Glutamine metabolism affects T cell signaling and function

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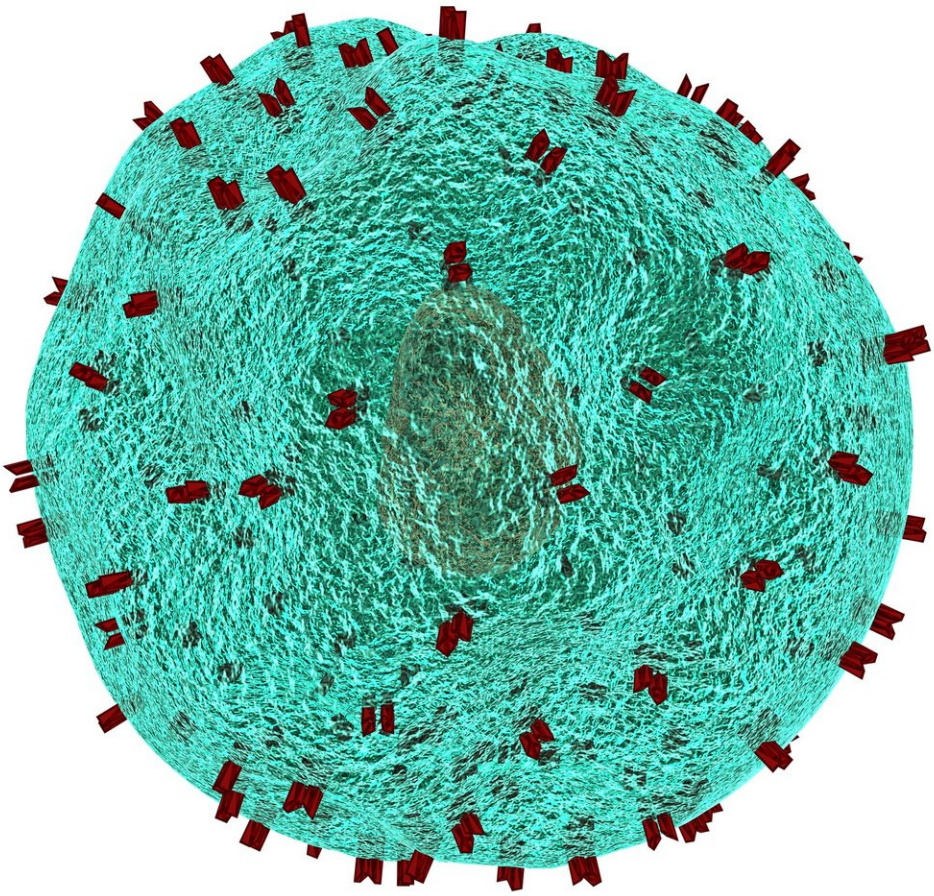

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The cellular nutrient glutamine launches a metabolic signaling pathway that promotes the function of some immune system T cells and suppresses others, Vanderbilt researchers have discovered.

They show that a drug that inhibits glutamine metabolism—currently in clinical trials as an anticancer agent—might also be useful as a treatment for inflammatory and autoimmune diseases. The study, published online this week in the journal *Cell*, also suggests strategies for using the drug to enhance cancer immunotherapies.

Jeffrey Rathmell, Ph.D., Cornelius Vanderbilt Professor of Immunobiology, and his colleagues have focused on trying to understand how a cell integrates its nutrients and metabolism with its function. They previously demonstrated the importance of the cellular fuel glucose for the activation and function of T cells that drive inflammation and eliminate pathogens.

In the current work, they turned their attention to another major fuel: glutamine, which has primarily been studied in the context of cancer cell metabolism. Several companies are developing drugs that inhibit glutamine metabolism to reduce cancer cell growth and proliferation.

The investigators expected that inhibiting glutamine metabolism—like blocking glucose metabolism—would prevent T cell activation and function. They used a drug that inhibits the first step in glutamine metabolism, an enzyme called glutaminase. They also studied mice with targeted genetic deletion of the glutaminase gene.

The researchers were surprised to find that certain T cells—those that

mediate antiviral and anticancer responses—performed better in the absence of glutaminase activity. Other T cells involved in inflammatory and autoimmune diseases performed worse.

"We were intrigued that one metabolic perturbation could have a very different impact on the function of subsets of T cells," said Marc Johnson, a graduate student who led the studies.

The findings fit with studies of glutamine metabolism in cancer cells, said Rathmell, who is also professor of Pathology, Microbiology and Immunology.

"This compound (that inhibits glutaminase) works in some tumors and doesn't work in others. What Marc found is that it's the same for T cells: some T cells need this pathway, and some don't," Rathmell said. "If we block the pathway, the autoimmune T cells don't do so well, but the anticancer T cells do better."

The researchers demonstrated in mouse models of allergic asthma, inflammatory bowel disease, and chronic graft-versus-host disease that eliminating glutaminase activity protected against inflammation and disease.

"The glutaminase inhibitor has a remarkable safety profile, and we think it could be repurposed in potentially quite a variety of inflammatory and autoimmune diseases," Rathmell said.

To examine the impact of inhibiting glutaminase on T cells that mediate anticancer responses, the investigators used the drug in a mouse model of CAR (chimeric antigen receptor) T-cell therapy. CAR T cells are cancer-killing T cells that have been genetically engineered to recognize specific cancer cells.

In the mouse model, the researchers found that treatment with the glutaminase inhibitor improved CAR T-cell function, but the enhanced function was lost over time. A shorter exposure to the inhibitor improved CAR T-cell function, and the T cells persisted for a longer period of time.

"One of the problems with CAR T-cell therapy is survival of the engineered cells," Johnson said. "We think that a short treatment with a glutaminase inhibitor might improve the persistence of CAR T cells."

The findings have implications for current clinical trials of a glutaminase inhibitor in combination with immunotherapies called checkpoint inhibitors, Rathmell said.

"Our data suggest that the combination of drugs might work best if you give the glutaminase inhibitor for a short period of time and then remove it."

The investigators are testing varied dosing schedules in mouse models of cancer.

The researchers also probed the mechanistic changes resulting from glutaminase inhibition and demonstrated that the glutamine metabolic pathway—usually thought of as only generating energy—is tightly integrated with cell signaling and gene expression.

"By changing this metabolic enzyme, we're affecting a downstream metabolite that directly changes chromatin and gene accessibility and gene expression," Rathmell said. "As a concept, this idea that metabolic pathways are signaling pathways is relatively new."

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