From HIV to cancer, IL-37 regulates immune system

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A University of Colorado Cancer Center study published in this month's *Proceedings of the National Academy of Sciences* describes the activity of a recently discovered communication molecule of the body's immune system, Interleukin 37 or IL-37. It has been known to limit inflammation and the current study reports its activity in the adaptive immune system: IL-37 inhibits the ability of the immune system to recognize and target new antigens.

"Knowing this mechanism that underlies IL-37's effect on the immune system now allows us to study IL-37 function and perhaps dysfunction in a wide range of diseases," says Mayumi Fujita, MD, PhD, investigator at the University of Colorado Cancer Center, associate professor in the CU School of Medicine Department of Dermatology, and the paper's senior author.

For example, knowing that IL-37 helps to create overall immune system sensitivity could allow researchers to manipulate IL-37 levels to sensitize the immune system to recognize and target tumor tissue, or desensitize the immune system in auto-immune conditions like rheumatoid arthritis in which the immune system acts over-aggressively toward healthy tissue.

IL-37 is one of the 38 known interleukins that carry messages in the immune system. The current study shows that IL-37 works through the regulation of dendritic cells, which trap, process and present new antigens. Dendritic cells are formed in bone marrow and migrate to parts

of the body that commonly come in contact with new antigens, for example skin or the lining of the gut. Immature dendritic cells are in a state of readiness, waiting at these common points of first contact to trap new antigens. Mature dendritic cells trap an antigen and then migrate with the antigen to lymph nodes where they work to coordinate the immune response to the new antigen.

The current study shows that IL-37 encourages the formation of semi-mature dendritic cells that migrate to lymph nodes but fail to present antigens in a way that create an immune response. It is as if IL-37 helps to maintain dendritic cells in a state of semi-immature readiness, rather than allowing them to become sensitized to new antigens.

In fact, the study showed a cascade of diminished immune system response in mice with IL-37, including lower CD40, IL-1b, IL-6 and IL-12, all of which are involved in creating an immune response.

"This implies that IL-37 may be a basic component of immune system regulation, with IL-37 levels affecting many other pieces of the overall response," Fujita says.

When researchers transplanted dendritic cells isolated from the lymph node of IL-37 mice and also dendritic cells isolated from wild-type (regular) mice into new mice, they saw much less "antigen challenge" in mice that had received dendritic cells from IL-37 sources; these IL-37-expressing dendritic cells failed to sensitize the immune system and thus failed to create an immune response.

"This is a case in which our understanding of basic biology could translate into applications across many disease types," Fujita says.

More information: Suppression of antigen-specific adaptive immunity by IL-37 via induction of tolerogenic dendritic cells, *Proc Natl*

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