

Key for AIDS Gateway Found

Protein helps virus to enter cell

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Scientists may at last have found a crucial doorway used by the AIDS virus to gain entry into human cells, a protein that could mean the development of an entirely new family of AIDS drugs.

The protein, dubbed with the cumbersome moniker CC CKR-5 is present on human cells in the earliest stages of HIV infection, researchers said yesterday, suggesting it is probably the key portal of entry for the Human Immunodeficiency Virus.

“CD4 [a receptor identified in 1989] is what the virus sticks to,” Dr. Ned Landau of the Aaron Diamond AIDS Research Center in Manhattan said yesterday. “It’s the Velcro, or anchor, But CC CKR-5 is the virus’s gateway.”

The finding, announced by three separate laboratories, was one of two key advances that were unveiled yesterday. Researchers also said they have determined that the CC CKR-5 gateway can be blocked by chemicals

called chemokines, which tend to herd immune-system elements into infected areas, causing local inflammation.

“Three chemokines in particular – MIP-1 alpha, MIP-1 beta and RANTES – seem to serve as powerful inhibitors of HIV entry, according to John Moore, who led a team of researchers from the Aaron Diamond Center and a small Tarrytown biotech firm, called Progenics Pharmaceuticals.

When the research team looked closely at immune-system cells from New Yorkers who seemed to be resistant to HIV infection, Moore said, it was discovered that they were producing more than the normal amount of those particular chemokines.

“We’re very excited,” Landau said, “because this [the research announced yesterday] offers tremendous insight into the transmission and replication of HIV. And because this now exposes a prime target against which drugs can be developed.”

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Just last month, Dr. Edward Berger of the National Institute of Allergy and Infectious Disease announced the discovery of fusin, a protein that sits on the surface of human T-cells (white blood cells) in the later stages of the disease. Berger then showed that the AIDS virus must stick onto both CD4 and fusin to get into a human lymphocyte.

CC CKR-5 meanwhile, is found on both T-cells and other ubiquitous immune-system cells such as macrophages. More importantly, CC CKR-5 is the receptor used by the types of HIVs that are contagious between people: fusin, in contrast, serves as the gateway for later-stage HIVs that are particularly lethal, but rarely transmissible.

Berger headed one of three research teams who discovered the CC CKR-5 protein. His report will be highlighted tomorrow in the journal *Science*.

Landau collaborated with New York University School of Medicine physician Dan Littman on a study of the types of HIV found typically in people who are in the early stages of infection. They found HIVs bound to CC CKR-5 receptors and isolated those receptors for careful analysis. Landau's results, and the results found by Moore, appear today in the journal *Nature*.

The discoveries are an important step in attempting to block AIDS transmission.

In a 1995 paper, Dr. Robert Gallo, now at the University of Maryland in Baltimore, announced discovery of the role that chemokines play in blocking the spread of HIV. He then hypothesized that chemokines

blocked the virus by holding back some as-yet undiscovered receptor molecule on the surface of human cells. Ten months later, Berger found that hypothesized receptor, fusin. And now, the discovery of CC CKR-5 helps to complete the research circle.

The next step, scientists say, is to turn this knowledge into a treatment or drug. Researchers are pursuing several paths of inquiry:

- Berger, for instance, is studying dendritic cells – the types of cells found in the mouth and genitalia that are the first to be infected by HIV. He is looking for similar gateway receptors on those cells and expects they will be different from fusin and CC CKR-5. Moore is also studying dendritic cells.

- Researchers at several laboratories are looking for such receptors for SIV, the primate AIDS virus.

- And Progenics is testing the first of a series of products in the laboratory that it hopes will block HIV, using these chemokines pathways. The Gallo lab is also in hot pursuit of a chemokines-based drug to block HIV.

The payoff could be enormous, going well beyond AIDS. Chemokines represent a whole class of more than 30 recently discovered chemicals that mobilize the immune system.

Various chemokines appear to play a role in arthritis, Alzheimer's disease, asthma, malaria, even cancer. Adding AIDS to the chemokines list only ups the ante for the pharmaceutical industry. Dozens of companies are already hot on the trail of chemokines blockers, modifiers and stimulators, which are aimed at raising or lowering the levels of these apparently critical chemicals.

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