Direct proof of how T cells stay in 'standby' mode

May 5 2011

the white blood cells that act as the police of the immune system—are in what immunologists call a "quiescent state," a sort of standby mode. For years, scientists have wondered if quiescence occurred by default or whether T cells need to work at remaining silent. Now, researchers at The Wistar Institute provide the first direct proof that a protein, called Foxp1, actively maintains this state of quiescence in T cells until the cells are called upon by other parts of the immune system.

Their findings, which appear online through *Nature Immunology* ahead of print publication, could one day enable researchers to activate T cells to fight diseases such as cancer, which can go undetected or unrecognized by the immune system. In fact, the researchers report that knocking out the Foxp1 protein in mice activates T cells, allowing the cells to work in their policing function.

"T cell quiescence has been a big mystery in immunology with some obvious and profound implications for treating illness by manipulating the immune system," said Hui Hu, Ph.D., senior author of the study and assistant professor in the Immunology Program at The Wistar Institute. "We believe we have provided evidence that quiescence is not just a passive, default state, and we are now beginning to understand the molecular mechanisms by which it happens."

Mature T cells are generated in the thymus, an organ located in front of heart, and then exit into the periphery. There, these T cells are in a "naïve," quiescent state, awaiting orders to act. Activation primarily

requires antigen-presenting cell, which offers up an antigen (a particle that the immune system recognizes as "foreign") to the T cell Receptor (TCR). This activated TCR, then, gives the T cell specificity.

Foxp1 is a transcription factor, a protein that binds to DNA and causes the cell to read—or transcribe—specific genes. The Hu laboratory had previously shown that the Foxp1 protein is important for T cell development in the thymus. In order to understand how Foxp1 operates in mature T cells, the researchers used an inducible deletion model system where they could choose to delete the gene's activity after the cells have already matured.

In studying these Foxp1-less T cells, Hu and his colleagues discovered that naive T cells without Foxp1 become activated and proliferate in response to the protein IL-7, without antigen triggers. Hu and his colleagues discovered that Foxp1 represses the expression of the receptor for IL-7, and some other key signaling, in regulating T cell quiescence.

Foxp1, the researchers found, is similar to a related transcription factor, called Foxo1, a well-studied protein with numerous roles in both cancer and aging. In T cells, Foxo1 helps induce the creation of IL-7 receptors, which allows the T cell to receive the IL-7 signal. Foxp1, they found, directly competed with Foxo1's DNA binding spot, thereby limiting the number of IL-7 receptors each T cell has. Such inter-protein competition helps maintain a balanced state within the cell, Hu says.

Among their key findings, Hu believes, is that removing Foxp1 can cause T cells to proliferate without triggering the TCR. "Antigenic specificity is the key characteristic of T cells and our adaptive immunity," Hu. Said. "We never thought a naive T cell could be activated without stimulation through the T cell receptor."

"It came as such a surprise that the deletion of Foxp1, basically the removal of an essential negative regulation, could lead naive T cells to bypass overt antigen recognition and become activated with effector functions," Hu.

According to Hu, his laboratory, in collaboration with fellow laboratories at Wistar, are now investigating the possibility of knocking out Foxp1 to stimulate T cells in the tumor microenvironment.

"Many cancers cause local T cells to become effectively unresponsive or 'quiescent,' thereby allowing tumors to grow unimpeded by the immune system," Hu said. "We suspect that the tumor cells may 'hijack' the cell-intrinsic quiescence mechanism. In addition, many tumor antigens are poorly immunogenic. By manipulating Foxp1 expression, we may bypass the poor tumor antigen stimulation and restore T cell activation within tumors in the hopes that the immune system will clear away cancerous cells."

Provided by The Wistar Institute