Multiple doors for HIV to enter cells

Just last month, scientists triumphantly announced that they had identified fusin, a protein on the surface of immune cells that some strains of the AIDS virus use to gain entry to the cells (SN: 5/11/96, p. 293). Now, in a discovery that offers an explanation for why some people exposed to the virus remain uninfected, several research groups report that the HIV most commonly found in people actually infects via CC-CKR-5, a different protein on the surface of immune cells.

The HIV that requires CC-CKR-5 "is the kind of virus transmitted during sex. It's the kind of virus transmitted in 90 to 95 percent of cases and the kind of virus that predominates in people for many years," says John P. Moore of Rockefeller University in New York.

Like fusin, CC-CKR-5 is a receptor, a protein that normally binds to extracellular molecules and transmits signals into the cell. Though investigators don't know what molecules fasten onto fusin, they do know that CC-CKR-5 binds chemokines, proteins secreted by immune cells to attract other immune cells.

As it turns out, CC-CKR-5 is the receptor for RANTES, MIP1-alpha, and MIP1-beta, chemokines already attracting the attention of AIDS investigators. Last year, a group led by Robert C. Gallo and Paolo Lusso of the University of Maryland's Institute of Human Virology in Baltimore described test-tube studies indicating that secretion of these three chemokines by immune cells can suppress HIV (SN: 12/9/95, p. 388).

More recently, investigators headed by Rockefeller's William A. Paxton reported in the April NATURE MEDICINE that some homosexual men who are HIV-negative despite frequent sexual exposure to the virus generate greater than normal amounts of the three chemokines. Similar results are emerging from a study of hemophiliacs who remain uninfected despite having received HIV-contaminated blood, says Gallo.

Taken together, these results suggest that the binding of chemokines to CC-CKR-5 can sometimes prevent HIV from infecting a person, investigators contend. To do this, the bound proteins may physically block the virus' access to CC-CKR-5 or they may signal a cell to remove such receptors from its surface.

At least three different research groups have recently linked HIV's ability to infect immune cells to CC-CKR-5. Rockefeller's Tatjana Dragic and her colleagues, including Moore and Paxton, describe their results in the June 20 NATURE. That issue contains a similar report by HongKui Deng of New York University Medical Center in New York and his coworkers.

The third report on CC-CKR-5, scheduled to appear in the June 28 SCIENCE, results from a collaboration headed by Philip M. Murphy and Edward A. Berger, both of the National Institute of Allergy and Infectious Diseases in Bethesda, Md. Berger's group reported the discovery of fusin last month.

One line of evidence presented by all three research groups is that the addition of CC-CKR-5's gene to HIV-resistant cells that do not normally manufacture the receptor can make the cells susceptible to the virus.

Small differences in the proteins that make up the outer surface of HIV determine whether a particular strain depends upon fusin or CC-CKR-5, say investigators. The lab-grown HIV strains used to identify fusin differ from those usually transmitted between people, but they resemble the viruses that emerge in some people after years of infection, says Moore.

Berger speculates that HIV's evolution into fusin-dependent strains may mark an important transition in the progression of an infection, perhaps signifying that an HIV-positive person will soon start showing signs of AIDS.

The body's production of RANTES, MIP1-alpha, and MIP1-beta may actually spur HIV to use proteins other than CC-CKR-5, notes Robert W. Doms of the University of Pennsylvania Medical Center in Philadelphia. Doms' group has found at least one HIV strain that can infect cells using either fusin or CC-CKR-5. The group also has evidence that some strains can use other, still-unidentified proteins. "It's going to become quite complicated," predicts Doms.

Both fusin and CC-CKR-5 present tantalizing targets for drugs that would deny HIV access to cells, researchers agree. Yet disrupting the normal role of these receptors—their binding of chemokines—may prove as dangerous as the AIDS virus itself, the investigators caution.

"Since these are normal cellular proteins, you have to worry about what side effects you will get by interfering with them," observes Berger. —*J. Travis*

Dioxins: New attempts to smoke them out

Dioxins appear to be raining down from the atmosphere in quantities significantly higher than can be accounted for by all the major activities known to create them, a new study finds.

Louis P. Brzuzy and Ronald A. Hites of Indiana University in Bloomington collected soils from 107 sites around the globe and analyzed them for dioxins and for furans, a group of chemicals similar to dioxins. These unintentionally produced families of chlorinated pollutants represent an almost ubiquitous toxic legacy of humanity's industrial activities.

To estimate the global load of dioxinlike compounds, the two scientists extrapolated the concentrations they measured to areas of comparable climate, geography, and economic development.

Acknowledging large uncertainties associated with their estimates, Brzuzy and Hites nonetheless conclude in the June ENVIRONMENTAL SCIENCE & TECHNOLOGY that the worldwide rain of dioxins and furans onto land totals about 12,500 kilograms per year. That's roughly four times the amount suggested by estimates of emissions, which include 1,130 kg/yr from municipal waste incineration, 1,000 kg/yr from cement kilns, and 350 kg/yr from burning trees and other plants, or biomass.

This discrepancy, they say, suggests that there are major unknown sources, that diffuse sources may be larger than appreciated, or that known sources may be more variable than occasional measurements have suggested.

Valerie M. Thomas of Princeton University agrees that the new inventory is suggestive of unaccounted-for sources of dioxins. However, uncertainties in both the production and the deposition of these pollutants "are still too big to conclude there is a discrepancy," she argues.

Indeed, the rates of dioxin and furan production from biomass burning that she and Thomas G. Spiro of Princeton have calculated are 10 times higher than the rates cited in the new report. If accurate, she observes, her rates alone would inflate the overall contribution of biomass to 3,500 kg/yr—doubling the Indiana team's total global estimate for dioxinlike emissions and halving that group's discrepancy between emissions and deposition.

An in-house study by the Environmental Protection Agency, also in the June ENVIRONMENTAL SCIENCE & TECHNOLOGY, identifies a possible means of cutting emissions of these compounds. It shows that burning high-sulfur fuels, such as coal, along with trash can dramatically cut the creation of dioxins and furans in municipal incinerators.

The key was to roughly quintuple the sulfur typically found in materials fed into these furnaces, notes Brian K. Gullett of EPA in Research Triangle Park, N.C., a coauthor of the study. His data indicate that the extra sulfur forced the chlorine naturally present in the wastes and fuel to form primarily hydrogen chloride (HCl) rather than the molecular chlorine (Cl_2) needed to build dioxins.

In some tests, burning high-sulfur fuel with simulated trash reduced an incinerator's dioxin and furan emissions by about 90 percent. —*J. Raloff*