AIDS RESEARCH

Novel Protein Delivers HIV to Target Cells

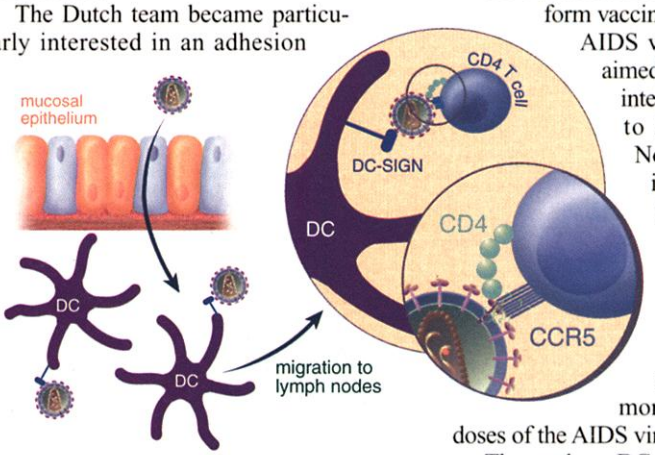
HIV may well be the most studied virus of all time, yet the steps between its introduction into the body by sexual intercourse and an established infection still remain mysterious. Now, tumor immunologists have joined with AIDS researchers to uncover intriguing evidence that a little-understood protein may play a key role in HIV infection, enabling the virus to sneak behind the body's defenses. In addition to elucidating the mechanism of sexual transmission of AIDS, these findings may open new possibilities for AIDS vaccines.

The work, described in two papers in the 3 March issue of *Cell*, focuses on a protein dubbed DC-SIGN that juts from the surface of dendritic cells, sentries that alert immune system central when invaders breach the body's borders. The papers reveal that DC-SIGN behaves like fingers on the arms of dendritic cells, helping them carry HIV from the mucosal lining of the cervix or rectum to remote lymph nodes. There, DC-SIGN hands HIV over to $CD4^+$ T lymphocytes, the immune system cells that the virus readily infects and destroys, eventually leading to AIDS.

The researchers also show that when HIV is bound to DC-SIGN, the virus remains viable for several days longer than it would on its own, thus increasing the odds that a tiny dose of the virus will reach its target. "It's very elegant work," says Douglas Richman, an AIDS researcher at the University of California, San Diego, who has studied the interaction of HIV and dendritic cells. "It proposes another ingenious way in which HIV exploits the immune system to create mischief."

The discovery that DC-SIGN appears to play a critical role in HIV infection began in the lab of Yvette van Kooyk, a tumor immunologist at the University Medical Center St. Radboud in Nijmegen, the Netherlands. Van Kooyk, Carl Figdor, Teunis Geijtenbeek, and their co-workers were not studying AIDS but were investigating how dendritic cells and T lymphocytes interact. Work by Ralph Steinman of The Rockefeller University in New York City and others had established that dendritic cells initiate an immune response by "presenting" foreign antigens such as viruses to the T lymphocytes. The T lymphocytes then send other immune troops into battle. But details about this antigen presentation have remained sketchy, including how dendritic cells and T cells attach to each other using so-called adhesion molecules on the cell surfaces.

The Dutch team became particularly interested in an adhesion molecule called ICAM-3 that is abundant on T cells. In one of the two *Cell* papers, the Dutch researchers describe how they isolated a new dendritic cell protein that binds ICAM-3 much more strongly than anything previously studied. (They called it DC-SIGN because it is a dendritic cell–specific, ICAM-3–grabbing nonintegrin.)



Protein power. DC-SIGN delivers HIV to $CD4^+$ lymphocytes.

Only later did the connection to AIDS turn up, as described in the second *Cell* paper. To the Dutch researchers' surprise, a database search revealed that in 1992 scientists at Bristol-Myers had found an identical protein in placental cells. The Bristol-Myers team did not link the protein to dendritic cells but did describe how it strongly binds gp120, HIV's surface protein that allows it to grab onto the cells it infects.

The Dutch tumor specialists decided to join forces with Dan Littman's team, which studies HIV entry mechanisms at New York University's Skirball Institute of Biomolecular Medicine. In a series of test tube experiments, the researchers demonstrate that, contrary to their initial hunches, HIV does not use DC-SIGN to slip into dendritic cells. Rather, DC-SIGN enhances HIV's ability to infect CD4 cells, in part by binding tightly to the virus and stabilizing it during the journey from mucosa to lymph nodes. This stabilization makes a huge difference: Another experiment showed that HIV bound to DC-SIGN could still infect CD4 cells after 4 days, while HIV alone lost its infectivity in less than a day. "This certainly gives the dendritic cell a lot more capability of stealth," says Steinman.

On a practical front, the findings may inform vaccine design. To date, many AIDS vaccine designers have aimed to elicit antibodies that interrupt the fusion of HIV to its CD4 cell targets. Now, they might seek to induce antibodies that block the binding of DC-SIGN to gp120, derailing the infection prior to HIV-CD4 fusion. Studies can also now ask whether such antibodies can protect monkeys given infectious doses of the AIDS virus.

The work on DC-SIGN also underscores the benefits that can accrue when "newcomers" from other disciplines turn fresh eyes on long-standing questions, in this case, about HIV infection. Says van Kooyk, "You never know how science will work out."

–JON COHEN

STEM CELLS

Protest Leads Europeans To Confess Patent Error

Prodded by environmental activists, politicians, and the media, the European Patent Office (EPO) has said that it made a mistake last December in granting too broad a patent on a method to isolate genetically engineered stem cells. Last week EPO offi-

Solid front. Activists use bricks to block entry to the European Patent Office in Munich, urging "no patents on life."

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