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Strengthening fragile immune memories to fight chronic infections

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After recovering from the flu or another acute infection, your immune system is ready to react quickly if you run into the same virus again. White blood cells called memory T cells develop during the infection and help the immune system remember the virus and attack it if it comes back.

But chronic infections such as those caused by viruses like HIV and hepatitis C are different. If the immune system can't clear the infection out of the body fast enough, the memory T cells that initially developed against the virus upon first encounter are lost. This poses a challenge for vaccine development.

Researchers at the Emory Vaccine Center have identified the conditions that make memory T cells slip away during persistent infections. They have also shown that a molecule called 2B4 on memory cells causes them to slow down during chronic infections. The results are published online this week in the journal Immunity.

The results have implications for vaccine design. The authors emphasize the importance of having vaccines that encourage the immune system to quickly control a potentially chronic infection or prevent it from gaining a foothold – a task that some experimental vaccines against HIV's cousin SIV have accomplished.

"In a chronic infection, the memory T cells become so tightly regulated that they eventually are ineffective," says first author Erin West, an

Emory graduate student in immunology and molecular pathogenesis. "This is why it's so important to have that initial strength at the beginning."

West and most of the co-authors are in the laboratory of Rafi Ahmed, PhD, director of the Emory Vaccine Center and a Georgia Research Alliance Eminent Scholar. Researchers from Harvard Medical School also contributed to the study, including W. Nicholas Haining and Cox Terhorst.

West and her colleagues studied mice infected by a meningitis virus which establishes a chronic infection. A weaker form of the virus can be cleared from the body in a couple weeks. They tracked naïve T cells as well as memory T cells' responses to infections that varied in dose and persistence.

A molecule called 2B4 appears on memory T cells that are activated during chronic infections and slows them down, the Emory team found. This level of regulation probably helps control the immune system and prevents it from developing dangerous over-inflammation, West says.

"Perhaps the body says 'I can't take care of this, so I will shut down,' before too much inflammation and damage occurs," she says.

Emory researchers have identified other molecules that produce "immune exhaustion" on T cells such as PD-1, but 2B4 is different because it seems to specifically regulate memory T cells. If memory T cells are engineered to lack 2B4, they are better able to persist during a chronic infection, although it's not clear whether the cells are then more effective at fighting the infection, West says. Blocking 2B4 might be a way to enhance immune responses against chronic infections, but more information is needed about how it works, she says.

The researchers also found that memory T cells need more "help," in the form of signals from other T cells, in the setting of chronic infection. This is a reversal of the situation in acute infections, where memory T cells are quicker to respond and need less help, she says.

In the paper, the Emory team cites a HIV vaccine tested in Thailand that was shown to have some ability to block initial infection, and an experimental hybrid vaccine against SIV designed by scientists in Oregon that has shown similar effects. They suggest that their results could be used to tune future vaccine design efforts and take advantage of these successes.

More information: E.E. West et al. Tight Regulation of Memory CD8+ T cells Limits Their Effectiveness during Sustained High Viral Load. *Immunity* (posted online August 18, 2011).

Provided by Emory University