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Regulation of B cell entry into the cell cycle

EA Clark

Address: University of Washington, Department of Microbiology, Seattle, USA

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B cells are induced to enter the cell cycle by ligation of the B-cell receptor (BCR) complex and by Toll-like receptor (TLR) agonists. B-cell activation is regulated by molecules with several distinct modes of action: A first example, the adapter molecule Bam32 (B-lymphocyte adapter of 32 kDa), helps promote BCR-induced cell cycle entry, while the secondary messenger superoxide has the opposite effect. Bam32 and superoxide may fine tune BCR-induced activation by competing for the same limited resources including Rac1/2 and/or the plasma membrane phospholipid PI(3,4)P2. A second example, the BCR-associated co-receptor CD22, inhibits BCR-induced proliferation by binding to novel CD22 ligands on B cells and dendritic cells. Regulators of B-cell survival and death also influence B-cell transit through the cell cycle. Caspase 6 normally is simply classified as an effector caspase in cell death pathways; but in B cells caspase 6 negatively regulates CD40- and TLR-dependent G1 entry, in part by controlling levels of phosphorylated retinoblastoma (Rb) protein. Caspase 6 deficiency predisposes B cells to differentiate rather than proliferate after stimulation. The Bcl-2 family member, Bim, is normally classified as a 'pro-apoptotic' protein; but in B cells, it exerts a positive regulatory effect on cell cycle entry, which is opposed by Bcl-2. New insights into how B-cell transit through the cell cycle is controlled may lead to thoughtful design of drugs that selectively target pathogenic B cells.