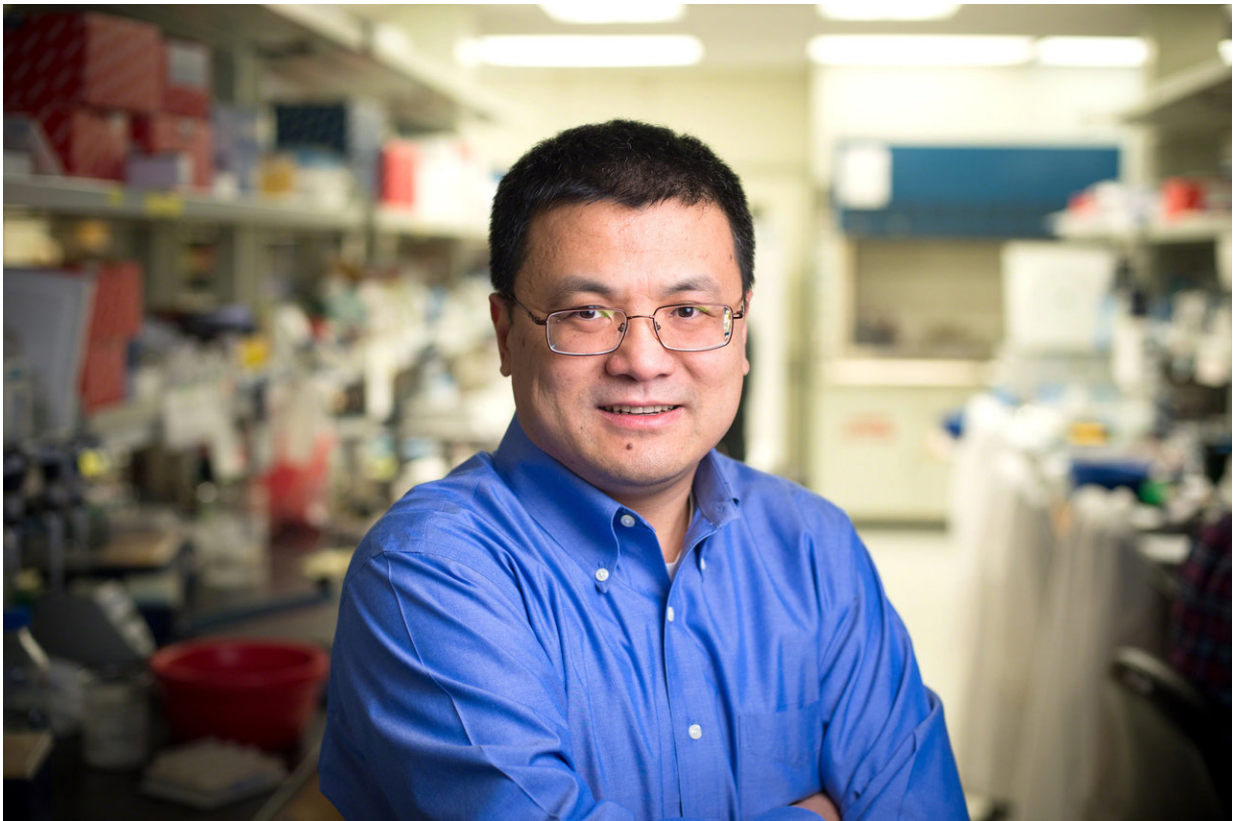


Scientists identify a protein complex that shapes the destiny of T cells

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Corresponding author Hongbo Chi, Ph.D., and colleagues identified the mechanism that determines how T cells specialize during their development. Credit: St. Jude Children's Research Hospital

Like a mentor helping medical students choose between specialties, a protein complex helps shape the destiny of developing T cells, St. Jude

Children's Research Hospital scientists have reported. The research appears today in the journal *Science Immunology* and adds to growing evidence of the critical role cell metabolism plays in the immune system.

The [protein complex](#) is mTORC1, which regulates cell growth and metabolism. St. Jude immunologists found mTORC1 acts in response to cues from in and around developing T cells and intersects with metabolic activity, to influence whether the cells become conventional or unconventional T cells. To their surprise, researchers found that disrupting mTORC1 led to metabolic changes that favored development of unconventional T cells at the expense of conventional T cells.

The research comes amid excitement about harnessing the immune system to fight cancer, tame autoimmune diseases and combat infectious diseases. "We know that conventional and unconventional T cells are fundamentally different," said corresponding author Hongbo Chi, Ph.D., a member of the St. Jude Department of Immunology faculty. "They express different [cell surface receptors](#). The cells have different functions. But until now the mechanism that helps decide their fates has remained largely unknown."

T cells play a central role in the adaptive immune system, functioning like elite commando units trained to find and eliminate specific viruses and other threats. T cell development occurs in the thymus after immature (precursor) cells in the bone marrow travel there to mature and specialize. Their specialty is signaled partly by protein [receptors](#) on the cell surface known as T [cell receptors](#) (TCRs) or antigen receptors. T cells depend on the T cell receptors to recognize targets and respond to changing conditions.

In humans, the vast majority of T cell receptors have an alpha (α) protein chain and a beta (β) chain. These are conventional T cells that circulate widely and reside in the spleen and lymph nodes. A smaller

number of T cells carry receptors made from a gamma (γ) and a delta (δ) protein chain. They belong to the family of unconventional T cells that are found in the gut, skin and other barrier tissues.

Working with mouse models and developing T cells in the laboratory, Chi and his colleagues showed that activation of mTORC1 revs up energy production through glycolysis and oxidation to fuel anabolic metabolism and promote development of $\alpha\beta$ T cells.

When investigators disabled mTORC1, metabolism was disrupted, which was associated with a reduction in the $\alpha\beta$ T cells and an increase in $\gamma\delta$ T cells. Deleting a key component of mTORC1, a protein called RAPTOR, disabled mTORC1 and altered the metabolic balance in developing T cells. The change reduced anabolic metabolism but increased levels of toxic molecules called reactive oxygen species (ROS) and upregulated activity along a molecular pathway that promotes cell growth.

The change enhanced development of $\gamma\delta$ T cells in the thymus and hindered development of $\alpha\beta$ T cells.

Researchers also reported expression of signature genes associated with $\gamma\delta$ T cells was enhanced in mice when RAPTOR was deleted from the mTORC1 complex.

"This research establishes mTORC1-driven metabolic signaling as a decisive factor in determining the fate of developing T cells and suggests metabolic processes are a fundamental mechanism that connects external signals with internal processes to guide the fate of immune [cells](#)," Chi said.

More information: K. Yang et al., "Metabolic signaling directs the reciprocal lineage decisions of $\alpha\beta$ and $\gamma\delta$ T cells," *Science Immunology*

(2018). [immunology.sciencemag.org/look ... 6/sciimmunol.aas9818](https://immunology.sciencemag.org/look...6/sciimmunol.aas9818)

Provided by St. Jude Children's Research Hospital

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