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A LIPID KINASE COUSIN COOPERATES TO PROMOTE CANCER

Brandon Beagle and David A. Fruman*

Department of Molecular Biology & Biochemistry, University of California, Irvine, Irvine, CA 92697 USA

Abstract

Phosphoinositide 3-kinases (PI3Ks) are considered promising drug targets in oncology. In this issue of *Cancer Cell*, Schmid et al. demonstrate that the PI3K γ isoform is required for inflammatory myeloid cells to traffic to tumors. Though tumor cells do not express PI3K γ selective inhibition of this isoform suppresses tumor growth and angiogenesis.

Entry of inflammatory cells into the tumor microenvironment is now considered a key feature of tumorigenesis, promoting hallmarks of cancer including angiogenesis and invasion (Hanahan and Weinberg, 2011; Mantovani and Sica, 2010). Consequently, agents targeting inflammatory cell recruitment might have therapeutic benefit in cancer while avoiding the intrinsic propensity of cancer cells to become drug-resistant. The signals that attract myeloid cells from the blood to enter tumor tissue are complex, and act through multiple distinct receptor subtypes (Figure 1). This presents a challenge for identifying a suitable target for drug development. A paper in the current issue (Schmid et al., 2011) demonstrates that diverse extracellular factors converge upon a single signaling enzyme (PI3K γ) to trigger myeloid cell adhesion to endothelial cells (ECs). Specific blockade of PI3K γ is sufficient to reduce tumor inflammation and angiogenesis, indirectly suppressing the growth of tumors *in vivo*.

The study starts by addressing the question of which integrins mediate the attachment of myeloid cells to ECs and invasion into tumors. In the experimental models used, monocyte-derived cells rather than neutrophils are the major subset of myeloid cells that populate and persist in tumor tissue (Figure 1). The tumor cells as well as resident myeloid cells secrete soluble factors that recruit additional myeloid cells, amplifying inflammation. These factors include chemokines that signal through G protein-coupled receptors (GPCRs), VEGF that activates receptor tyrosine kinases (RTKs), and cytokines such as IL-1 β that signal via the TLR/IL-1R family of receptors that are coupled to intracellular tyrosine kinases (TKs). Surprisingly, each of these diverse stimuli promoted adhesion to EC through activation of the same integrin molecule, $\alpha 4\beta 1$. This led the investigators to hypothesize that a common signaling pathway is triggered by diverse receptors on myeloid cells to increase the avidity of $\alpha 4\beta 1$, a process called “inside-out” signaling. Testing of a large panel of chemical inhibitors indicated that PI3Ks might be key intermediates in the inside-out signaling pathway.

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*Correspondence: dfruman@uci.edu.

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PI3Ks are a family of lipid kinases that phosphorylate phosphatidylinositol (PI) and its derivatives to generate 3-phosphorylated phosphoinositides (Vanhaesebroeck et al., 2010). The main product of class I PI3Ks, phosphatidylinositol-3,4,5-trisphosphate (PIP₃), initiates signaling pathways essential for cell growth, proliferation, survival and migration downstream of growth factors and oncoproteins. Two PI3K enzymes (PI3K α and PI3K δ) are primarily activated by TK-based signals. A third isoform, PI3K β , can be activated either by TKs or by GPCRs. Genetic analysis of human cancer has shown that the PI3K α isoform plays a dominant role (Figure 1). Gain-of-function mutations in the *PIK3CA* gene, which encodes the catalytic subunit PI3K α , are found in a broad spectrum of tumors, with incidence of 30–40% in some cancer subtypes (Samuels and Ericson, 2006). PI3K β and PI3K δ activity might also be important in some tumors (Ciraolo et al., 2008; Jia et al., 2008; Lannutti et al., 2011). The fourth member of the class I PI3K subgroup, PI3K γ , has received less attention as a drug target in oncology for two main reasons. First, PI3K γ is activated by GPCRs but has not been demonstrated to function in signals emanating from TKs, which are the dominant drivers of the cancer phenotype. Second, PI3K γ is mainly found in leukocytes, with few tumors showing prominent expression or function of this isoform. Hence, one would not expect selective inhibitors of PI3K γ to suppress directly the proliferation or survival of most cancer cells. Yet what if PI3K γ is integral for the function of other cells in the tumor microenvironment?

Schmid et al. provide abundant evidence to support this idea. The team used a variety of experimental approaches to assess the role of PI3K γ : knockout mice; knock-in mice with a kinase-dead mutation in PI3K γ ; selective inhibitors of PI3K γ and other isoforms; and RNAi-mediated knockdown. In each case, interfering with PI3K γ function strongly blocked the activation of integrin α 4 β 1. In addition, receptor-mediated increases in PIP₃ and phosphorylation of the PI3K effector AKT were absolutely dependent on PI3K γ and not other isoforms. The results were comparable whether the cells were stimulated through GPCRs (with the chemokines SDF-1 α or C5a), through RTKs (with growth factors VEGF or CSF-1) or via receptors linked to cytoplasmic TKs (with cytokines IL-1, IL-6 or TNF α). Further, only PI3K γ knockdown prevented myeloid cells from trafficking to tumors in mice. This indicates that whatever the mix of chemotactic factors present *in vivo*, the signal to invade the tumor requires only the PI3K γ isoform.

These results challenge the paradigm that PI3K γ functions exclusively in GPCR signaling. To lend weight to this observation, the investigators undertook a major effort to understand the biochemical mechanisms that allow the PI3K γ isoform to couple to TK-based signals. They show that treatment of myeloid cells with VEGF-A causes the cognate RTK (VEGFR1) to physically associate with PI3K γ but not other class I isoforms. They define a pathway in which RTK engagement promotes activation of the Ras GTPase, which recruits and activates PI3K γ via its regulatory subunit p87 (Figure 1). A distinct regulatory subunit, p101, plays a complementary role in activating PI3K γ downstream of GPCRs and Ras in this system. It will be interesting to see whether this division of labor is common to other leukocyte subsets. A key experiment showed that knockdown of p87 and p101 had additive effects on suppressing myeloid cell trafficking to tumors in mice. This indicates that chemotactic factors *in vivo* likely include distinct stimuli acting through TKs and GPCRs.

Suppressing PI3K γ clearly prevents accumulation of certain myeloid populations in tumors; does this have any impact on tumor growth? Schmid et al. demonstrate that transplanted and spontaneous tumors develop more slowly in PI3K γ -deficient mice. In each model, suppression of PI3K γ resulted in impaired angiogenesis. This probably results from the absence of myeloid cells that secrete angiogenic factors such as VEGF (Figure 1), rather than a defect in ECs. Indeed, bone marrow chimera experiments showed that the defective cell type in the tumor microenvironment is of hematopoietic origin. Treating mice with

selective PI3K γ inhibitors also reduced tumor growth, even though the compounds had no direct impact on cancer cell proliferation *in vitro*. A key experiment showed that PI3K γ inhibitors do not further reduce tumor growth in wild-type mice bearing PI3K γ -deficient blood cells. These results demonstrate that PI3K γ inhibitors act via a cancer cell-extrinsic manner to suppress tumor-associated inflammation and angiogenesis.

Drug discovery pipelines include a growing number of PI3K inhibitors in clinical trials for oncology, autoimmunity, allergy and other disease states (Workman et al., 2010). Until now, PI3K γ has been considered mainly as a target for inflammatory diseases such as arthritis (Ruckle et al., 2006), and the development of PI3K γ -selective compounds has been slower than other target profiles. Although the conclusions of Schmid et al. need to be validated in other models, the current data support the novel conclusion that the anti-inflammatory potential of PI3K γ inhibitors might be harnessed to disrupt the tumor microenvironment and slow the progression of cancer. The fact that most solid tumor cells do not express PI3K γ should limit the development of resistance to PI3K γ inhibitors. These considerations should increase momentum for PI3K γ inhibitor programs. To be sure, there remain challenges to developing treatments targeting cancer inflammation. Should such agents be given as preventive therapy, or will they be effective in treating established malignancies? These questions can be addressed initially through additional preclinical studies. If PI3K γ -targeted agents can limit the growth of established tumors, an important implication is that drugs targeting all class I PI3Ks (or just PI3K α and PI3K γ) should be more effective than selective PI3K α inhibitors, even in patients whose tumors are driven by *PI3KCA* mutations.

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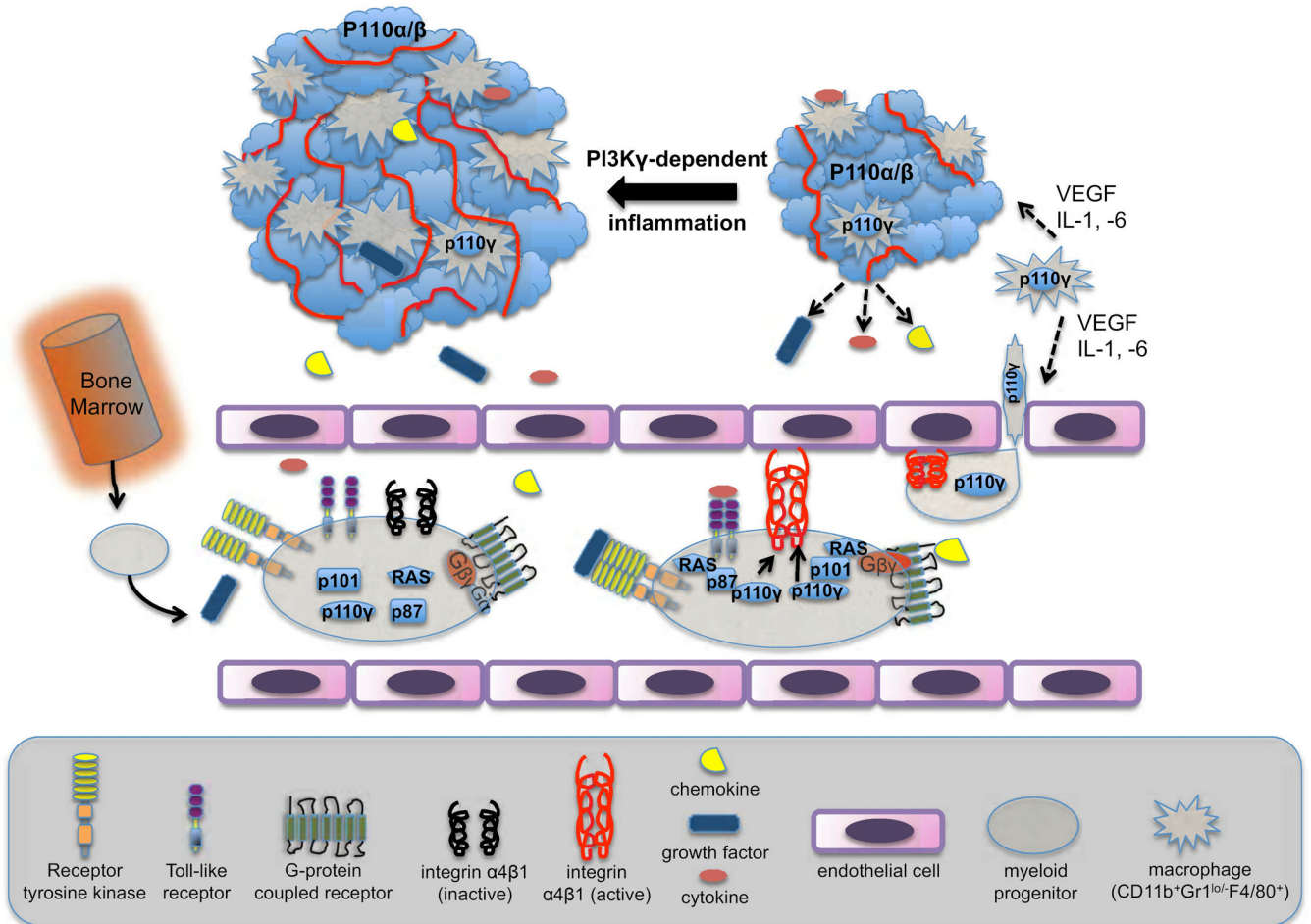


Figure 1. p110 γ in myeloid cells mediates adhesion to endothelial cells, driving tumor inflammation and progression

Bone marrow-derived myeloid cells enter tumor sites by first adhering to endothelial cells in the local vasculature. Adhesion is driven by extracellular signals that increase avidity of the integrin $\alpha 4\beta 1$. The extracellular signaling molecules are produced by both the tumor cells and local macrophages and include chemokines, growth factors and cytokines. Receptors for these diverse ligands each stimulate PI3K γ , linking to the catalytic subunit p110 γ through either the p87 or p101 regulatory subunits and through the Ras GTPase. Myeloid cells entering the tumor mature into macrophages (CD11b⁺Gr-1^{lo}F4/80⁺) that secrete a partially overlapping set of chemotactic and angiogenic factors. The inflammation associated with progressive recruitment of myeloid cells enhances tumor growth and angiogenesis.