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## Deceptive Strategy Shields HIV from Destruction

Howard Hughes Medical Institute researchers and their colleagues have discovered one way in which the human immunodeficiency virus (HIV) wins its cat-and-mouse game with the body's immune system.

The study, published in the March 20, 2003, issue of the journal *Nature*, shows that HIV-1, a common strain of the virus that causes AIDS, uses a strategy not seen before in other viruses to escape attack by antibodies, one of the immune system's prime weapons against invading viruses and bacteria.

Viruses typically vary the protein sequence, or epitope, of the viral envelope that acts as a docking station for antibodies. This variation alters the docking region on the virus and prevents antibodies from grabbing hold and targeting the virus for destruction. HIV-1, in contrast, continuously changes the arrangement of large sugar molecules studded across its gp120/41 protein coat so that those docking regions for antibodies are obstructed.

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The research team, led by Howard Hughes Medical Institute investigator [George M. Shaw](#) at the University of Alabama at Birmingham (UAB), dubbed the mechanism an evolving "glycan shield," and said the discovery was a surprise. Shaw and his colleagues were just as surprised at the rapidity and extent to which the replicating virus population in infected patients escaped antibody recognition.

"Before these findings, the role of antibodies in combating the virus that causes AIDS was not altogether clear. The new data suggest a more active role for HIV-1-neutralizing antibodies in virus containment and an

unexpected mechanism of virus escape," he said.

"We found that the neutralizing epitopes on the virus did not change, but instead other parts of the viral envelope mutated, generally in a way that altered specific amino acids to which carbohydrates normally attach," Shaw said. "These changes in glycan molecules prevent the binding of neutralizing antibodies to the virus surface through steric inhibition, thereby enabling the virus to avoid antibody-mediated elimination."

The findings show that the immune system does try to fight HIV, and they offer a reason why the virus often wins the battle, he said. "The glycan shield mutates at a faster rate than the immune system can change in order to keep up."

Despite the resourcefulness of the virus, Shaw said there is hope for the development of an effective vaccine to protect those people who are currently uninfected but at risk of becoming infected. "While neutralizing antibodies are obviously unable to completely eliminate HIV-1 from infected patients, the fact that they are sufficiently potent as to result in the sequential elimination of one virus population after another suggested that if uninfected patients were vaccinated against HIV-1 with an appropriate immunogen, then neutralizing antibodies in this setting could conceivably have a far greater impact," he said.

Better yet, Shaw said, may be the idea of combining an immunogen that elicits neutralizing antibodies with other components of the human immune system, including cytotoxic T-lymphocytes.

In the course of their work, Shaw and his colleagues developed a new strategy for detecting HIV-1 antibodies that prevent entry of the virus into human cells. The investigators reasoned that since variants of HIV-1 that are resistant to antiretroviral drugs can be detected in the bloodstream of AIDS patients, if neutralizing antibodies were present and did affect virus replication *in vivo*, then by testing patients for strains of the virus that had become resistant to antibodies, they could infer their presence and their biological activity.

Using a modification of a laboratory assay that they had developed previously to test for viral drug resistance, the investigators demonstrated that not only were HIV-1-neutralizing antibodies present, but they were potent enough to completely eliminate sensitive strains of the virus from the bloodstream of patients in a matter of weeks. The bad news is that these "weaker" strains were replaced by successive strains of the virus that were resistant to each new battery of neutralizing antibodies.

The researchers next examined the genetic changes in HIV-1 that resulted in the neutralization-resistant phenotype and discovered mutations in the viral envelope that caused changes in the attachment of the glycan molecules.

The discovery extends a picture of a virus that contains a "silent face" composed of masses of large glycan molecules that obscure its true nature to the immune system. However, in order for HIV-1 to engage CD4 cells, part of its attack machinery, including its receptor-binding surface and projecting variable loops, must remain accessible to cellular receptors for the virus. The evolving glycan shield, together with other mechanisms of antibody avoidance, contributes to this process, Shaw said.

When the virus initially infects a person without immunity to HIV, it is able to grow unrestricted until the first set of antibodies develops that recognizes proteins within or protruding from holes in the shield. But by then, the virus has randomly mutated its glycan shield, as well as other regions of the envelope, to uncover different working areas, conferring a strong survival advantage to viral particles that cannot now be "seen" by antibodies, which also change their structure in pursuit of the virus. But the cat (the immune system) cannot keep up with the wily mouse (the virus), Shaw said.

The virus "changes its silent face around in such a way that these large sugar molecules occlude new antibodies that develop in the patient. In this way, the virus maintains the ability to prevent each successive round of evolving antibodies from attaching," he said. Shaw emphasized that the evolving glycan-shield mechanism of antibody escape, although new, is but one of several mechanisms available to HIV-1 that allow for viral persistence in the face of an evolving antibody repertoire. "The trick," he suggested, "will be to understand these multiple mechanisms more fully and to find the Achilles' heel. We are not there yet."

Other researchers working with Shaw included Peter Kwong at the National Institutes of Health Vaccine Research Center; Princeton University investigators Natalia Komarova and Martin Nowak; and UAB investigators Xiping Wei, Julie Decker, Shuyi Wang, Huixiong Hui, Jesus Salazar-Gonzalez, Maria Salazar, Michael Saag, J. Michael Kilby, John Kappes, Xiaoyun Wu, and Beatrice Hahn.