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Study pinpoints how a normally defensive immune response can help HIV

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Researchers have identified how a normal response to infection, one that usually serves to limit the amount of inflammation, actually contributes to disease progression and viral persistence in HIV-infected patients.

The findings, published in the May 19 issue of the journal *Science Translational Medicine*, offer important opportunities for further research, both for treatment of long-term persistence of HIV in those who are infected and for prevention of infection in those who are not, according to the study team.

The study, led by UCSF researchers, focused on the body's production of an enzyme called indoleamine 2,3-dioxygenase 1 (IDO1). To prevent the harm associated with chronic inflammation, the body typically turns on IDO1, which then serves to suppress inflammation and immune responses. In the setting of HIV infection, the authors found that IDO1 can instead alter the balance between two types of T-cells that have opposing functions.

One type of immune cell, called Th17, releases interleukin-17, a cytokine that has a central role in maintaining the integrity of the mucosal barrier in the gut. The other type, named Treg, prevents inflammation in a non-specific manner and can also turn off immune responses against viruses such as HIV.

The authors found that induction of IDO1 by HIV results in loss of Th17 cells and a relative increase in Tregs. This change in the balance of Th17

cells and Tregs allows bacteria to cross the mucosal barrier of the gut, initiating new inflammatory reactions in the process. At the same time, the increased number of Tregs may prevent the immune system from attacking HIV in areas of the body where strong HIV-specific immune responses are most needed. The altered Th17/Treg balance, in sum, leads to an endless cycle of inflammation induced by the invading microbes, more induction of IDO1, and continued loss of Th17 cells.

“In most instances, reducing inflammation following immune system activation to fight infection is beneficial. But, in HIV disease, this can establish a reinforcing cycle that is strongly linked to disease progression and that may help HIV to persist in patients, said study lead co-author, Jeff Mold, PhD, from the UCSF Division of Experimental Medicine. “Mucosal defenses are breached, microbes cross over, and inflammation results. This leads to increasing IDO1 activity, continued changes in the balance of Th17 and Treg cells, further weakening of the mucosal defenses, and even more inflammation.”

The findings represent the next step in a series of research studies reported previously by the same group of investigators, showing that SIV infection of monkeys leading to AIDS is associated with a similar change in Th17 and Treg balances. The change in T cell balance was not observed in another primate, African green monkeys, where infection with SIV is harmless and does not cause disease.

In the current study, the investigators looked at IDO1 activity in HIV-infected human subjects at various stages of disease and in healthy non-infected subjects.

“We confirmed that IDO1 activity is associated with HIV disease progression. But we went further and also looked at the Th17 and Treg balance, and found that the change in the ratio leading to decreasing Th17 cells is also associated with HIV disease progression,” said study

lead co-author, David Favre, PhD, formerly at UCSF, now with the National Immune Monitoring Laboratory, Montreal.

With pharmacological inhibitors of IDO1 in development and currently in clinical trials for cancer immunotherapy, the finding may lead to new therapeutic approaches for assisting in the control of HIV disease, noted the study team.

“Most of an infected person’s own immune responses that are known to affect HIV disease outcomes cannot be manipulated or altered clinically and, hence, have not really had much of an impact for patients. This work, however, is very different, as it has uncovered several possible pathways that might be addressed clinically with developing or available therapeutics,” said study co-author, Steven Deeks, MD, professor of medicine at the UCSF Division of HIV/AIDS at San Francisco General Hospital.

IDO1 may play a role in the ability of HIV to persist in HIV-infected patients for their lifetimes, notwithstanding effective treatment with antiretroviral therapies.

“Steve Deeks and I are continuing to examine the role of IDO1 through a study recently announced by amfAR, the Foundation for AIDS Research, into whether the disruption of IDO1 will reduce the level of immune activation, which could then lead to a decrease in viral persistence,” said senior study author Joseph M. McCune, MD, PhD, chief of the UCSF Division of Experimental Medicine.

Provided by University of California - San Francisco

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