Study finds how protein blocks HIV life cycle in elite controllers

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Investigators from Massachusetts General Hospital (MGH) and the Ragon Institute of MGH, MIT and Harvard have learned more about one way the immune systems of elite controllers – those rare individuals able to control HIV infection without drug treatment – block a key step in the virus's life cycle. In a paper appearing in *Cell Host & Microbe*, the research team reports finding the mechanism behind the ability of p21, a protein best known as a tumor suppressor, to inhibit reverse transcription, the process of converting viral RNA into DNA.

"Many of the drugs currently being used to treat HIV infection target this essential viral replication step, but it's been uncertain whether reverse transcription can be naturally inhibited in a clinically significant way," says Mathias Lichterfeld, MD, of the MGH Infectious Disease Division, the paper's corresponding author. "Our studies show that a human enzyme is required for HIV reverse transcription and that the upregulation of p21 – an intrinsic inhibitor of similar enzymes – can block viral reverse transcription."

Fewer than 1 percent of individuals infected with HIV can naturally suppress viral replication without antiviral treatment, an ability that keeps viral levels low – sometimes to a level where they cannot be detected with standard assays – and prevents the HIV-induced breakdown of the immune system. Since 2006 researchers at the Ragon Institute have been leading the International HIV Controllers study to investigate factors underlying this rare ability, a project that has enrolled more than 1,500 controllers worldwide and has identified a number of immune factors that interfere with viral growth within CD4 T cells, the virus's primary targets.

In 2011, Lichterfeld led a team that found the expression of p21 was significantly elevated in CD4 cells of HIV controllers and that experimentally knocking out the protein's expression could increase viral replication in controllers' cells. That study showed that p21 expression interfered with both reverse transcription, which produces the viral DNA that will be integrated into the genome of infected CD4 cells, and with the production of new RNA molecules to be used to create new viral particles. The current study was designed to investigate the molecular mechanism by which p21 inhibits reverse transcription.

Since p21 is known to inhibit a family of enzymes called cyclin-dependent kinases (CDKs), the research team examined whether p21 inhibits reverse transcription by blocking a CDK enzyme. In a series of experiments they found that the activity of an enzyme called CDK2 is required to protect reverse transcriptase from breakdown by cellular enzymes, identified the site of CDK2's activity on the reverse transcriptase molecule, and showed that p21 inhibits reverse transcription of viral RNA by blocking the protective activity of CDK2.

"An important point is that p21 inhibits reverse transcription by an indirect mechanism that blocks a required human cellular enzyme but not by direct interaction with the virus itself," explains Lichterfeld, an assistant professor of Medicine at Harvard Medical School. "Pharmaceutical inhibitors of reverse transcription act by binding to the reverse transcriptase molecule, a process that the virus can circumvent by sequence mutations. Moreover, this study gives a great example of how much HIV depends on human proteins to replicate and how this dependence exposes the virus to specific inhibitory effects of the immune system. We hope that identifying this new viral vulnerability that is naturally exploited in HIV controllers may help us design new strategies that can someday lead to a drug-free remission of HIV infection in many more infected individuals."

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