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Maintaining immune balance involves an unconventional mechanism of T cell regulation

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New findings from St. Jude Children's Research Hospital reveal an unconventional control mechanism involved in the production of specialized T cells that play a critical role in maintaining immune system balance. The research appears in the current online edition of the scientific journal *Nature*.

The work focused on white blood cells known as regulatory T cells. These cells are crucial for a balanced immune response. Regulatory T cells suppress other immune system components in order to protect healthy tissue from misguided immune attacks or to prevent runaway inflammation.

St. Jude researchers showed that a molecular complex called mTORC1 uses an unconventional process to serve as a rheostat, controlling the supply and function of regulatory T cells. Loss of mTORC1 activity impairs the regulatory T cells that suppress the immune system's inflammatory response. The mTORC1 complex is part of the mTOR pathway, which was thought to inhibit rather than promote the number and function of regulatory T cells.

"These results challenge the prior view of the mTOR pathway as an inhibitor of these key immune cells and highlight the role of the mTORC1 complex in regulating the T cells that are vital for controlling inflammation," said Hongbo Chi, Ph.D., an associate member of the St.

Jude Department of Immunology and the paper's corresponding author.

The findings also identified the mechanism mTORC1 uses in programming regulatory T cells to function as immune suppressors. Chi said the results should aid efforts to develop new drugs for use in organ transplantation or for treatment of autoimmune disorders.

For this study, researchers used specially bred mice to explore the mTOR pathway's role in the function of regulatory T cells. Investigators demonstrated mTORC1's importance by selectively deleting genes that carry instructions for making key elements of mTORC1 and a related complex. The deletion that targeted mTORC1 resulted in dramatically reduced immune suppression by regulatory T cells and the mice rapidly developed a fatal inflammatory disorder.

Researchers also showed that mTORC1 works by integrating signals from two immune receptors on the cell surface with cholesterol metabolism. With the right input, mTORC1 promoted production of regulatory T cells and cemented their role as suppressors of immune activity.

In another twist, investigators linked that suppressive function to cholesterol and lipid metabolism. Rather than relying on more conventional strategies of immune regulation, researchers showed how regulatory T cells depend on the metabolic pathway to control production of molecules CTLA4 and ICOS, which are responsible for immune suppression. Production of CTLA4 and ICOS by regulatory T cells decreased as lipid metabolism dropped. "We are just starting to appreciate the importance of lipids in the immune system, particularly in the function of regulatory T cells," Chi said.

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