Body's Proteins Suppress AIDS Virus

After a frustrating, almost decade-long quest for HIV-fighting molecules naturally secreted by the body's immune cells, investigators have finally found a quartet of proteins that suppresses the replication of the deadly AIDS virus in infected cells. The discoveries represent a major development in AIDS research, offering the hope of novel therapies and clues to how some individuals successfully defend themselves for years against HIV's onslaught.

The search began in 1986, when Jay A. Levy of the University of California, San Francisco School of Medicine and his colleagues reported that a class of immune cells called CD8 can suppress the replication of HIV within nearby CD4 cells, the immune cells that the AIDS virus infects and uses to reproduce itself.

Levy and others quickly established that CD8 cells can secrete one or more soluble molecules that hinder HIV. Ever since, investigators have speculated that the factors may explain many long-term survivors, people infected with HIV who have not developed AIDS.

CD8 cells secrete only small quantities of the suppressive molecules, which makes it difficult to purify them. "The identity of the factor, or factors, has been elusive," says Bruce Walker of Massachusetts General Hospital in Boston.

In a report in the Dec. 7 NATURE, a German group headed by Reinhard Kurth of the Paul Ehrlich Institute in Langen has now identified one of the elusive factors as interleukin-16 (IL-16), a little-studied protein that attracts CD4 cells. Three other small proteins, known to recruit immune cells for the inflammatory response, also impede HIV replication inside CD4 cells, further reports a group led by Robert C. Gallo and Paolo Lusso of the University of Maryland's Institute for Human Virology in Baltimore.

In work done at the National Cancer Institute in Bethesda, Md., Gallo and his coworkers modified CD8 cells to reproduce indefinitely. From these immortal cells, the researchers gathered enough secreted material to purify several proteins for testing. Three proteins—rantes, mip1-alpha, and mip1-beta—significantly thwart HIV's reproductive ability in laboratory cell cultures, the investigators will report in the Dec. 15 SCIENCE. Administered together, the three molecules stop HIV without harming infected cells, they say.

"When you add these factors, the virus shuts down," says Gallo colleague Anthony DeVico of Advanced Bioscience Laboratories in Kensington, Md.

Kurth's group uncovered IL-16's similar antiviral talents through studies of African green monkeys, which remain healthy despite infection by a simian equivalent of HIV. The investigators demonstrated that the monkey's IL-16 dramatically reduces the production of infectious HIV by infected cells. Human IL-16 also has antiviral properties, although possibly weaker, they report.

Neither group professes to know the exact mechanism by which the proteins suppress HIV, though both suggest that the molecules bind to CD4 cell surface molecules, sending into the cell's interior signals that halt virus replication.

The major issue provoked by identification of these molecules is whether their ability to suppress HIV production in test tubes reflects a natural antiviral role. "Does [viral suppression] actually occur in the body, and is it an important part of the body's defenses against HIV?" asks David Baltimore of the Massachusetts Institute of Technology.

Scientists now plan to test whether African green monkeys will develop AIDS-like symptoms if antibodies neutralize the protective proteins and whether the proteins stop HIV replication in other primates. They'll also examine concentrations of the proteins in human blood. "It would be exciting if long-term survivors have higher serum concentration than rapid progressors," says Kurth.

Walker cautions that the demonstrated viral suppression of the four proteins is weaker or, at best, only comparable to that of other potential AIDS drugs.

Furthermore, the discovered molecules are part of the intricate network of molecules, called cytokines, that immune cells use to communicate with each other. "It's going to be difficult to impact one cytokine without setting off a chain reaction of events," comments Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Md. Other interleukins have serious side effects or even kill when given at inappropriate doses, says Kurth.

Identifying these soluble HIV-suppressive factors "is very important and very interesting, but we've been down this road before, and it's a majestic leap from the test tube to the human body," concludes Fauci. —*J. Travis*

DNA tests identify hoatzin's cousins

The closest relatives of the hoatzin, a blue-faced South American bird, are neither turkeys nor chickens, as many bird experts had assumed; they are cuckoos, a new study concludes. The finding shows that 220 years of research on the hoatzin was no wild-goose chase.

Since describing the bird, *Opisthocomos hoazin*, in 1776, ornithologists have had problems pinpointing its closest kin, as the hoatzin looks and acts so unlike other birds. It digests its food, for example, the way a cow does, in a chamber above its stomach (SN: 10/21/89, p.269).

Scientists have disagreed most recently over whether hoatzins are closer to cuckoos or to galliforms such as pheasants, chickens, and turkeys. Galliforms are among the most ancient of birds, while cuckoos appeared more recently.

Stuart Strahl/Pickering Creek Environmental Center, Easton, Md.

S. Blair Hedges of Pennsylvania State University in University Park and his colleagues compared the DNA sequences of hoatzins and 13 other types of birds, they report in the Dec. 5 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. The scientists examined DNA from one nuclear gene and two mitochondrial genes. They found that hoatzin DNA most closely resembles cuckoo DNA.

Scientists finally clear up hoatzin's ancestry.

The scientists conclude, however, that the hoatzin belongs next to the cuckoo's nest, not in it, because the species' DNA and structural differences. For example, the cuckoo has two forward and two backward toes, while the hoatzin has three forward and one backward.

Indeed, the team recommends placing hoatzins in their own suborder, Opisthocomi, in the Cuculiformes order. All other members of the order, such as cuckoos, should then come under the suborder Cuculi.

The finding serves as an "eye-opening example of how molecular data can resolve phylogenetic relationships," says Hedges. Morphology "has tricked people for a long time."

Paul DeBenedictis of the State University of New York Health Science Center at Syracuse says that Hedges and his colleagues should have compared the hoatzin with a wider variety of birds. Still, he believes that "most ornithologists will accept what [the researchers] have to say," concerning the hoatzin's kin. — *T. Adler*