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New study shows how T cell's machinery dials down autoimmunity

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A St. Jude Children's Research Hospital study shows that T cells, the body's master immune regulators, do not use simple on/off switches to govern the cellular machinery that regulates their development and function. Rather, they possess sophisticated molecular controls that enable them to adjust their function with exquisite precision. Such subtle adjustment enables T cells to modulate their development and function, including avoiding autoimmunity.

In autoimmune disease, rather than attacking invading microbes, the immune system attacks the body's own organs, tissues or cells. Some 80 autoimmune diseases are known, including type 1 diabetes, multiple sclerosis, rheumatoid arthritis and lupus.

"Among the many mysteries surrounding autoimmune diseases is why they can sometimes take decades to manifest themselves," said Dario Vignali, Ph.D., associate member in the St. Jude Department of Immunology. "Our findings hint that this delayed onset could be explained by subtle defects in the molecular controls on T cells." Such T cells are white blood cells whose duties include shutting down the immune system when it has done its job and suppressing T cells that can attack the body.

Vignali is the senior author of a report on this work that appears in the advance online publication of the journal *Nature Immunology.*

The researchers explored the function of T cell receptors, proteins that

span the cell membrane of T cells. These receptors receive outside signals that instruct T cells to develop, proliferate and transmit those signals into the cell. The St. Jude investigators sought to understand why T cell receptors need many copies of switch-like components called immunoreceptor tyrosine-based activation motifs (ITAMS). ITAMs are components of the CD3 adaptor proteins that attach to the T cell receptor and help transmit the control signals from the T cell receptor into the cell.

“The ITAMs we studied are little molecular tags inside the cell by which the T cell receptor communicates to the rest of the cell,” Vignali said. “The mystery we wanted to address was why the T cell receptor needs 10 ITAMs to do its job. Why not just have a simple on/off switch?”

To explore the role of multiple ITAMs, Jeff Holst, Ph.D., the paper’s first author and a St. Jude postdoctoral scientist, used a technique developed in the Vignali lab to produce mice whose T cells have variations in the number and type of functional ITAMs. The technique involved using a virus as a genetic cargo-carrier to transport genes for different combinations of normal and mutant non-functional ITAMs into the mouse cells.

The researchers found that reducing the number of normal ITAMs caused the mice to develop autoimmune disease. However, the investigators also found that some mice with fewer than normal functional ITAMs did not become sick with autoimmune disease. Vignali said this finding suggests that it is not just the number of ITAMs, but also their type that may influence T cell function.

“We theorized that there were two possibilities why the immune system needs so many ITAMs,” he said. “One is that the requirement was purely quantitative, and that the ITAMs were there for signal amplification. The second possibility is that different ITAMs do slightly different

things—they do have slightly different structures, so maybe they bind to some signaling molecules better than others; and their positions in the T cell receptor are different. So, while our primary observation is that quantity is more important than ITAM type, we also found that type has some influence."

The researchers' analyses of the immune systems of the altered mice indicated that reducing the number of normal ITAMs crippled a process called "negative selection." In this process, the immune system rids itself of immature T cells that might attack the body's own cells, causing autoimmune disease. Vignali said that these findings might provide insight into how autoimmune diseases start.

"One implication of our findings is that a relatively small defect in the efficiency of signal transduction through the T cell receptor could give rise to a subtle failing in negative selection, which gives rise over a long period of time to a few overly active T cells that might initiate autoimmunity," Vignali said. "Clearly from our studies there is the possibility that you don't really need a very big reduction in T cell receptor signal strength to have a defect in negative selection."

The study also showed that different T cell functions required different numbers of functional ITAMs. "We were surprised to find that many ITAMs were required to make T cells divide and expand, but only one or two was required to make T cells secrete cytokines," Vignali said. Cytokines are soluble proteins used by cells of the immune system to communicate and send messages to one another. Vignali said these basic findings represent only the beginning of more detailed studies of the role of ITAMs in T cell function.

"We believe this idea that T cell signaling acts more like a rheostat than an on/off switch offers significant new insights into how T cell development and function is controlled," Vignali said.

Source: St. Jude Children's Research Hospital