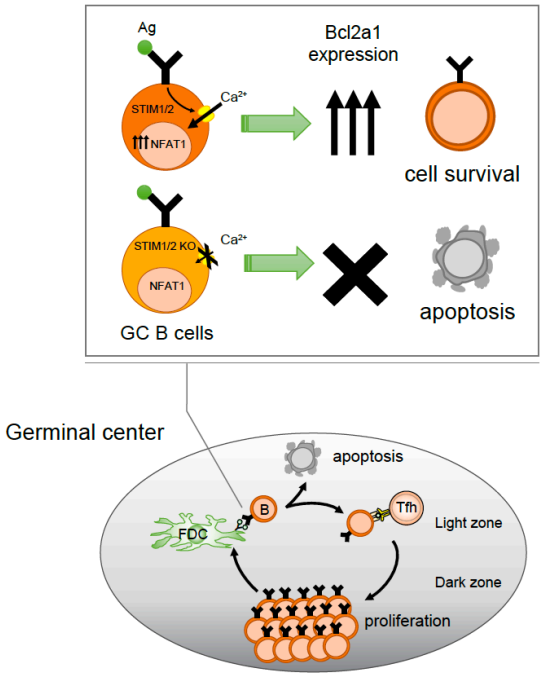
STIM-mediated calcium influx regulates maintenance and selection of germinal center B cells

Germinal centers (GCs) are specialized microenvironments where antigen (Ag)-specific B cells undergo antibody affinity maturation and clonal expansion. Positive selection of high-affinity GC B cells is driven by Ag internalization through their B cell receptor (BCR) and presentation to follicular helper T (Tfh) cells. However, the requirements of BCR signaling in GC B cells remain poorly understood. Store-operated Ca^{2+} entry, mediated by stromal interacting molecule 1 (STIM1) and STIM2, is the main Ca^{2+} influx pathway triggered by BCR engagement. Yutaro Yada, Masanori Matsumoto, Tomohiro Kurosaki, Yoshihiro Baba, and the research group showed that STIM-deficient B cells have reduced B cell competitiveness compared to wild-type B cells during GC responses. B cell-specific deletion of STIM proteins decreased the number of high-affinity B cells in the late phase of GC formation. STIM deficiency did not affect GC B cell proliferation and Ag presentation but led to the enhancement of apoptosis due to the impaired upregulation of anti-apoptotic Bcl2a1. STIM-mediated activation of NFAT was required for the expression of Bcl2a1 after BCR stimulation. These findings suggest that STIM-mediated survival signals after Ag capture regulate the optimal selection and maintenance of GC B cells.

Graphical Abstract



GCs are comprised of a dark zone where B cells undergo clonal expansion and somatic hypermutation in the immunoglobulin gene and a light zone where B cells capture Ags on follicular dendritic cells (FDCs) and present these to Tfh cells. In the light zone, high-affinity GC B cells receive a survival signal through induction of the anti-apoptotic bcl2a1 gene, which is required for NFAT activation by STIM-mediated Ca^{2+} influx upon Ag stimulation. Thus, the B cell survival after Ag recognition in GCs may promote affinity maturation by increasing the probability of receiving Tfh cell assistance.

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Authors: Yutaro Yada†, Masanori Matsumoto†, Takeshi Inoue, Akemi Baba, Ryota Higuchi, Chie Kawai, Masashi Yanagisawa, Daisuke Kitamura, Shouichi Ohga, Tomohiro Kurosaki* and Yoshihiro Baba*
(†First author, *Corresponding author)

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