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Step in breakdown of HIV proteins essential to recognition, destruction of infected cells

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A key step in the processing of HIV within cells appears to affect how effectively the immune system's killer T cells can recognize and destroy infected cells. Researchers at the Ragon Institute of MGH, MIT and Harvard have found that – as HIV proteins are broken down within cells, a process that should lead to labeling infected cell for destruction by CD8 T cells – there is a great variability in the stability of resulting protein segments, variations that could significantly change how well cells are recognized by the immune system. Their report appears in the June *Journal of Clinical Investigation*.

"We have identified a novel mechanism by which HIV escapes recognition by virus-specific cytotoxic T cells, says Sylvie Le Gall, PhD, of the Ragon Institute, the paper's senior author. "This discovery may help us better understand the immune-system failure that characterizes HIV infection and provide information critical to the successful development of immune-system-based therapies."

CD8 T cells that have been programmed to target and destroy HIV-infected cells recognize those cells through tiny bits of viral protein, called peptides, displayed on the cell surface. Details of how HIV proteins are broken down into peptides and loaded onto the specialized molecules, called MHC Class I, that carry them to the cell surface are not well understood. Also unknown is whether particular HIV peptides are more effective than others in flagging cells for destruction.

Le Gall and her team first discovered that HIV peptides reduced to a

length of 8 to 11 amino acids within infected cells varied greatly in their stability, with some breaking down further within seconds and others remaining unchanged for nearly an hour. Collaborators David Heckerman, MD, PhD, and Carl Kadie from Microsoft Research analyzed the biochemical features of 166 HIV peptides and identified particular structural patterns associated with either stability or instability. The researchers then showed that substituting a stability-associated structural motif for an instability motif significantly increased peptide stability, and vice-versa.

The stability of a peptide within the cell can significantly affect how much peptide is available to be loaded onto MHC Class I molecules and displayed on the cell surface. The authors found that several known HIV mutations significantly reduced peptide stability – one common mutation virtually abolished the cell-killing action of CD8 T cells. The Microsoft team members have developed a model to predict the probable stability of specific HIV peptides, but more research is needed to determine how variations in stability affect the presentation of the peptide segments called epitopes to CD8 cells and whether changes in peptide stability lead to a more efficient immune response.

"Efforts to develop T-cell-based vaccines need to focus on producing epitopes that elicit the most protective response," says Le Gall, an assistant professor of Medicine at Harvard Medical School. "Modulating peptide stability offers a unique way of regulating epitope presentation in favor of producing the most effective defence against HIV."

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