HIV, rivals duel in cells

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— HIV's preferred target — are infected with a mutant form of the virus that lacks Vif.

That work — and that of laboratories following up on those findings — has uncovered an unusual sequence of events that were the topic of much discussion last month at the 11th Retrovirus Conference, the annual mid-winter AIDS meeting in the United States.

It turns out that lymphocytes produce a substance that's been given the unwieldy name APOBEC3G. It's a member of a family of enzymes whose job is to edit RNA or DNA, the strands of genetic material that constitute genes.

The various APOBEC enzymes — there are nearly a dozen — make specific changes in a gene's message. These are the equivalent of rewriting a word or two in a paragraph. That, in turn, alters the gene's meaning in small but significant ways.

This system of gene editing makes the storage of information more economical. Genes whose messages differ by only a word or two don't have to be spelled out separately in the cell's genome. Instead, the cell can store one version — and the minor variations can be created by editing that template once it's transcribed, or copied.

APOBEC3G, however, is an editor grown tired of wearing green eyeshades and thanklessly editing copy. APOBEC3G dreams of being a secret agent. It wants to turn its pencil into a lethal weapon.

When an AIDS virus lacking Vif infects a lymphocyte, molecules of APOBEC3G shadow the newly replicating virions. In a process that's not fully understood, the enzyme slips inside the viral envelope just before the envelope is sealed and the virion buds off from the cell.

When that virion attaches to another cell and infects it, the material it unloads includes APOBEC3G.

Transcribing and copying its genes into the cell's DNA is an essential step in HIV's replication. As the virus goes about this inside the newly infected cell, APOBEC3G goes to work, too. It edits — and edits and edits and edits. It edits the viral DNA transcript to a point where the message is such an unreadable mess that the cell tears it up. This stops replication and breaks the chain of infection.

This, at least, is what happens in APOBEC3G's dreams. But it isn't what happens in reality very often. That's because HIV virions lacking Vif don't exist in the wild — and for an obvious reason. They cannot make more of themselves when APOBEC3G is around.

In reality, nearly all wild-type strains of HIV do have Vif. It is HIV's own secret agent, evolved over time to neutralize APOBEC3G. Although many details of the mechanism are still undiscovered, Vif appears to work this way:

As APOBEC3G trails a developing virion inside an infected cell, Vif — which has been made in the cell from one of HIV's genes during the replication process — lies in wait for it. As the editing enzyme is just about to sneak into the viral envelope, Vif intercepts it.

In a scene that would make the old Soviet KGB proud, this adventure-seeking editor, clearly an amateur in a world of professionals, is calmly led away from the budding virion.

Vif is quickly joined by other proteins named cullin, elongin and ubiquitin. Together they lead the hapless enzyme into a cellular structure called a proteosome — the Room Where Very Bad Things Happen. There, quite literally, APOBEC3G is liquidated.

How much this particular fight contributes to the body's war of attrition against HIV is uncertain.

"It has been obvious during the recent years that we come down [to defeat], but not without a fight," Didier Trono of the University of Geneva told the scientists at the conference. "Even though we get outsmarted at the end, we give a good game to the virus."

Armed with these insights, scientists are hoping to change the outcome of the game.