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Second pathway behind HIV-associated immune system dysfunction identified

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Researchers at the Partners AIDS Research Center at Massachusetts General Hospital (PARC-MGH) may have discovered a second molecular "switch" responsible for turning off the immune system's response against HIV. Last year members of the same team identified a molecule called PD-1 that suppresses the activity of HIV-specific CD8 T cells that should destroy virus-infected cells. Now the researchers describe how a regulatory protein called CTLA-4 inhibits the action of HIV-specific CD4 T cells that control the overall response against the virus. The report will appear in the journal *Nature Immunology* and is receiving early online release.

"We've shown that a known regulator of the immune system, CTLA-4, is present in elevated levels on the virus-specific CD4 cells that should be managing the body's response against HIV, says Daniel Kaufmann, MD, of PARC and the MGH Infectious Disease Unit, a co-first author of the paper. "We also found that CTLA-4 expression rises as HIV infection progresses and that the molecule switches off CD4 cell function in a way that appears to be reversible."

Expression of the CTLA-4 protein is known to be elevated on activated T cells, those that have encountered a pathogen and are multiplying rapidly to mount an immune response. Studies in cancer patients have shown that the molecule serves to dampen the immune response, and some preliminary investigations in animals and humans have suggested a potential role in HIV infection. The current study was designed to examine how CTLA-4 may be involved in the dysfunction of HIV-

specific T cells that leads to the immune-system breakdown of AIDS.

The researchers first found that CTLA-4 was overexpressed on the HIV-specific CD4 T cells of infected individuals who had not yet received antiviral treatment. Levels were highest in those with symptoms of acute infection and second highest in chronically infected participants. CTLA-4 expression was lowest among a group of participants whose immune systems were naturally able to suppress HIV replication without antiviral medications – "elite controllers" in whom viral levels are too low to be detected.

Elevated CTLA-4 expression also correlated with signs of disease progression – increased viral load and reduced overall CD4 count. While antiviral treatment caused viral loads to drop significantly after treatment began, it resulted in only modest and slow drops in CTLA-4 expression. In vitro tests of the effects of blocking the CTLA-4 molecule improved the function of HIV-specific CD4 cells. Comparing the effects of blocking CTLA-4 with those of blocking PD-1 or both molecules produced functional improvements that varied considerably between participants, signifying a complex relationship between the pathways controlled by the two molecules.

"Both of these pathways contribute to dysfunction of HIV-specific T cells and both may be considered targets for therapeutic intervention. But since their mechanisms are so complicated, further study is needed before clinical trials can be planned," says Kaufmann, an instructor in Medicine at Harvard Medical School (HMS).

"Understanding why the immune system fails to control HIV is essential for development of vaccines and new therapies" said Bruce Walker, MD, director of PARC-MGH and senior author of the study. "These studies suggest that the immune system is turning itself off prematurely in HIV-infected persons, and the big challenge now is to figure out if we

can turn it back on, getting it to do what it is supposed to do, without causing collateral damage in the process." Walker is a professor of Medicine at HMS and a Howard Hughes Medical Institute (HHMI) investigator.

Source: Massachusetts General Hospital