Lipid homeostasis mediated by cholesterol synthesis supports B cell responses to vaccination

Sterol regulatory element-binding protein (SREBP) signaling regulates cellular lipid homeostasis. We discovered that SREBP signaling in B cells is crucial for antibody responses and the generation of germinal centers and B cell memory compartments in response to vaccination. These results provide mechanistic insights that couple sterol metabolism to the quality and longevity of humoral immunity.

This is a summary of:
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The question

Generation of high-affinity antibodies and antigen-specific memory B cells is a central feature of the adaptive immune response against pathogens. An improved understanding of the pathways that regulate B cell activation and memory formation is crucial for the development of vaccines that induce robust and sustained protective immunity. Using systems vaccinology approaches, involving the multi-'omic' profiling of immune responses to vaccination in humans, we identified a blood gene signature of the sterol regulatory element-binding protein (SREBP) pathway that was induced within a few days of vaccination and was tightly correlated with the ensuing antibody and follicular T cell responses[1]. Despite the crucial role of SREBP signaling in the pathogenesis of metabolic diseases[2,3], its role in the immune system is poorly understood. The activity of SREBPs is dependent on SREBP cleavage-activating protein (SCAP)[2]. A previous study suggests that the depletion of SCAP in T cells causes a severe block in $CD8^+$ T cell activation[3], but the role of SREBP signaling in other cell types, including B cells and dendritic cells, is unclear.

The observation

To investigate the role of SREBP signaling in modulating immune responses, we generated knockout mouse strains with B-cell-specific or $CD11c^+$ antigen-presenting cell (APC)-specific deletion of *Scap* and examined the responses of the mice to immunizations with adjuvanted protein or live viral vaccines. We examined cell cycle progression, metabolic reprogramming and SREBP signaling by comparing wild-type and SCAP-deficient B cells for their responses to the B cell receptor CD40 (also known as tumor necrosis factor receptor superfamily member 5) and Toll-like receptor signals. We also performed RNA sequencing (RNA-seq) and metabolomics studies to further understand the role of SREBP signaling in B cells.

The ablation of SCAP in $CD11c^+$ APCs had no effect on immune responses to immunization. By contrast, SREBP signaling in B cells was crucial for antibody generation in response to protein immunization and live viral vaccines. SREBP signaling was dispensable for B cell development and maintenance at homeostatic state. However, mice deficient in SREBP signaling in B cells could not mount effective antibody responses and were defective in forming germinal centers and bone marrow plasma cells after immunization (Fig. 1a). RNA-seq analysis identified several pathways associated with SCAP deficiency in activated B cells (Fig. 1b). SREBP signaling was required for metabolic reprogramming in stimulated B cells. SCAP-deficient B cells could not proliferate after mitogen stimulation, a defect that could be largely rescued by cholesterol supplementation. Deletion of SCAP specifically in germinal center B cells, using activation-induced cytidine deaminase (AID) promoter–Cre recombinase, reduced lipid raft content and cell cycle progression and led to disrupted germinal center responses.

The implications

The origin of this study was our previous systems vaccinology work in humans, which revealed a correlation between sterol metabolism controlled by the SREBP pathway and antibody responses to vaccination[1]. This finding highlights the power of systems vaccinology in providing mechanistic insights, and suggests that such an approach may be valuable in exploring the effect of lipid-lowering agents on immune responses to vaccination in humans.

Sterol metabolism is a major target for treating and preventing cardiovascular diseases. For example, statins, a commonly prescribed medicine, inhibit the enzyme required for cholesterol synthesis, which is downstream of SREBP signaling. Notably, the use of statins has been associated with reduced antibody responses to influenza vaccines[4], and individuals who take statins and are vaccinated against influenza are more likely to develop severe respiratory illness from influenza than vaccinated people who do not take statins[5]. Our findings suggest a possible mechanism by which these treatments might interfere with B cell metabolism to reduce vaccine immunity and effectiveness. By contrast, SREBP signaling can be potentially targeted to treat diseases caused by hyperactivation of humoral responses, such as certain types of autoimmunity and allergy.

In this study, SCAP deletion impairs the formation of memory compartments, probably owing to defective germinal center response, as the germinal center is the major source of these long-lived memory compartments. Further studies using mouse models with depleted SREBP signaling in established memory compartments are needed to determine how SREBP signaling may affect the maintenance and function of established memory B cells and long-lived plasma cells.

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EXPERT OPINION

"This study provides new and interesting insights into B cell biology, demonstrating that B-cell-specific deletion of SCAP, an important regulator of SREBP, does not affect the survival of resting mature B cells. In addition, the study provides a thorough analysis of metabolic reprogramming in mitogen-stimulated cells (with metabolites and transcriptome analyses), which is a good resource and can complement other published studies or be used for comparison to assess variability of these kinds of experiments across different laboratories." **Julia Jellusova, Technical University Munich, Munich, Germany.**

FIGURE

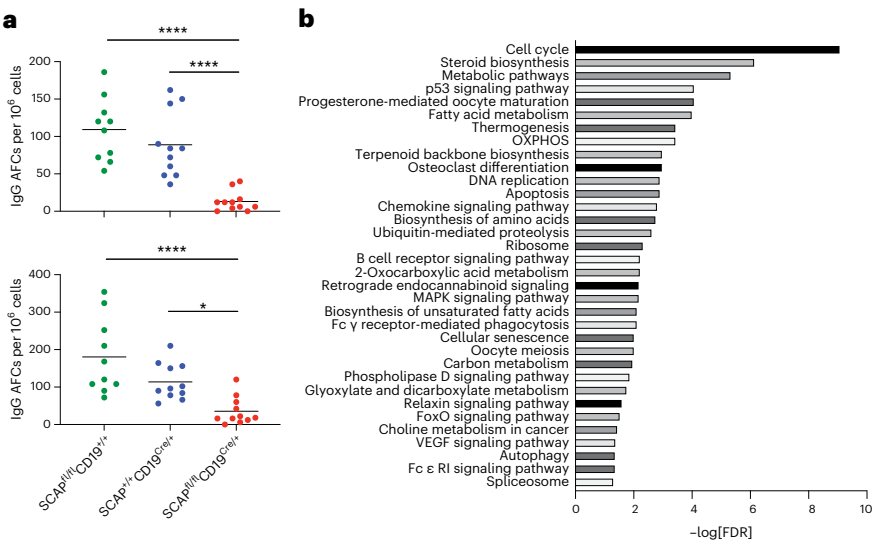

Fig. 1 | SCAP–SREBP signaling regulates several pathways to support B cell responses. a, Control mice (*Scap*$^{+/+}$*Cd19*$^{cre/+}$ and *Scap*$^{fl/fl}$*Cd19*$^{+/+}$) and mice with B-cell-specific deletion of SCAP (*Scap*$^{fl/fl}$*Cd19*$^{cre/+}$) were immunized with NP-OVA (a 4-hydroxy-3-nitrophenylacetyl hapten conjugated to ovalbumin). Two weeks after inducing memory recall responses with an NP-OVA boost, antibody-forming cells (AFCs) in the bone marrow were analyzed by ELISPOT for NP2 (top) and NP14 (bottom). Data are mean values, with each dot representing one mouse. *$P < 0.05$, ****$P < 0.0001$, one-way ANOVA followed by Tukey's multiple comparisons test. **b**, Splenic B cells from SCAP-deficient and control mice were stimulated with anti-CD40 antibody for 24 hours. RNA-seq analysis identified pathways (ranked by false discovery rate (FDR)) that were altered in SCAP-deficient B cells.

BEHIND THE PAPER

We followed up on our previous systems vaccinology study and started this project by asking which immune cell types can be affected by deficiencies in SREBP signaling. This study is the result of great teamwork. During the crucial stage of this study, the COVID-19 outbreak forced us to suspend our ongoing experiments and minimize our mouse colony. After reopening, our animal maintenance team worked extremely hard to re-establish our strains so that we could quickly continue our studies. During manuscript revision, W.L. moved to Indiana University to establish his own laboratory. We are thrilled to see that both laboratories worked together for the revision, which substantially improved the manuscript. **B.P. & W.L.**

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FROM THE EDITOR

"Sterol biosynthesis is required for CD8⁺ T cell metabolic reprogramming after activation. Here, the authors show that SCAP, a regulator of sterol biosynthesis, is needed in stimulated B cells for metabolic reprogramming, in vitro proliferation, efficient lipid raft formation and the survival of germinal center B cells in vivo." **Stephanie Houston, Senior Editor, *Nature Immunology.***