

Researchers map metabolic signaling machinery for producing memory T cells

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Immunologists at St. Jude Children's Research Hospital have mapped the previously unknown biological machinery by which the immune system generates T cells that kill bacteria, viruses and tumor cells.

The findings have multiple implications for how the adaptive immune system responds to infections to generate such memory T cells. The experiments revealed mechanisms that inhibit development of the long-lived memory T cells that continually renew to protect the body over time. Blocking these inhibitory mechanisms with pharmacological or genetic approaches could boost protective immunity against infection and cancers.

The researchers also discovered a subtype of memory T cells that they named terminal effector prime cells. Mapping the pathway that controls these cells raises the possibility of manipulating this pathway to enhance the ability of the immune system to kill microbes and cancer cells.

Mapping the control pathway also provided the insight that diet may have a greater influence on immune function than previously thought.

Led by Hongbo Chi, Ph.D., of the Department of Immunology, the research appears today in the journal *Cell*. The first authors are Hongling Huang, Ph.D., and Peipei Zhou, Ph.D., of Immunology.

CRISPR-assisted mapping of the metabolic machinery

When the body encounters an infection, the immune system begins to generate effector T cells to attack the invading bacteria or viruses. There are two types of these T cells. One type is the memory precursor cells, which can develop into memory T cells that persist long-term to protect the body. These are the T cells that vaccinations generate. The second type are short-lived terminal effector T cells, which have immediate cytotoxic activity.

In this study, researchers sought to map the metabolic machinery that

controls how the [immune system](#) decides to produce memory T cells. Chi and his colleagues focused on the little-known mechanisms that inhibit the generation of this type of T cell.

The scientists used a gene-manipulating technology called CRISPR to sift through more than 3,000 metabolism-controlling genes in mouse cells. The goal was to discover genes that regulated the "fate" of effector T cells and memory T cells.

Nutrients play an unexpected role in T cell fate

The research revealed a previously unknown role that [nutrients](#), such as amino acids and certain sugars, play in regulating T cell fate. To the investigators' surprise, the analysis identified nutrient-related pathways that suppressed memory T cell production.

"The preconceived notion about nutrients' role in immune cell function was that the cells rely on nutrients as an energy source and for [building blocks](#)," Huang said. "But our study provides another view—that nutrients are involved in inhibitory pathways, and that deprivation of certain nutrients or metabolites might be good for adaptive immunity.

"It seems to suggest that what you eat and drink may have a greater influence on immune function than previously appreciated," Huang said. "This will be an important pathway for future research."

New T cell subtype identified

The studies also revealed a new subtype of effector T cell, which they named terminal effector prime cells. Blocking development of these cells may be key to enhancing T cell-mediated immunity. The researchers' work identified a pathway that controls the transition of

developing T cells from an intermediate stage to mature terminal effector prime cells.

The researchers found they could manipulate this pathway to keep terminal effector prime cells at this intermediate stage that would induce them to proliferate to produce more memory T [cells](#). "These findings highlight the possibility of targeting this [pathway](#) to boost protective immunity against both infections and tumors," Chi said.

"We are extremely excited by these findings," Chi said. "By identifying this nutrient signaling axis, our studies provide new biological insights and therapeutic targets for enhancing memory T cell responses and protective immunity against pathogens and tumors."

More information: Hongling Huang et al. In vivo CRISPR screening reveals nutrient signaling processes underpinning CD8+ T cell fate decisions. *Cell*. February 25, 2021 DOI:doi.org/10.1016/j.cell.2021.02.021

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