New pathway regulates immune balance and offers promising drug development target

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St. Jude Children's Research Hospital scientists have identified a new pathway that helps control the immune balance through reciprocal regulation of specialized T lymphocytes, which play very different inflammatory roles.

Investigators also determined that two drugs working in different ways to dampen the inflammatory response in patients with multiple sclerosis or following organ transplantation target this new mechanism. Further research into the pathway might lead to new medications to block other autoimmune disorders or to new anti-rejection drugs, researchers said. The work is published in the current online issue of *Nature Immunology*.

T cells are the white blood cells responsible for both driving and modulating the immune response. This work focuses on a mechanism at work as T cells differentiate into the more specialized T-helper 1 (Th1) cells that drive inflammation or the regulatory T cells that work to shut it down and protect healthy tissue from a misguided immune attack.

"The success or failure of the immune response requires T cells to make the right decision about their fate," said Hongbo Chi, Ph.D., assistant member of the St. Jude Department of Immunology and the paper's senior author.

"In this paper we describe the receptor that controls the cell fate determination of different subsets of T cells; controlling the choice to become either an inflammatory or a regulatory T cell," Chi said. Earlier

work from Chi and others linked the receptor, S1P1, to other aspects of T cell functioning.

Researchers also found surprising evidence T cell response is regulated by a lipid the T cell secretes rather than a protein known as a cytokine. If confirmed, Chi said the finding would mark the first time a lipid, rather than a protein, served such a signaling function in T cells.

For this study, investigators used both cultured cells and specially bred mice to link the S1P1 receptor to the fate of the two sub-groups of T cells. Stimulating S1P1 activates a pathway that drives the cell to become a pro-inflammatory Th1 cell. Th1 cells rally other immune components to act against infection and other threats. At the same time, S1P1 activation down regulates differentiation of regulatory T cells. The S1P1-dependent effect on both sub-groups of T cells relies on its ability to dampen signaling through another pathway in the T cell; this second pathway uses a different molecular route to influence the T cell's fate, working through cytokine TGF-beta activation of a signaling molecule called Smad3.

"There is a reciprocal change between the two cell subsets. With this system, T cells that do not become regulatory T cells have a tendency to become T helper type 1 cells," Chi said.

The S1P1 pathway is also targeted by the anti-rejection drug rapamycin, which is used to protect organ transplant patients, and FTY720, which has the promise to become the first oral therapy for use against relapsing multiple sclerosis. This study is the first to show both work in part by modulating this molecular pathway.

The work expands on earlier research from Chi's laboratory showing the S1P1 receptor played a central role in inhibiting the development and function of regulatory T cells. "In this paper, we show that the receptor

controls differentiation of conventional T cells as well," he said, specifically Th-1 cells. S1P1 also plays a role in the movement of T cells throughout the body.

Researchers are now focused on understanding the pathways in more detail. The questions include how S1P1 activates the mTOR pathway. Once activated, mTOR, a protein kinase complex, works to dampen signaling along the TGF-Beta - Smad3 pathway, thereby promoting Th1 cell differentiation at the expense of regulatory T cells.

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