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**TITLE:** ENHANCED T CELL PROLIFERATION IN THE ABSENCE OF MURINE P85 $\alpha$  SUBUNIT OF PHOSPHOINOSITIDE 3-KINASE

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**Abstract:**

Phosphoinositide 3-kinase activation has been shown to be important for lymphocyte proliferation and survival. Targeting the gene that encodes the major regulatory isoform p85 $\alpha$  and its spliced variants has been shown to reduce B cell development and proliferation. However, T cells were unaffected by loss of p85 $\alpha$ . This suggested that p85 $\alpha$  might be the essential regulatory subunit for T cell activation. To test this hypothesis, mice lacking p85 $\alpha$  were studied. B cell development, proliferation, and antibody secretion were unaltered in p85 $\alpha$  knock out cells. Unexpectedly, T cells lacking p85 $\alpha$  showed a marked increase in proliferation when stimulated with anti-CD3 plus IL-2. Both CD4 and CD8 T cells completed more cell divisions and a decrease in apoptosis was observed. To discover which genes were differentially expressed we used DNA microarrays, and found lower levels of caspase-6 mRNA in p85 $\alpha$  knock out T cells. Caspase-6 enzyme activity was reduced to a similar extent in p85 $\alpha$  deficient T cells. Increased T cell accumulation was also documented *in vivo* following infection of p85 $\alpha$   $-/-$  mice with Mouse Hepatitis Virus (MHV). Together, these results suggest a unique negative role for p85 $\alpha$  in T cell signaling.