

Researchers identify new mechanism of blocking HIV-1 from entering cells

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Publishing in *PLoS Pathogens*, researchers at from the Kimmel Cancer Center at Jefferson have found a novel mechanism by which drugs block HIV-1 from entering host cells.

Cellular invasion by HIV-1 requires the concerted action of two proteins on the viral surface: gp120 and gp41. The function of gp41 is to get the viral contents into the interior of the host cells. This requires the association of two distinct regions of gp41 called N-HR and C-HR. Anti-HIV-1 agents known as fusion inhibitors target the N-HR or C-HR and disrupt their association, which prevents the virus from entering into the host cell. One drug that works like this is Fuzeon (Roche), and there are other agents in the pipeline.

But blocking the N-HR/C-HR association is not only mechanism by which fusion inhibitors prevent HIV-1 entry, according to Michael Root, M.D., Ph.D., assistant professor of <u>Biochemistry</u> and <u>Molecular Biology</u> at Jefferson Medical College of Thomas Jefferson University. The inhibitors also induce irreversible deactivation of gp41.

"After these drugs bind, they seem to shuttle gp41 into a dead conformation from which the protein cannot recover," Dr. Root said. "Importantly, the speed of this drug-induced deactivation greatly influences how potent a drug is at preventing HIV-1 infection."

When the inhibitors bind to the gp41 C-HR, the protein rapidly deactivates before inhibitors have time to dissociate. But when the



inhibitors bind to the gp41 N-HR, deactivation takes a very long time, and many inhibitors can readily unbind. To potently inhibit HIV-1 entry, a C-HR targeting fusion inhibitor can have a relatively low affinity, but an N-HR targeting fusion inhibitor must bind extremely tightly.

A major drawback to using Fuzeon and related drugs that target N-HR is the rapid emergence of HIV-1 strains resistant to the drugs. Dr. Root's study suggests that the resistance phenomenon is related to the slow speed of gp41 deactivation induced by these fusion inhibitors. HIV-1 appears to have more difficulty developing resistance to drugs that can remain bound to gp41 for much longer than gp41 takes to deactivate, even if the drugs are no more potent than Fuzeon against the original HIV-1 strain. Armed with this knowledge, Dr. Root and his team have developed a new strategy to improve the antiviral activities of N-HRtargeting fusion inhibitors.

These unexpected properties of HIV-1 fusion inhibitors are a consequence of the short time interval these drugs have to work. The N-HR and C-HR are only accessible to drug binding in a short-lived "intermediate state" that occurs right before N-HR/C-HR association. Most pharmaceutical agents bind targets that exist for long times, but a growing class of drugs target similar, short-lived intermediate states. These drugs include local anesthetics, antibiotics and immunosuppressive agents used in clinical practice. The results of this study might also be extended to understand the activities and limitations of these drugs.

Source: Thomas Jefferson University (<u>news</u> : <u>web</u>)

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