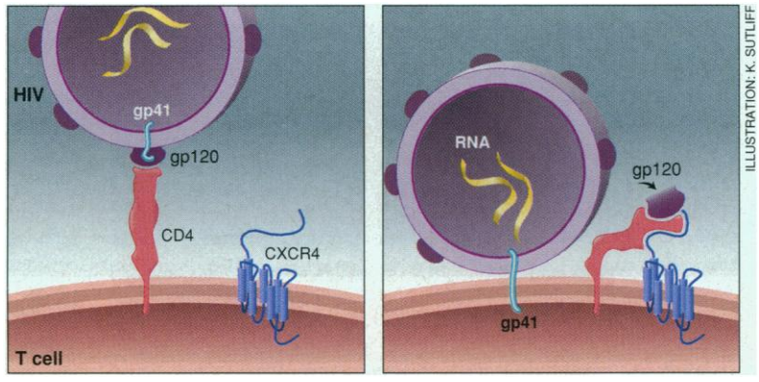
The Golding lab's search for that cofactor relied on a technique called immunoprecipitation, which uses antibodies to fish specific molecules out of molecular aggregates. Specifically, the researchers added gp120 to CD4-bearing T cells and then chopped up, or lysated, the mix. They then immunoprecipitated the lysates with antibodies to either CD4 or gp120. By analyzing the molecular weights of the resulting precipitates, they discovered that an unknown protein appeared to be linked to the gp120-CD4 complex.

But before Golding could identify the protein, Edward Berger of the National Institute of Allergy and Infectious Diseases beat her to the punch. He reported in the 10 May issue of *Science* (p. 872) that, using a molecular biological approach that sifted through myriad possible cofactors, he had found the mysterious one needed for entry: It was CXCR4 (formerly fusin, LESTR, or HUMSTR), a cell-surface receptor for a chemokine. Subsequent studies have shown that CXCR4 is just one of several chemokine receptors used by different strains of HIV to infect cells (*Science*, 21 June, p. 1740). But until now, no one knew whether CXCR4 and its cousins were behaving as actual coreceptors, to which the virus actually binds, or whether they had a less direct role, such as signaling a cell to allow HIV to enter without ever touching the virus.

Even though Golding's lab didn't win the race, that work led to the current findings. As the researchers show, the unknown protein they had immunoprecipitated earlier with the gp120-CD4 aggregate indeed was CXCR4, suggesting that the chemokine receptor shakes hands directly with the virus. "The important insight is that [HIV entry] is an interaction between gp120 and the chemokine receptor," says Dan Littman of New York University, whose lab was one of the first to uncover the links between HIV and chemokine receptors.

Alexandra Trkola, who works in John Moore's lab at the Aaron Diamond AIDS Research Center in New York City, has reached a similar conclusion. Earlier this month at a chemokine meeting in San Francisco, she presented evidence that gp120 also binds to another chemokine receptor that has been implicated in HIV infection. Trkola and co-workers focused on CCR5, a chemokine receptor used by strains of the virus that predominate when a person first becomes infected. Still more evidence that HIV binds to chemokine receptors is on its way from Joseph Sodroski, Craig Gerard, and co-workers at Harvard Medical School. Both the Harvard and Aaron Diamond studies are in press at *Nature*.

Now researchers are starting to speculate about just how this double handshake results in viral entry. Previous studies by Moore, Sodroski, and others have shown that after CD4 and gp120 bind, the complex goes through a "confirmational change," twisting to expose different parts of the proteins. This conformational change, contend several investigators, is what allows the complex to bind to the chemokine receptor. Then "things get murky," cautions the University of Pennsylvania's Doms. Golding shares the popular view that after the chemokine receptor has fused with the CD4-gp120 complex, the bottom part of HIV's envelope protein, gp41, pops away from gp120 and, in effect, gaffs the cell membrane (see drawing). The chemokine receptor completes the process by "chaperoning" the gp120-CD4 complex into the cell.



Come on in. After docking onto a T cell's CD4 receptor, HIV's gp120 binds to chemokine receptors like CXCR4, allowing gp41 to breach the cell membrane.

This scenario is far from proven, but researchers are already imagining new ways to lock out the virus, which may ultimately help both infected and uninfected people. For example, antibodies that block the binding between chemokine receptors and gp120 might slow down or halt the onset of AIDS in HIV-infected people. Similarly, a vaccine that could teach the immune system to produce antibodies that block this interaction might protect uninfected people. So the new data are not only intellectually satisfying to investigators who want to understand every move HIV makes as it slips into the cell's inner sanctum; they are also opening doors in researchers' minds about how to close the door on HIV.

–Jon Cohen