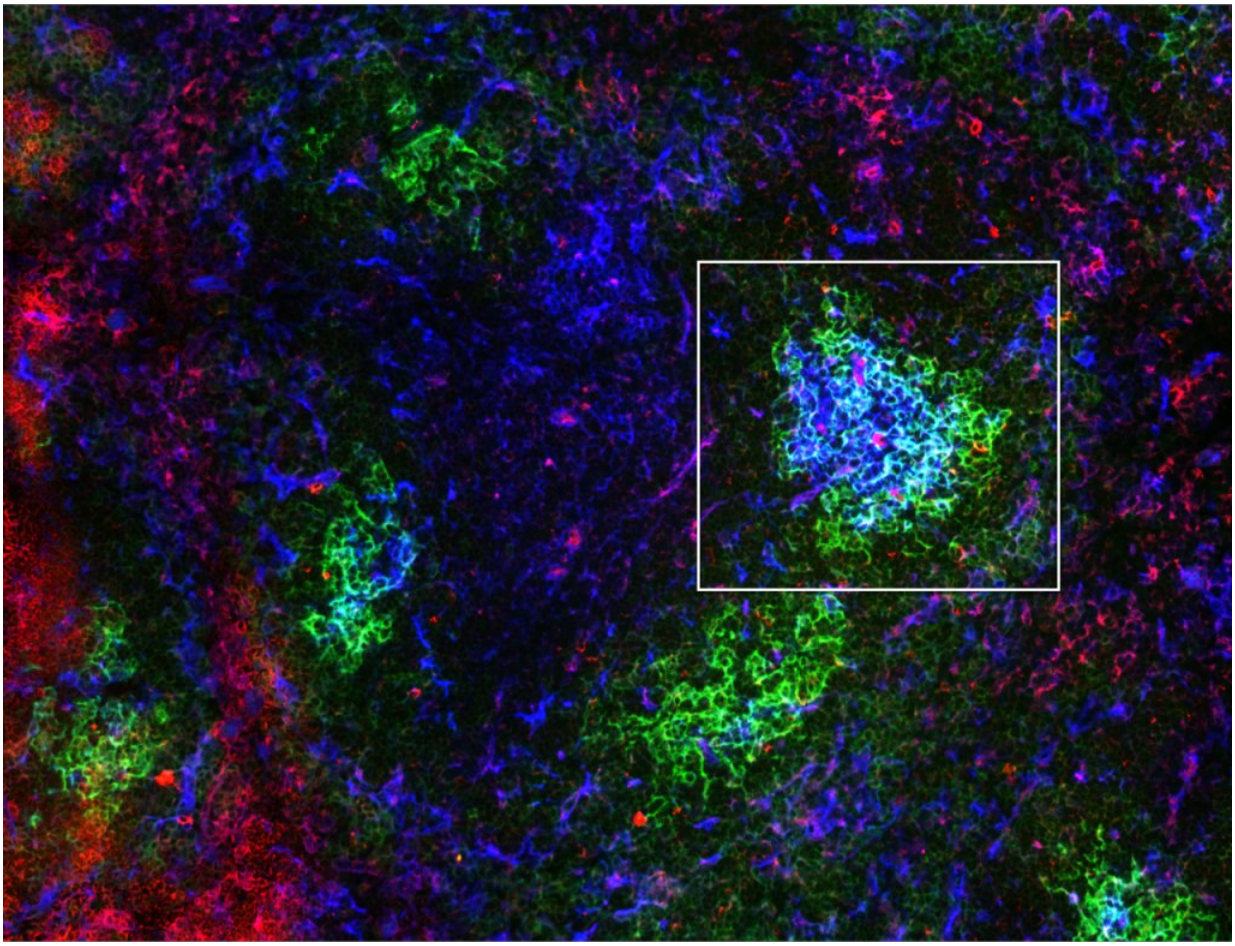
MedicalXpress

Research helps explain how B cell metabolism is controlled

January 23 2017



Germinal center (rectangle) in the spleen of an immunized mouse, showing inactivated GSK3 (magenta) in B cells (blue) near follicular dendritic cells (green). Credit: Laboratory of Robert Rickert, Ph.D., at Sanford Burnham Prebys Medical Discovery Institute

B cells, the lymphocytes best known for making antibodies, live a complex life. They start developing in the bone marrow and then move through the spleen, lymph nodes and blood, taking on tasks that range from recognizing foreign substances to replication, quiescence, and generating a lasting memory of pathogens. But little is known about how B cell metabolism adapts to each of these environments, insights that may improve our understanding of B cell diseases, such as non-Hodgkin's lymphoma.

"Our research shows that the protein GSK3 plays a crucial role in helping B cells meet the energy needs of their distinct states," says Robert Rickert, Ph.D., director of the Tumor Microenvironment and Cancer Immunology Program at Sanford Burnham Prebys Medical Discovery Institute (SBP). "It acts as a metabolic sensor, or checkpoint, that promotes the survival of circulating B cells while limiting growth and proliferation of B cells in germinal centers. The findings are particularly relevant for certain B cell pathologies, including lymphoma subtypes, where there is an increased demand for energy to support the hyperproliferation of cells in a microenvironment that may be limited in nutrients."

B cells have different metabolic needs depending on their environment. In the blood, circulating B cells are quiescent, consuming little energy. In germinal centers—the sites within lymph nodes where mature B cells cluster—B cells proliferate and undergo hypermutation of their antibody genes to generate high-affinity antibodies. These processes require enormous amounts of energy, so these B cells consume lots of sugars, fatty acids and amino acids.

The new study, published today in *Nature Immunology*, found that GSK3 adjusts metabolism to match each of these needs. In circulating B cells, GSK3 limits overall metabolic activity, while in proliferating B cells in germinal centers, GSK3 slows glycolysis and production of

mitochondria.

GSK3 function is essential for B cell survival in germinal centers. To understand why, Rickert's team looked at how B cells in these regions generate energy, and found that because these B cells are so metabolically active, they consume nearly all available glucose. That switches on a secondary, less efficient but non-oxygen-dependent means of generating energy called glycolysis. High glycolytic activity leads to accumulation of toxic reactive oxygen species (ROS), as does rapid manufacture of mitochondria, which tend to leak the same chemicals. Thus, by restraining metabolism in specific ways, GSK3 prevents ROS-induced cell death.

"Our results were really surprising," Rickert commented. "Until now, we would have thought that slowing metabolism would only be important for preventing B cells from becoming cancerous—which it indeed may be. These studies provide insight into the dynamic nature of B cell metabolism that literally 'fuels' differentiation in the germinal center to produce an effective antibody response"

"It's not yet clear whether or how GSK3 might be a target for future therapies for B cell-related diseases, but this research opens a lot of doors for further studies," Rickert said. "To start with, we plan to investigate how GSK3 is regulated in lymphoma and how that relates to changes in metabolism. That research could lead to new approaches to treating lymphoma."

More information: GSK3 is a metabolic checkpoint regulator in B cells, *Nature Immunology*, nature.com/articles/doi:10.1038/ni.3664

Provided by Sanford-Burnham Prebys Medical Discovery Institute

Citation: Research helps explain how B cell metabolism is controlled (2017, January 23) retrieved 25 April 2024 from https://medicalxpress.com/news/2017-01-cell-metabolism.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.