Metabolic signaling plays a crucial role in regulating specialized T cells

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Nicole Chapman, Wei Su and Hongbo Chi of St. Jude Children's Research Hospital. Credit: St. Jude Children's Research Hospital

Effector regulatory T cells (eTreg cells) are a specialized subset of white blood cells that keep the immune system in check. St. Jude Children's

Research Hospital scientists have revealed the metabolic signaling mechanisms that regulate function of eTreg cells. The work may aid efforts to better understand and treat inflammatory diseases. The findings were published online today in *Cell Metabolism*.

"This process is quite fascinating to us, and helps explain how metabolites can drive selective signaling pathways to enforce the differentiation, persistence and function of eTreg cells," said corresponding author Hongbo Chi, Ph.D., of St. Jude Immunology. "We were looking specifically at suppression of autoimmunity that can develop spontaneously in our models, but we also know Treg cells play a role in multiple diseases."

Although eTreg cells are involved in prevention of autoimmune diseases, including lupus and rheumatoid arthritis, they are detrimental in other diseases, such as cancer. Understanding how metabolic signaling regulates Treg cell heterogeneity or function may help scientists develop more specific drugs to target these pathways to help treat disease. How metabolic pathways regulate the differentiation and persistence of eTreg cells, especially at the level of intracellular signaling, has been unclear until now.

Metabolic pathways exert control

The researchers showed that two-way metabolic signaling that intersects with T cell receptor signaling is critical to regulating eTreg cell function.

Investigators identified a class of metabolites called isoprenoids that are essential for the suppressive activity of activated Treg cells such as eTreg cells. Isoprenoids are required for cellular processes called posttranslational lipid modifications, specifically protein farnesylation and geranylgeranylation. These processes are mediated by Fntb and Pggt1b, respectively. Disruption of these processes by Treg cell-specific

deletion of Fntb or Pggt1b causes mice to develop autoimmunity.

Further research into the metabolic signaling mechanisms revealed the discrete details of Treg cell-mediated immune suppression downstream of T cell receptor signaling. Fntb acts through two parallel pathways to promote eTreg cell persistence: the protein kinase mTORC1, which regulates metabolic reprogramming of Treg cells, and the immune receptor ICOS. Pggt1b enforces signaling through the small G protein Rac to support eTreg cell differentiation.

"We were able to dissect how metabolic regulation controls eTreg cell differentiation and maintenance," said first author and graduate student Wei Su of St. Jude Immunology. "This bidirectional interplay between intracellular signaling and metabolism allows eTreg cells to maintain the self-tolerance in our body."

"These pathways have been of long-standing interest outside of the immune system for a way to inhibit inflammatory responses," said study author Nicole Chapman, Ph.D., of St. Jude Immunology. "Our study provides a deeper understanding of the molecular interplay between signaling and metabolism and could allow for more potent and selective targeting of downstream metabolic functions in Treg cells."

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