
Cancer
Cell
Volume 21
Number 4
April 17, 2012
www.cellpress.com
Visualizing Host Contribution
to Chemoresistance

CALming Down T Cell Acute Leukemia

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DOI 10.1016/j.ccr.2012.03.025

Signaling from class I phosphoinositide 3-kinase (PI3K) is often deregulated in leukemia and lymphoma, but which isoforms are involved in T cell acute lymphoblastic leukemia (T-ALL) was not known. In this issue of *Cancer Cell*, Subramaniam et al. show that T-ALL can be tamed by inhibiting γ and δ PI3K isoforms.

Class I phosphoinositide 3-kinase (PI3K) activate fundamental pathways controlling survival, proliferation, and metabolism and thus represent crucial players in cancer development. Despite activating similar signaling cascades, the four human class I PI3Ks, each of which is composed of a regulatory subunit and one of the four p110 catalytic subunits (p110α, β, γ, and δ), show non-redundant roles in oncogenesis. For example, *PIK3CA*, the gene encoding p110α, is frequently mutated in cancers originating from different organs, including the mammary gland, colon, prostate, and brain (Wong et al., 2010). On the contrary, the p110β isoform does not accumulate mutations but plays a critical role in specific tumors, such as PTEN-deficient (Jia et al., 2008) or ErbB2-driven (Ciraolo et al., 2008) cancers. Similarly, the leukocyte-specific p110δ isoform is usually intact in human cancers, yet it drives B cell malignancies including chronic lymphocytic leukemia and mantle cell lymphoma (So and Fruman, 2012).

The fourth PI3K catalytic isoform, p110γ, is mainly expressed in leukocytes, and its role in cancer is only now starting to emerge. In white blood cells, p110γ usually drives G protein coupled receptor (GPCR)-mediated responses and shapes various forms of inflammatory reactions by controlling macrophage and neutrophil migration to chemotactic cues (Ghigo et al., 2010). Similar to p110δ, p110γ is also highly expressed in B and T lymphocytes but with a role considered minor so far, probably not affecting trafficking but rather specific differentiation steps. In T cell development, p110γ and p110δ together control the β selection process, allowing thymocytes to mature to the double positive (DP) stage. In these maturation steps, p110δ is required to modulate signals that originate from the pre-T cell receptor (TCR) complex, whereas p110γ is necessary for signals that derive from CXCR4 activation (Figure 1). Deletion of *PTEN* from developing thymocytes allows an unopposed activation of both p110s, resulting in abnormal passage to the DP stage in the absence of a mature TCR as well as in the development of T cell leukemia (So and Fruman, 2012).

Despite the ability of p110γ to cause transformation when overexpressed in cultured cells (Kang et al., 2006), direct evidence for its role in human cancer was missing. The ability of PI3Kγ to activate the classical PI3K pathway, triggering AKT, GSK3, and S6K phosphorylation, was long considered a business mainly for innate immunity aficionados. Nonetheless, recent evidence indicates that PI3Kγ is a key player in the inflammatory reactions that contribute to tumor progression and spreading (Schmid et al., 2011). In addition, PI3Kγ has also been found to drive, in immunocompromised patients, angioproliferative tumors induced by the Kaposi's sarcoma-associated virus, where its oncoviral receptor vGPCR couples to PI3Kγ to induce AKT/mTOR signaling (Martin et al., 2011).

The article by Subramaniam et al. (2012) in this issue of *Cancer Cell* further extends this notion and shows that PI3Kγ functions in concert with its cousin PI3Kδ to support development of T cell acute lymphoblastic leukemia (T-ALL). How did Subramaniam et al. (2012) discover these unexpected findings? They reasoned that the PI3K/AKT signaling pathway is frequently activated in T-ALL driven by PTEN loss (found in about 40% of T-ALL patients) rather than by activating mutations of *PIK3CA* that are found commonly in solid cancers (Wong et al., 2010). Therefore, other class I PI3Ks likely were involved in T-ALL. Developing thymocytes are thought to be the normal counterpart of transformed T-ALL cells, and the activities of both PI3Kδ and PI3Kγ are required to sustain normal thymic development and thymocyte survival (So and Fruman, 2012). Thus, Subramaniam et al. (2012) set out to define the PI3K isoform involved in T-ALL by introducing null mutations in *Pik3cg* and *Pik3cd*, which encode for p110γ and p110δ respectively, in a mouse model of T-ALL induced by conditional PTEN loss in T cells. To their surprise, in strict similarity with normal T cell development, both p110δ and p110γ were necessary to sustain T-ALL development, whereas single mutants had no antitumor effect (Figure 1). Deletion of PTEN in the absence of both p110δ and p110γ was not associated with increased AKT phosphorylation, thus indicating a negligible role for the other two class I PI3K isoforms, PI3Kα and PI3Kβ, in the development of either normal T cells or leukemia.

These findings are interesting for several reasons. First, they reaffirm the concept of a strong interconnection between T cell development and T cell leukemia, similarly to other T-ALL oncogenes. For example, Notch1 plays crucial roles in T cell differentiation and is frequently mutated in T-ALL (Aifantis et al., 2008). The essential PI3Kδ and PI3Kγ signaling functions in T cell development could thus be retained and exploited by leukemic cells. Second, these results clearly show an additive role for p110δ and p110γ in T cell leukemia but

also point out for the first time a specific contribution of p110γ to the survival and growth of a hematologic malignancy. This is new, because the only PI3K isoform thought to be involved in leukemia and lymphomas so far was PI3Kδ, a direct effector of tyrosine phosphorylation events downstream of CD28 and CD19 in T and B cells, respectively. The involvement of p110δ in B cell tumors such as chronic lymphocytic leukemia has recently gained great attention, as selective inhibitors such as CAL-101 have provided encouraging results in combined phase I/II clinical trials with cases of full remission (So and Fruman, 2012). Third, these results pave the way for novel therapeutic targeting in T-ALL. Indeed, Subramaniam et al. (2012) went on to prove this point. They tested derivative compounds of CAL-101 and found that CAL-130 works as a specific dual inhibitor of p110γ and p110δ. When given to mice, CAL-130 closely reproduced the thymic phenotype of double *Pik3cg*- and *Pik3cd* null mutants. Strikingly, and more importantly, CAL-130 prolonged survival of PTEN null mice and reduced human T-ALL growth by inducing apoptosis due to a block of the AKT-mediated survival pathway. Although further experimentation and clinical trials are required to fully access the efficacy and toxicity, mice treated with the currently available compound did not show major signs of toxicity. The future possibility of treating patients with a p110γ/p110δ dual inhibitor that in principle avoids the undesirable systemic effects that may be linked to pan-PI3K inhibition, such as diabetes, is particularly attractive. Whether this approach can be widened to other T lymphomas, which may also depend on both p110γ and p110δ for their growth, or if it is effective only in PTEN-deficient T-ALL remains to be established. Future studies will likely better define the spectrum of efficacy of PI3Kδ and PI3Kγ targeting in T-ALL with different genetic defects as well as in a larger set of hematological malignancies.

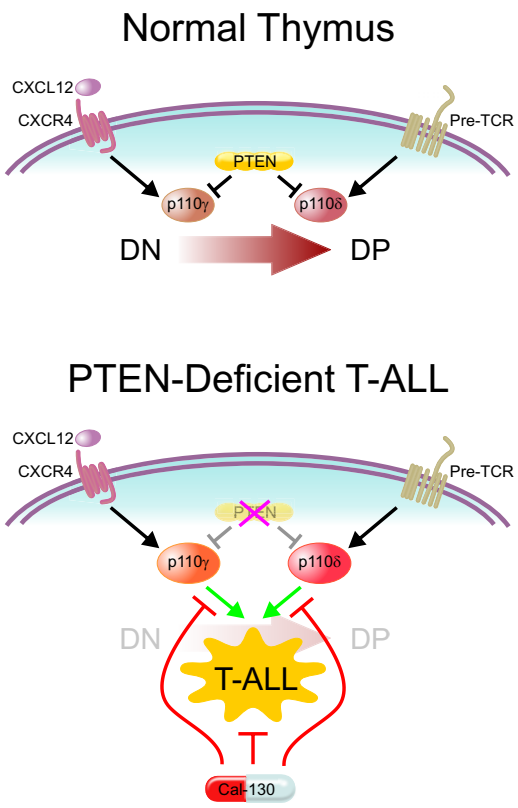

Figure 1. Role of PI3Kδ and PI3Kγ Isoforms in the Development of Normal Thymocytes and T-ALL

(Top) Signal transduction events leading to differentiation of T cells from the double negative (DN) to the double positive (DP) stage.

(Bottom) Loss of PTEN leads to unrestrained p110γ and δ activity and T-ALL. The use of the drug CAL-130 inhibits these two p110 PI3K isoforms, thus blocking T-ALL.

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