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Effective HIV control may depend on viral protein targeted by immune cells

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An effective response of the immune system's 'killer' T cells against infection with HIV may depend on exactly which viral protein is targeted, according to an international group of researchers. A new study finds that HIV-infected individuals in whom virus-specific CD8 T cells are targeted against the Gag protein have lower viral levels than do those with CD8 responses directed against other viral proteins. The report from the Partners AIDS Research Center at Massachusetts General Hospital (PARC-MGH), the University of Oxford and University of KwaZulu-Natal in South Africa is receiving early online release in *Nature Medicine*.

"Understanding which immune responses are effective in control of HIV is of critical importance in vaccine development," says Philip Goulder, MD, PhD, of PARC-MGH and Oxford, the senior author of the study. "Previous approaches have focused on a 'more is better' approach, seeking to generate responses against a broad range of viral proteins, but these results challenge that dogma."

While many strategies for developing a vaccine to control HIV focus on the activity of the CD8 T lymphocytes that recognize and destroy virus-infected CD4 T cells, the fact that even patients in the last stages of AIDS can have measurable CD8 responses indicates that those responses are not always effective. To investigate how variations in CD8 response alter the ability to control HIV, the research team enrolled almost 600 South African patients who had not yet been treated for their HIV infections.

The researchers comprehensively mapped the CD8 responses against all viral proteins and also investigated whether the versions of HLA Class I molecules involved in the immune system's recognition of HIV protein fragments made a difference. When new viruses are produced within an infected cell, Class I molecules grab viral fragments and display them at the cell surface, thereby alerting CD8 cells that the cell has been infected and should be destroyed. Earlier studies, including a 2004 Nature report from the same group, showed that the genetically determined version of an individual's HLA Class I molecules could strongly influence immune control of HIV.

The current study found that only CD8 responses against the Gag protein were associated with significantly reduced viral levels and that individuals with responses against several different Gag fragments had even lower viral loads. In contrast, those with stronger responses against other HIV proteins – including Env, a protein that is the focus of several vaccine studies – had higher viral levels indicating poorer control of HIV.

In people receiving no antiretroviral treatment, the improved HIV control associated with Gag-specific CD8 response would probably translate into asymptomatic infection for more than a decade, compared with progression to AIDS within two to three years of infection in those with no Gag responses. The reason why patients' particular HLA Class I molecules are linked to different HIV disease outcomes now appears to be related to the number of Gag fragments displayed by different versions of the Class I molecule.

Mechanisms underlying the different effects of the protein-specific immune responses are unknown and require further investigation. The researchers suggest that responses against proteins like Env might be inherently less effective or might only be generated in response to elevated viral loads. Therefore, the findings of this study, which reflect

chronic HIV infection, might not apply in situations in which vaccination generates an immune response before infection occurs.

"The possibility that there may be fundamental differences between the impact of Gag and non-Gag CD8 responses on the ability to control HIV has clear relevance to vaccine development," says Goulder, who is an associate professor of Medicine at Harvard Medical School.

Source: Massachusetts General Hospital