

Title: PROLIFERATION AND SURVIVAL OF ACTIVATED B CELLS REQUIRES SUSTAINED ANTIGEN RECEPTOR SIGNALING AND PHOSPHOINOSITIDE 3-KINASE ACTIVATION

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Abstract

Proliferation and survival of activated B cells requires sustained antigen receptor signaling and phosphoinositide 3-kinase activation

Clonal expansion of T cells is driven by autocrine growth factors and can proceed even after brief exposure to antigen. T cell-derived growth factors and surface molecules can also promote proliferation of B cells activated via the B cell receptor (BCR). Here we investigate the extracellular and intracellular signals that drive cell cycle progression of activated primary B cells in the absence of T cell help. We find that brief engagement of the B cell receptor is sufficient to induce a single cell division, but that survival and successive cell divisions requires sustained receptor stimulation. Activation and subsequent proliferation is also partially inhibited by the addition of the Fab fragment of anti-IgM both prior to and following stimulation, further demonstrating the requirement for sustained BCR activity. Both early and late BCR signals are blocked by inhibitors of phosphoinositide 3-kinase and mammalian target of rapamycin (mTOR), and are associated with S6 kinase activation and increased cell size. The requirement for ongoing antigen receptor signaling can be overcome by engagement of CD40 but only partially by interleukin-4 (IL-4). Proliferation driven by lipopolysaccharide also requires sustained exposure to the stimulus. These findings reveal the existence of checkpoints that may limit T-independent B cell responses when antigen exposure is transient.

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