

Inositol (1,4,5) trisphosphate 3 kinase B regulates the development, tolerance and activation of B lymphocytes.

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B cell antigen receptor (BCR) signaling regulates the development and function of B cells. Recently, we have described a novel ENU-induced mouse mutant, *Ms T less*, lacking (Itpkb), which converts inositol (1,4,5) trisphosphate (IP3) to the soluble second messenger inositol (1,3,4,5) tetrakisphosphate (IP4). Itpkb is essential for T cell development, mice lacking Itpkb display a complete block in T cell positive selection at the CD4+CD8+ double positive stage in the thymus and impaired TCR-induced Erk activation. Itpkb is also expressed in B-lymphocytes; however its role in B cell development is not known. Detailed analysis of B cell development in Itpkb null animals and mixed bone marrow chimeras revealed an incomplete block in the T2 to the mature stage of B cell development, a point of B cell positive selection. Interestingly, mature B cells present in Itpkb null animals display an anergic phenotype– they fail to proliferate and up-regulate co-stimulatory markers after sIg-crosslinking but show normal responses to stimulation with anti-CD40 or LPS. The sIg signaling defects are important in vivo, as Itpkb-null mice fail to generate an antibody response following immunization with the T-cell independent antigen TNP-Ficoll, and immunization of mixed bone marrow chimeras with the T-cell dependent antigen TNP-KLH failed to elicit activation of Itpkb null B cells. Biochemical analysis of sIg signaling of Itpkb null B cells revealed that these cells display normal activation of proximal tyrosine kinases Lyn, and Btk, but reduced phosphorylation of PLC- γ . IP3 production following receptor activation is unchanged and Itpkb null B cells show elevated Ca²⁺ influx compared to normal B cells. Defects in the activation of Erk-Mapk, protein kinase D and NF- κ B and are observed following sIg-crosslinking of Itpkb null B cells. Simulation of Itpkb null B cells with the DAG mimic PdBu was able to partially rescue the signaling and proliferation defects suggesting that lack of DAG production as a result of incomplete PLC- γ activation may account in part for the observed signaling defects. These data highlight Itpkb as a critical regulator of B cell development and activation and suggest a role for Itpkb in regulating B cell tolerance.