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HIV Hijacks Immune Cells to Enter the Body

Researchers have discovered how the human immunodeficiency virus (HIV) first enters the body through mucosal surfaces such as the rectum, cervix and uterus.

The *in vitro* findings strongly suggest that HIV enters the body by attaching itself to immature immune cells, called dendritic cells, on mucosal surfaces. After infecting dendritic cells, HIV then hitches a ride into the lymphoid tissues, where the virus proceeds to infect the rest of the immune system.

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— **Dan R. Littman**

Dendritic cells are normally the watchdogs of the immune system, patrolling skin and mucosal surfaces. When dendritic cells "see" a foreign invader, such as a microorganism, they capture it, shred it and display pieces of proteins from the invading pathogen on their surfaces. These displayed proteins serve to alert other immune system cells, such as T cells, that the body is under attack.

In the March 3, 2000, issue of *Cell*, the Dutch and American research teams report that they have identified a specific dendritic cell receptor, called DC-SIGN, to which HIV attaches. In the *Cell* article, the researchers speculate that drugs or vaccines that target this receptor might thwart the virus's entry into the body.

The collaborating research teams were led by Yvette van Kooyk and Teunis Geijtenbeek at the University Medical Center St. Radboud, Nijmegen, The Netherlands and Douglas Kwon and Dan Littman at the Howard Hughes

Medical Institute (HHMI) at New York University Medical Center.

"We've had a reasonably good understanding of the molecules involved in allowing the virus to enter the cell," said Littman. "But we lacked a broader understanding of what actually happens in the body during infection, and that ignorance has contributed to our difficulties in developing therapies and vaccines.

"I hope that this finding will contribute to a better understanding of the infection process, as well as yield new insights into how the virus has adapted to its host," he said.

In 1992, researchers at the Bristol-Myers Squibb Pharmaceutical Research Institute described a glycoprotein on the surface of human placental tissue that binds to the HIV envelope protein gp120. In later studies, van Kooyk's research group discovered that the surface of immature dendritic cells contained a receptor protein (which is now known to be DC-SIGN) that normally allows the dendritic cells to attach to T cells. It turned out that the molecules studied by van Kooyk's team and the researchers at Bristol-Myers Squibb Pharmaceutical Research Institute were identical. Furthermore, van Kooyk's team showed that antibodies against DC-SIGN could inhibit HIV infection in clusters of dendritic cells and T cells.

Because DC-SIGN is found exclusively on dendritic cells and has a high affinity for gp120, the Dutch group contacted Littman's laboratory to initiate a collaboration to determine whether HIV attachment to DC-SIGN might serve as a portal of entry for HIV.

Studies in Littman's laboratory by Geijtenbeek and Kwon revealed that the virus did, indeed, attach to dendritic cells via DC-SIGN, but that it did not subsequently infect these cells. Instead, the virus uses the dendritic cell en route to infecting T cells.

In addition to having a role in early HIV infection, DC-SIGN may also be exploited by the virus in other ways, said Littman. "While this molecule is probably very important in HIV's infection on mucosal membranes, it may also be important in the lymphoid organs, because a great many dendritic cells reside there as well," he said.

The scientists say that they plan to study whether blocking DC-SIGN could provide the basis for a drug that prevents HIV infection. "Since these studies have only been done *in vitro*, we now must validate their importance in animals. This can be done, for example, by testing in monkey models of HIV whether we can prevent mucosal infection by blocking the virus's interaction with DC-SIGN.

"If these findings are validated *in vivo*, DC-SIGN could become a key target for trying to block at least the early stages of HIV infection," said Littman. Since the key components of gp120 that bind to DC-SIGN are likely to be conserved across many strains of HIV, vaccines that elicit antibodies that prevent the union of gp120/DC-SIGN could prove widely effective.

The researchers also plan to explore how HIV avoids degradation when it attaches to dendritic cells.

"The virus might somehow disable the dendritic cell's destructive mechanism, creating for itself a sort of 'stealth weapon' by which it can enter the body," said Littman.

Another intriguing possibility, he said, is that people with genetic variations in DC-SIGN might show resistance to HIV infection, as has been found in other people with genetic variations in other molecules important for HIV infection.