

Title: ROLE OF PHOSPHOINOSITIDE 3-KINASE p85 α IN TRANSFORMATION OF B LINEAGE CELLS BY ABL ONCOGENES

Authors: Michael G. Kharas*, Jonathan A. Deane*, Karen O'Bosky, Stephane Wong, Owen Witte and David A. Fruman

Abstract:

Two oncogenic forms of Abl tyrosine kinase, v-Abl and the 190kDa isoform of BCR-Abl, transform pre-B cells in mice. Activation of phosphoinositide 3-kinase (PI3K) has been implicated in growth and survival of cells transformed with Abl oncogenes. However, it is not clear which PI3K isoforms act downstream of v-Abl and BCR-Abl. We reported previously that mice with a disruption in the *Pik3r1* gene, encoding the class IA PI3K regulatory isoforms p85 α , p55 α and p50 α , have impaired B cell development and function. Here we show that both v-Abl and BCR-Abl can transform B lineage cells lacking *Pik3r1* gene products, though the efficiency of transformation is reduced. Transformed cell lines exhibit compensatory upregulation of other regulatory isoforms, suggesting selective pressure to maintain class IA PI3K signaling. Consistent with this, cell cycle arrest and/or apoptosis were increased in cells expressing a dominant negative p85 or PTEN phosphatase, or following treatment with a global PI3K inhibitor. These observations indicate that class IA regulatory subunits have required but redundant functions in pre-B cell transformation by Abl oncogenes