Discovery of how immune cells sense nutrients offers new therapeutic insight

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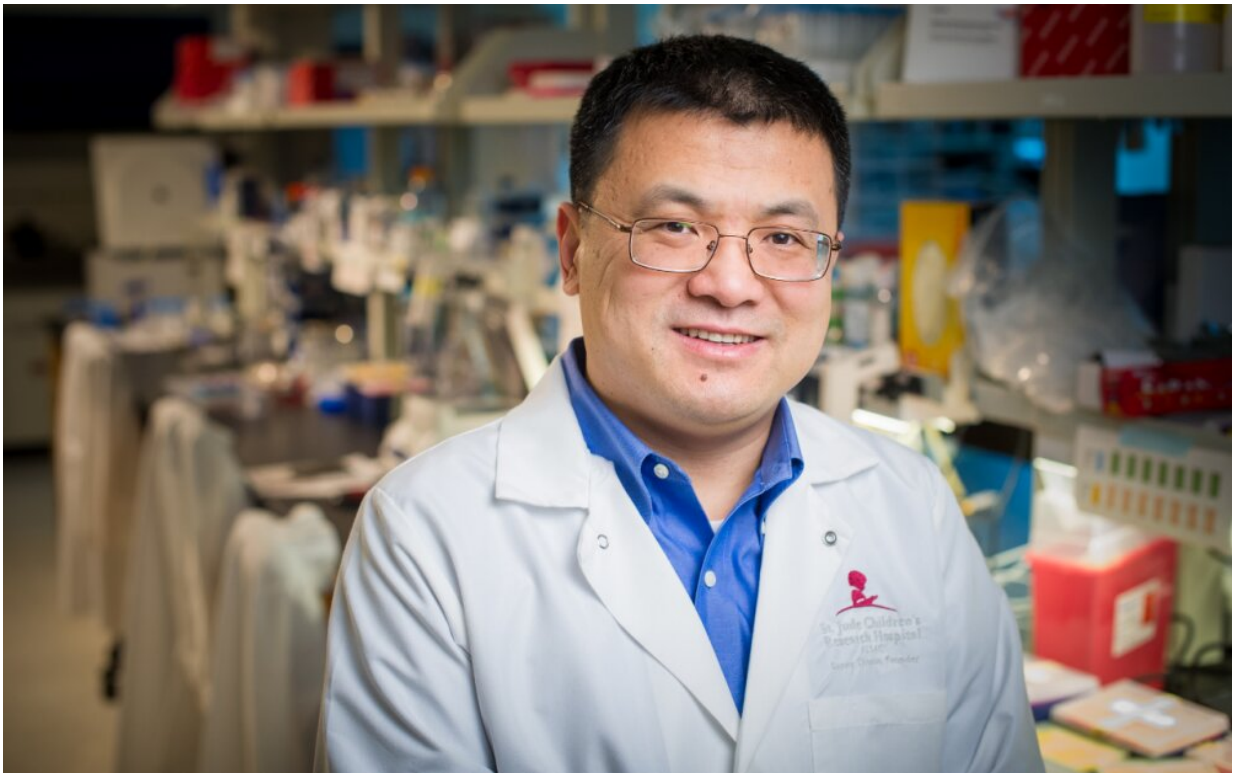

Hongbo Chi, Ph.D., St. Jude Department of Immunology, corresponding author of a new paper published in *Nature* that explores the nutrient-sensing machinery of regulatory T cells. Credit: St. Jude Children's Research Hospital

Activating the immune system to battle infections or cancers depends on more than detecting the threat. The immune system must also detect

whether its cells have sufficient nutrients to fuel the immune response.

St. Jude Children's Research Hospital immunologists have identified the biological switches that constitute the nutrient-sensing machinery of regulatory T cells. Identifying these enzymatic components is just the beginning of mapping and understanding the nutrient-sensing mechanisms in the T cell regulatory networks.

"These maps will provide new targets for treatments to fight infections and enhance the immune response in cancer immunotherapies," said corresponding author Hongbo Chi, Ph.D., of the St. Jude Immunology department. The findings may also enable development of more effective vaccines. The findings appeared today in *Nature*.

mTORC1 and immune regulation

mTORC1 is a key enzyme switch in the cell's nutrient-sensing machinery. In this study, researchers sought to identify the regulatory enzymes that link mTORC1 with the immune system function.

The investigators used CRISPR to identify the genes that encoded those enzymes. The process was like picking out the key puzzle pieces from a pile of different puzzles. Using CRISPR to target each of the approximately 20,000 genes in the mouse genome, the researchers screened T cells that were stimulated under conditions that enforce low or high mTORC1 activity.

Researchers then identified dozens of genes that either activated or inactivated mTORC1. The findings included some previously unknown regulators.

To discover how the proteins encoded by the genes fit into regulatory networks, the scientists used large protein databases to track how the

proteins interacted in cells. This process was like figuring out how the puzzle pieces fit together.

Researchers used the protein-protein interaction data to identify functional "modules" that constituted regulatory networks involved in mTORC1 nutrient-sensing in T cells.

Just the beginning

The discoveries of how these enzymes fit into the nutrient-sensing regulatory network is just the beginning. "In this paper, we focused on only a few major pathways, but we have identified several hundred candidate proteins, so there are many more to be studied," Chi said.

As the full extent of the nutrient-sensing machinery of T cells emerges, it will offer important new therapeutic opportunities. "We have shown how mTORC1 is regulated to support T-cell priming in fighting infection," Chi added. "Learning how to manipulate this pathway has the potential for both treating infections and for enhancing vaccines."

Regulatory T cells also play a role in enabling tumors to evade the immune system. Therefore, targeting the mTORC1 nutrient-sensing pathways has the potential for modulating regulatory T cell function in cancer immunotherapy.

Support for bidirectional metabolic signaling

The findings support and expand upon a concept called "bidirectional metabolic signaling" in immunity. The immune system responds to external signals such as those produced from the diet or invading microbes as well as to internal nutrient signals. These signals tell the immune cells whether sufficient nutrient building blocks and energy

sources exist to power the immune response.

The nutrient-signaling machinery involving mTORC1 is evolutionarily conserved in other cell types, so these findings also offer insight into other physiological processes.

More information: Lingyun Long et al, CRISPR screens unveil signal hubs for nutrient licensing of T cell immunity, *Nature* (2021). DOI: 10.1038/s41586-021-04109-7

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