AIDS RESEARCH

Does a Common Virus Give HIV a Helping Hand?

PARIS—The major focus of basic AIDS research over the past 18 months can be summed up in one word: chemokines. The discovery that HIV hijacks the cell surface receptors for these immune system signaling molecules to force entry into its target cells has revolutionized the field and opened new avenues toward possible therapies. Now, research reported in this issue of *Science* suggests that HIV may have yet another port of entry into some cells. The findings implicate a common virus as a possible accomplice of HIV, helping the AIDS virus infect some types of cells and wreak havoc on the immune system.

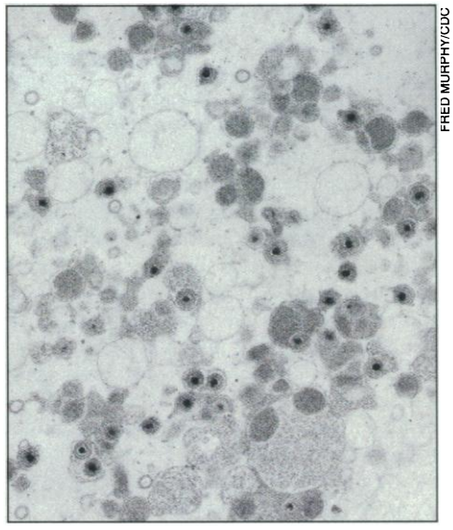
On page 1874, a team led by Marc Alizon at the Institut Cochin in Paris, in collaboration with Michel Seman at the University of Paris, reports that HIV may use a protein called US28 to enter some types of cells. US28 is produced by cytomegalovirus (CMV)—a member of the herpesvirus family that has long been a leading suspect as an AIDS cofactor. The protein is expressed in cells experimentally infected with CMV, and it had previously been shown to act as a receptor for the same chemokines that bind to CCR5, the chemokine receptor used by HIV strains that dominate during the early phases of infection.

Although the evidence supporting a cofactor role for CMV is contradictory and controversial, researchers say that if these new results hold up, they would imply a tighter symbiotic relationship between HIV and CMV than previously imagined. "The results are provocative and potentially important for HIV pathogenesis," says Philip Murphy, a chemokine-receptor expert at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

To determine whether US28 might act as HIV's accomplice, the French group inserted the US28 gene into a human laboratory cell line that HIV does not normally infect. Alizon's group then exposed these cells, which express the US28 protein on their surfaces, to various HIV strains. They also tested whether these modified cells fused with a second cell line engineered to carry proteins from HIV's outer viral coat. In these and related experiments, Alizon's team found that US28-bearing cells were easily infected by HIV strains that normally use the human chemokine receptor CCR5, and somewhat less easily by strains that use another human receptor, CXCR4.

These findings are being greeted with surprise. Over the past year, several labs working on chemokine receptors—including Murphy's—had conducted experiments similar to those of the Alizon team to test whether US28 helps HIV enter cells. "We all got negative results," Murphy says, "although none of us actually verified expression of US28 in the systems we were using, whereas Alizon *et al.* did."

Nevertheless, researchers who spoke to *Science* said there was no reason to doubt Alizon's results. "It is certainly believable," says David Posnett, an immunologist at Cornell University Medical College in New York who has studied CMV. "I'm just wondering what this all means in real life." Indeed, it is not yet clear whether the French group's results, which are restricted to laboratory cell lines, are relevant to HIV-infected people. "There is a total lack of information about when, where, and how much of US28 is expressed in people infected with CMV, and whether native US28 can support HIV entry into CMV-infected cells," says Murphy.



FRED MURPHY/CDC

Deadly partner? Cytomegalovirus *(above)* may help HIV to infect target cells.

Then there is the basic question that has always dogged research on CMV and AIDS: Is CMV just an opportunistic organism taking advantage of the immune suppression caused by HIV, or a true partner in destroying the immune system? "There is still a lot of debate in this area," says Thomas Folks, chief of the retrovirus diseases branch of the Centers for Disease Control and Prevention in Atlanta. Although numerous studies have shown that CMV can enhance transcription of HIV's genome in some cell types, epidemiological evidence that infection with both CMV and HIV leads to a worse outcome for patients has been hard to come by. The reason: Up to 80% of the general population, and almost all HIV-infected homosexual males, have been infected by CMV, which makes it very difficult to find CMV-free control groups to make comparisons. Infection rates are lower in children, however, and several recent studies have shown that children coinfected with HIV and CMV have a much higher death rate than that of those infected only with HIV.

If CMV is indeed a partner in HIV's immune system destruction, researchers will have to explain yet another puzzle: Although CMV is known to infect the brain and retina, there is little evidence that coinfection of CD4 T cells—HIV's main target—by both CMV and HIV is a common event. For example, a study published in the *Journal of Medical Virology* last year by Sylvia Bertram and her colleagues at the University of Freiburg in Germany concluded that less than one in 100 HIV-infected CD4 cells also harbored CMV. But Alizon and his colleagues hypothesize that CMV might in some cases transfer US28 to cells without actually entering them, which would allow US28 to act as an HIV receptor even in cells not directly infected with CMV.

Craig Gerard, a chemokine expert at Harvard Medical School in Boston, suggests another possible role for US28. Gerard proposes that CMV might allow HIV to expand the repertoire of cells it can attack by infecting cells that do not normally carry the chemokine receptors such as CCR5 or CXR4 which HIV normally hijacks. "If you add another chemokine receptor, you broaden the host range of infectible cells, in places like the central nervous system."

While the lack of hard evidence about US28's actual role in HIV-infected people makes most of these ideas purely speculative, the Alizon team's findings are sure to stimulate more research. "There is no doubt that many labs will act quickly" to try to confirm the results, says Murphy, adding: "If the authors are right, we will have to shift our thinking about CMV and AIDS from the present 'welfare' model—in which CMV is viewed as an opportunist taking advantage of the immunodeficiency caused by HIV—to a 'workfare' model, in which CMV earns its keep by providing HIV with another way to enter target cells. The idea that two different pathogens might act symbiotically this way to double-team the host is quite novel and interesting."

–Michael Balter