Mitochondrial protein synthesis identified as a potential therapeutic target in lymphoma

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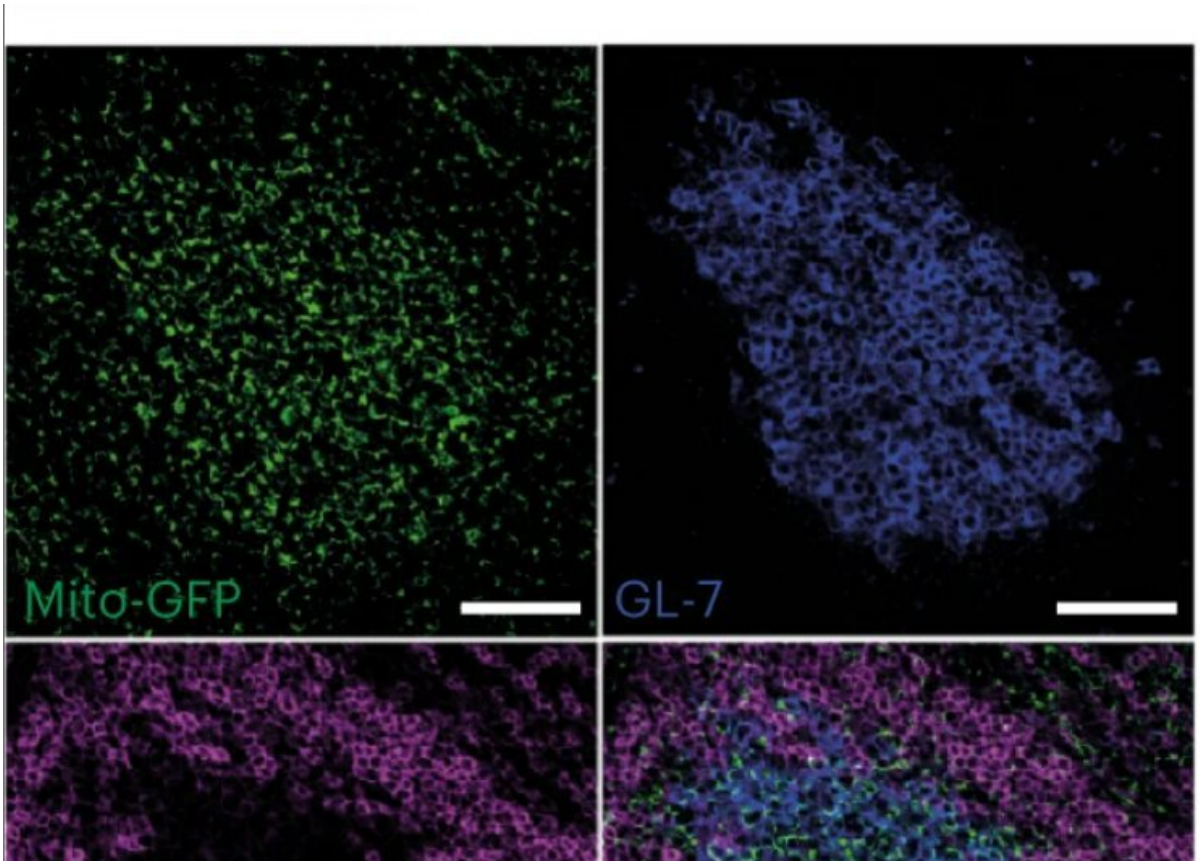

Spleen sections from mito-QC mice immunized with SRBC and analyzed on day 12. Scale bar, 50 μm. Representative of three independent experiments. Credit: *Nature Immunology* (2023). DOI: 10.1038/s41590-023-01484-3

A team led by Alex Clarke at the Kennedy Institute has identified how

high mitochondrial activity regulates antibody responses crucial for immunity but is also necessary for the development of lymphoma.

Published in *Nature Immunology*, their study reveals that B cells require high levels of mitochondrial activity to enter the germinal center (GC) reaction, a process essential for effective immune memory and long-lived antibody production but which can result in lymphoma if it goes wrong.

GCs are sites in lymph nodes and spleen which develop following infection or vaccination. Over several weeks, B cells compete with each other through natural selection to develop a receptor which is best able to bind its target. Part of this receptor can also be secreted, as antibody. For this to happen, just as in evolution, mutations in the DNA of B cells which encodes their receptors must occur and rarely these can be harmful, leading to lymphoma.

"Although we knew that B cells in the germinal center must have very active metabolism, how this was maintained and what might happen if it was disrupted was unknown," said Yavuz Yazicioglu, KTPS DPhil student and first author of the study. "We found that germinal center B cells have highly abundant mitochondria, which were synthesizing proteins required for energy generation."

They found that if they deleted the master regulator of mitochondrial protein synthesis, TFAM, B cells were unable to physically enter the GC reaction and so immunity was severely compromised. This was likely to be due to a build-up of toxic free radicals caused by mitochondrial damage.

"We wondered whether what we had found in normal germinal center B cells may also apply in lymphoma," said Alex Clarke, Wellcome Trust Clinical Research Career Development Fellow. "We found that germinal

center-derived lymphoma was just as dependent on mitochondrial protein synthesis as normal germinal center B cells."

Commenting on the significance of their findings, Alex added, "Our data show that mitochondrial protein synthesis is a potentially important therapeutic target in lymphoma which may be prioritized in the future."

More information: Yavuz F. Yazicioglu et al, Dynamic mitochondrial transcription and translation in B cells control germinal center entry and lymphomagenesis, *Nature Immunology* (2023). DOI: 10.1038/s41590-023-01484-3

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