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Truncated Title: p110 isoforms in cancer

Shidong Jia^{1,2}, Thomas M. Roberts^{1,2}, and Jean J. Zhao^{1,2,3}

¹Departments of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115 USA

²Departments of Pathology, Harvard Medical School, Boston

³Department of Surgery, Brigham and Women's Hospital, Boston, Massachusetts 02115 USA

Summary

Activation of the PI3K signaling pathway is frequently found in common human cancers, brought about by oncogenic RTKs acting upstream, PTEN loss, or activating mutations of PI3K itself. Recent studies have delineated distinct but overlapping functions in cell signaling and tumorigenesis for p110 α and p110 β , the two major catalytic subunits of PI3K expressed in the tissues of origin for the common tumor types. In most cell types studied, p110 α carries the majority of the PI3K signal in classic RTK signal transduction, while p110 β responds to GPCRs. Both p110 α and p110 β function in cellular transformation induced by alterations in components of PI3K pathway. Specifically, p110 α is essential for the signaling and growth of tumors driven by PIK3CA mutations and/or oncogenic RTKs/Ras, whereas p110 β is the major isoform in mediating PTEN-deficient tumorigenesis. While pan-PI3K inhibitors are currently being tested in the clinic, p110 isoform-specific inhibition holds forth promise as a therapeutic strategy.

Introduction

The phosphoinositide 3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate the 3'-hydroxyl group of phosphatidylinositol and phosphoinositides in response to extracellular stimuli [1–3]. These lipid products of PI3Ks act as second messengers to trigger diverse signaling cascades that mediate multiple cellular activities such as cell survival, proliferation and differentiation [1,4,5]. The PI3Ks are grouped into three classes, I, II and III, based on their structural characteristics and substrate specificity [1–3]. Of these the most commonly studied are the class I enzymes, which are activated directly by cell surface receptors. Class I PI3Ks are further divided into class IA enzymes that are activated by receptor tyrosine kinases (RTKs), G protein coupled receptors (GPCRs) and oncoproteins, and class IB enzymes that are regulated exclusively by GPCRs. To date, only class IA enzymes have been clearly implicated in human cancers. While this class of PI3K was initially identified two decades ago as an enzymatic activity associated with viral oncoproteins' transforming activity [6–9], the association of PI3K with human cancer was first made by the discovery that the tumor suppressor PTEN (phosphatase and tensin homolog deleted from chromosome 10) acts by antagonizing the lipid kinase activity of class IA PI3K in the late 1990s. Recent advances in cancer genomic technology have demonstrated that major

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Correspondence should be addressed to J.J.Z. (jean_zhao@dfci.harvard.edu).

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components within the class 1A PI3Ks, e.g. PIK3CA and PIK3R1, are frequently mutated in many common types of human cancers [10–13], placing this class of enzymes in the center stage of today's cancer research. In addition, gene-targeting and pharmacological studies have revealed that the class IA PI3K isoforms have far more distinct functions in cell signaling, metabolism, and tumorigenesis than was previously appreciated. Here we highlight recent findings with emphasis on how the two commonly expressed PI3K catalytic isoforms contribute to signaling and tumorigenesis, and discuss rational therapies that might be tailored to take advantage of isoform specificities.

Class IA PI3K isoforms

Class 1A PI3Ks are a collection of heterodimeric lipid kinases that consist of a p110 catalytic subunit and a regulatory subunit. The regulatory subunit mediates the receptor binding, activation, and localization of the PI3K enzyme [2,14]. In mammals, there are three genes, *PIK3R1*, *PIK3R2* and *PIK3R3*, encoding the p85 α (and its splicing variants p55 α and p50 α), p85 β and p55 γ regulatory subunits, collectively called p85 [1,15,16]. There are also three genes, *PIK3CA*, *PIK3CB* and *PIK3CD*, encoding highly homologous p110 catalytic isoforms, p110 α , p110 β and p110 δ , respectively. All p110s possess an N-terminal domain that interacts with p85 regulatory subunit, a Ras-binding domain (RBD), a C2 domain, a helical region and a C-terminal catalytic domain [15]. While the expression of p110 δ is largely restricted to the immune system, p110 α and p110 β are ubiquitously expressed [17,18].

In response to growth factor stimulation and the subsequent activation of RTKs, p110 catalytic subunit is recruited to the membrane via interaction of its p85 regulatory subunit with tyrosine phosphate motifs on activated growth factor receptors, or with intermediate adapter proteins such as IRS-1/2. The activated p110 catalytic subunit of PI3K primarily uses phosphatidylinositol 4,5-bisphosphate (PIP₂) as a substrate to generate phosphatidylinositol 3,4,5-trisphosphate (PIP₃). The small GTPase Ras, and more recently, GPCRs, can also couple to and activate the p110 subunit [19•,20•,21•,22]. Subsequently PIP₃ acts as a lipid second messenger promulgating signals via a high affinity interaction with pleckstrin homology (PH) domains in downstream effectors, such as serine/threonine kinases AKT and PDK1, to regulate multiple cellular processes, ultimately glucose uptake, glycogen synthesis, protein synthesis, proliferation, cell growth and survival. The tumor suppressor PTEN functionally antagonizes PI3K activity via its intrinsic lipid phosphatase activity, which reduces the cellular pool of PIP₃ by converting it back to PIP₂ [23–25].

A wealth of knowledge regarding the class IA PI3K regulation in cancer has come from systematic genetic/epigenetic analyses that have identified PI3K pathway components hijacked by cancer cells to enhance signaling through the PI3K network, including genetic or epigenetic inactivation of PTEN in brain and prostate cancers, amplification of the PIK3CA and AKT1, AKT2 and PDK1 genes in ovarian, breast and pancreatic cancers, as well as activating point mutations in *PIK3CA*, *PIK3R1* and *AKT1* in common types of human tumors [10–14,16,26,27]. The human disease phenotypes associated with activated PI3K pathway have been recapitulated in experimental models. For example, cell- or tissue-specific ablation of PTEN activates downstream signaling through AKT and induces neoplastic transformation in the mouse prostate, breast, and endometrium, etc [28–31]. PIK3CA with activating mutations and wild-type non- α class I PI3Ks are capable of acting as oncogenes in model systems [32,33•,34•,35•]. Transgenic over-expression of activated AKT1 in the murine prostate induces prostatic intraepithelial neoplasia (PIN) [36]. Thus, the PI3K-mediated signaling pathway plays a key role in fundamental cellular functions important in normal cellular homeostasis and malignant transformation.

Activating mutations in *PIK3CA*, but not *PIK3CB* are found in human cancer

During the past five years, *PIK3CA* has received a great deal of attention since the discovery that somatic missense mutations occur at high frequency in this gene in many human cancer types, including tumors of the brain, breast, colon, liver, stomach, lung, and ovary [10–13,37–39]. These mutations are largely point mutations predominantly clustered within three hotspots in helical and kinase domains: E542K, E545K and H1047R. Over-expression studies of these hotspot mutants in mammalian cells and chicken embryonic fibroblasts have confirmed them to be oncogenic gain-of-function mutations [32,33,40–42]. Though they showed lower oncogenic activity compared with the hotspot mutants, 14 out of the 15 non-hotspot mutants were also transforming, through the activation of the PI3K pathway [43]. Notably the discovery of p110 α activating mutations has important clinical implications for diagnosis, prognosis and therapy. For instance, *PIK3CA* activating mutations may provide a biomarker to predict clinical outcome, as *PIK3CA* mutations or low PTEN expression is associated with poor prognosis after trastuzumab therapy in Her2 positive breast tumors[44]. Moreover, PI3K inhibitors can rescue resistance to Her2 inhibitors [45–47].

Two recent structural studies of the p110 α /p85 α complex provide insights into the mechanisms by which hotspot mutations activate p110 α . Miled et al. [48] crystallized the p110 α ABD (aa 1-108) bound to the p85 α iSH2 domain (aa 431-600) and found that oncogenic mutations in the p110 α ABD are not at the p85 α iSH2 interface but in a polar surface patch that is a plausible docking site for other domains in the holo p110 α /p85 α complex. They also proposed, based on biochemical studies, that E545K helical domain oncogenic mutation disrupts an inhibitory charge-charge interaction with the p85 α nSH2 domain. Huang et al. [49] solved the structure between full-length p110 α and nSH2 domain of p85 α (aa 322-600) and found that many of the p110 α mutations occur at residues lying at the interfaces between p110 α and p85 α or between the kinase domain of p110 α and other domains within the catalytic subunit. Disruptions of these interactions may increase enzymatic activity. A separate cell-based genetic study found that different mechanisms underlie the hotspot mutations. Specifically, cellular transformation by the H1047R kinase domain mutant was found to depend on p85 binding while the interaction with Ras was critical for the E545K and E542K helical domain mutants [50].

In contrast to *PIK3CA*, cancer-specific mutations have not been reported in genes encoding the other class 1 PI3Ks. Although mutations in *PIK3CB* corresponding to oncogenic *PIK3CA* mutations fail to transform, over-expression studies demonstrate that wild-type or a constitutively activated version of *PIK3CB* is capable of acting as an oncogene in model systems [33,34], suggesting the oncogenic potential of *PIK3CB* amplification/overexpression found in colon cancer, glioblastoma, and endometrial cancer [51–53].

Distinct roles for p110 α and p110 β in development and cell growth

Selective knockouts in mice and p110 isoform-specific inhibitors have been valuable in delineating the functional roles for p110 α and p110 β . Traditional knockout of p110 α in mice leads to early embryonic lethality around embryonic day 9.5–10.5 [54,55]. Elegant studies with kinase-dead p110 knock-in mice have shown that the knock-in of homozygous kinase-dead p110 α (*PIK3CA*^{D933A/D933A}) causes early embryonic lethality at E10–11, whereas the heterozygous knockin yields smaller adult mice with markedly impaired insulin signaling [56]. Proliferative defects have been observed in p110 α -null embryos [54,55] and in embryos and MEFs of p110 α ^{D933A/WT} heterozygous for kinase-dead p110 α [56], indicating a kinase-dependent function for p110 α .

Knockout of p110 β also leads to early embryonic lethality at E3.5 associated with defective cell proliferation [54], as confirmed by the retarded cell growth seen in p110 β -null MEFs

[21••]. In contrast, homozygous knock-in of a kinase-dead allele of p110 β (PIK3CB^{K805R/K805R}) yields viable adult mice at roughly 50% of expected Mendelian ratios [19••]. Further, these mutant mice (PIK3CB^{K805R/K805R}) survive to adulthood [21••]. MEFs from PIK3CB^{K805R/K805R} mice proliferate normally [19••], as do p110 β -null MEFs reconstituted with a kinase-dead allele of p110 β [21••], or wild-type MEFs treated with p110 β -selective inhibitors [19••,57], suggesting that p110 β possesses a kinase-independent function in regulating cell proliferation and embryogenesis. Thus, the normal development and cell proliferation depend on the kinase activity of p110 α but probably rely largely on a scaffolding function of p110 β .

Distinct roles for p110 α and p110 β in growth factor signaling

Recent studies have shown that the p110 α isoform is the primary insulin-responsive PI3K associated with the IRS-1 complex, a key mediator of insulin, insulin-like growth factor-1 and leptin action [56••,58••]. In genetic analyses, the activation of AKT was impaired in p110 α -null MEFs upon stimulation by classical RTK ligands (EGF, insulin, IGF-1 and PDGF) [59••], and in fat and muscle tissue lysates of p110 α kinase dead knock-in mice in response to insulin [56••]. In pharmacological analyses, p110 α inhibitors blocked insulin mediated activation of AKT in myotubes and adipocytes [58••]. Furthermore, disruption of the interaction of p110 α with Ras selectively attenuated PI3K pathway signaling and cell proliferation stimulated by certain growth factors such as EGF but not PDGF [60••]. MEFs in which p110 β is ablated or replaced by a kinase-dead alleles of p110 β respond normally to growth factor stimulation via RTKs [19••,20••,21••]. Though there is a faster decline of insulin-evoked AKT activation in wild-type livers after treatment with a p110 β inhibitor for 30 or 60 minutes [19••], no significant change in AKT phosphorylation is observed after insulin challenge in livers lacking p110 β compared with wild type controls [21••]. This unexpected result is consistent with previous finding that p110 β has only a minor function in insulin signaling [56,58]. Instead, p110 β catalytic activity is actually required for AKT activation in response to GPCR ligands as demonstrated in multiple cell types by p110 β -specific pharmacological inhibition [19••,20••,58••], in murine cell types with p110 β ablation [20••,21••], or in MEFs with a p110 β kinase-dead allele knock-in [19••]. Knockdown of p110 β also attenuated LPA induced AKT activation in RAW 264.7 murine macrophage cells [61]. Thus, p110 α appears to carry the majority of the PI3K signal in classic RTK signaling whereas p110 β responds to GPCRs (Figure 1).

However, there is also evidence for functional redundancy or cooperation of class IA PI3K isoforms in insulin signaling under certain circumstances. Using HepG2 hepatoma cells, one study showed that p110 β inhibition by TGX-221 decreased insulin-stimulated Akt activation [19••], while a second study suggested that p110 α is required but is not sufficient to mediate insulin signaling; the combinational inhibition of p110 α /p110 β or p110 α /p110 δ , but not inhibition of p110 α alone, attenuated insulin signaling [62]. In J774.2 macrophage cells, insulin mediated activation of AKT was inhibited to a similar extent by inhibitors of p110 α , p110 β or p110 δ [62]. Notably, both cell lines express high levels of p110 β and p110 δ but low levels of p110 α [62].

It is possible that the apparently contradictory data on the potential role of p110 β in RTK signaling can be explained by the relatively weak kinase activity of p110 β and the relative strengths of the signals being studied (Figure 1). The specific lipid kinase activity of p110 β is significantly lower than that of p110 α [63]. Thus, in a cell with equal amounts of the two enzymes, only a small proportion of a moderate signal would be borne by p110 β , and knockout of p110 α would result in significant reduction in signal, roughly what is seen in p110 α KO MEFs responding to EGF and IGF/insulin [59••]. Signals from abundant receptors such as PDGFR, might actually still enough to fully activate AKT by activating

p110 β alone, even in the absence of p110 α [59••] (Figure 1). In cells where p110 β is present in sufficient excess of p110 α , the same logic would allow p110 β to carry a significant portion of the RTK signal.

Differing requirements for PIK3CA and PIK3CB in murine cancer models driven by oncogenic RTKs, Ras, and PI3K

Mutations are found in either one of various RTKs and/or in their proximal downstream signaling components including Ras, Raf and PI3K signaling pathways in most human cancers [16,64,65]. Data from a variety of experiments suggest that p110 α and, in some cases, p110 β perform a necessary role in oncogenic signaling from mutated RTKs and Ras (Figure 2). In fact, MEFs lacking p110 α are resistant to oncogenic transformation induced by oncogenic RTKs (IGF1-R, Her2/Neu, EGFR-L858R), oncogenic Ras or the viral oncoprotein termed polyomavirus middle T antigen (MT) [59••,66]. In Hs578t human breast cancer cells which express a mutant HRas but carrying wild-type PIK3CA and PTEN, inhibitors of p110 α but not p110 β block PI3K signaling, although they do not affect cell proliferation [67]. In Ras-driven mouse cancer models, knock in experiments have demonstrated that the direct binding of p110 α to Ras is required for an oncogenic allele of KRas to induce lung tumorigenesis and for formation of a skin carcinoma arising from a mutagen known to induce HRas mutations [60••].

p110 β can also function in response to oncogenic RTKs. Ablation of p110 β renders MEFs resistant to focus formation induced by HRas-G12V and EGFR-del mutants [21••]. A kinase-dead p110 β construct largely restored focus formation in p110 β -null MEFs, suggesting that p110 β was acting in part via a kinase independent mechanism in this assay, perhaps by rendering the cells less sensitive to oncogene induced stress [21••]. In a murine breast cancer model induced by the ERBB2, an RTK that signals through p110 α , tumor formation was partially blocked in the p110 β kinase dead knock-in animals, which showed fewer and smaller tumors than control mice [19••]. Thus, the kinase activity of p110 α and p110 β can contribute to cellular transformation and tumorigenesis downstream of RTKs (Figure 2). It remains interesting to explore the isoform redundancy considering the residual lesions in these tumor models.

Human tumors harboring oncogenic RTKs, Ras, and PI3K may be dependent on p110 α

Clearly p110 α is an obvious target in tumors driven by activating PIK3CA mutations. For example, p110 α isoform-specific inhibitors are most effective at inhibiting downstream PI3K signaling in a panel of breast cancer cells with mutant p110 α (MCF7, BT474, BT20, and BT47D etc) [67]. In medulloblastoma cells that feature over-expression of wild type p110 α , targeting p110 α isoform inhibits tumor cell proliferation, chemoresistance, and migration [68]. BEZ235, a dual inhibitor of PI3K/mTOR, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations [35••,69].

Recent study shows that tumors with mutant p110 α often possess mutations or alterations in other components of the PI3K pathway, such as Ras, ERBB2/ERBB3 or, in some cases, PTEN [38,70•,71]. PIK3CA mutations are found to be a late-stage event and occur almost exclusively in invasive tumors, whereas upstream mutations occur as frequently in early-stage and late-stage tumors. Additional mutations of PIK3CA augment the weak PI3K signaling activated by mutant Ras and PTEN, thus efficiently enhance oncogenic transformation [70•]. Pharmacological inhibition and knockdown studies show that signaling to downstream elements such as AKT is mediated by p110 α in breast, colon, and endometrial cancers with PIK3CA mutations and coexisting Ras, ERBB2/ERBB3, or PTEN

mutations [70•]. In agreement, in colon cancer cell lines (HCT116 and DLD1) harboring both mutant p110 α and KRas, somatic cell knockout [42] or shRNA-mediated inducible knockdown [72•] of p110 α inhibits downstream PI3K signaling, cell growth and transformation, and the maintenance of tumor xenograft.

Formation of PTEN-deficient murine and human tumors is often dependent on p110 β

Despite the surprisingly high rates of activating mutations in PIK3CA, loss of the PTEN lipid phosphatase still appears to be the most common mechanism of activation of the PI3K pathway in human cancers. The frequent activation of p110 α in human cancers and the negative regulation of PI3K by PTEN led to the general expectation that p110 α would be the major oncogenic driver downstream of PTEN loss.

Notably, in a mouse prostate tumor model driven by PTEN deficiency, ablation of p110 α has no effect on tumorigenesis [21••]. In contrast, p110 β ablation sufficiently inhibits the tumor formation in anterior prostates accompanied by concomitant diminution of AKT activation [21••]. Cell culture-based studies confirmed and extended this finding to other types of human cancer cell lines. For example, in PTEN-deficient human cancer cell lines (PC-3, U87MG, BT549) that represent three major cancer types (prostate, brain, and breast), knock-down of p110 β , but not p110 α , inhibits downstream activation of AKT, cell transformation, and the growth of PTEN-deficient cells and tumor xenografts [72•]. Similarly, down-regulation of p110 β suppresses the signaling and cell growth in PTEN-deficient glioma cells U251 [73]. Genetic studies have suggested that the kinase activity of p110 β is essential in cellular transformation caused by PTEN loss. For example, adding back a kinase-dead p110 β , but not its wild-type counterpart, impaired focus formation in PTEN-deficient PC3 cells depleted for endogenous p110 β [72•]. Further support for this idea comes from pharmacological studies using the p110 isoform-selective inhibitors in aforementioned PTEN-null cells [72•] and in PTEN-deficient breast and endometrial cancer cells [67,70•]. These studies demonstrate that PTEN-deficient tumor cells depend on p110 β and its catalytic activity for signaling and growth (Figure 3).

Though a number of recent studies have shown that p110 β plays a key role in transformation driven by loss of PTEN, it is likely that this reliance is dependent on the signaling input and genetic context of the tumor, factors that may not have been fully taken into account in the aforementioned experimental models. A case in point is the A2780 ovarian cancer cell line [72•] and five endometrial cancer cell lines [70•] which feature mutations in both PTEN and PIK3CA. In these cells, down-regulation of p110 α activity, but not p110 β activity, results in PI3K pathway inactivation and cell growth inhibition. In addition, recent study showed that a broad range of glioma cell lines, including cells carrying PTEN mutation, were sensitive to a dual p110 α /mTOR inhibitor [74]. It is perhaps best to consider PTEN as the brake that modulates PI3K signaling. In a given tumor driven by PTEN loss, the most relevant question in determining p110 isoform dependence is what receptors are providing the (weak) input signals that are amplified by loss of PTEN. If these signals arise from a GPCR, then p110 β will be the major isoform carrying the load. On the other hand, if stronger signals come from coexisting mutant RTKs, Ras or p110 α , which potentiate the total PI3K activity caused by PTEN loss, then the isoform dependency may be switched to p110 α (Figure 3). Thus, since the loss of PTEN presents an obvious target for therapeutic intervention in many tumor types, complexities in signaling regulation pose substantial challenges in therapeutic design and call for more detailed studies in a wider range of human cancer types.

PIK3CA in vascular development and tumor angiogenesis

Genetically engineered mouse models lacking PI3K catalytic subunits (p110 α , p110 β , p110 δ) have been used to probe p110-isoform selectivity in endothelial PI3K signaling, demonstrating that p110 α , but not p110 β/δ , exerts endothelial cell-autonomous functions by regulating endothelial cell migration during vascular development [75•]. Consistent with the known protective function of the p85 adaptor in stabilizing p110 catalytic subunits, mice lacking PI3K regulatory subunits (p85 α , p85 β , p55 α , p55 β) exhibited localized vascular abnormalities and showed decreased tumorigenesis [76•]. Interestingly, the mice expressing a p110 α mutant allele lacking the ability to interact with endogenous Ras display defective development of the lymphatic vasculature, resulting from defective signaling from VEGF-C to PI3K in lymphatic endothelial cells [60•]. Accordingly, PI3K inhibitors have been found to block tumor growth not only by targeting tumor cells but also via their effects on tumor vasculature as well [76•,77,78]. Thus, inhibition of class IA PI3K is a double-edged sword, targeting both tumor cells and the tumor's neovascular network.

Conclusions: Therapeutic potential of p110 isoform-specific inhibition in cancer

Encouraging data from the aforementioned studies have shown that PI3K inhibition can block the growth of tumors activated by oncogenic RTKs, p110 α mutants, and/or PTEN loss of function. However, early broad-spectrum PI3K inhibitors such as LY294002 or wortmannin often cause obvious side effects in insulin signaling and immune response, etc. More recent pan PI3K inhibitors have proved much less toxic in animal studies and in early human trials. However if PI3K inhibitors must be given for prolonged periods to be effective, as is the case for some tyrosine kinase inhibitors such as Glivec, there may be benefits in generating more selective agents. Recent advances in understanding the diverse roles of PI3K-p110 isoforms in cancer may hasten the development of p110 isoform-specific therapeutics with minimal side effects.

By targeting single isoforms potential drugs might avoid toxicity to the immune system, which is largely dependent on p110 δ and p110 γ for function. Similarly, since p110 α and p110 β seem to have independent roles in insulin responses and energy metabolism it is possible that a drug aimed at either one would have fewer side-effects than a compound that inhibits both. As we have seen above both p110 α and p110 β might be quality targets in particular tumor types. Thus p110 α plays an important role in cellular transformation and tumorigenesis induced by oncogenic RTKs and Ras [42,59•,60•,67–69,70•,72•]. Hence compounds targeting p110 α may work well in tumors featuring these lesions. Since RTK signals can also be dependent on p110 β in certain cases, it may be necessary to inhibit it as well in these tumors. In the case of Ras, recent data suggest that, although PI3K ablation will stop tumors from developing, a combination of PI3K and Raf pathway inhibition may be required to attack established tumors [35•]. Drugs targeting p110 α would also be expected to target the tumor vasculature, a tactic which has been found to be particularly effective in renal tumors among others. PTEN is now thought to be the second most commonly mutated tumor suppressor in humans, after p53. Recent studies show that p110 β is the dominant isoform carrying PI3K activity in PTEN-deficient tumors of brain, breast and prostate and endometrium [21•,53,67,70•,72•,73]. Thus p110 β inhibitors could be of use in these tumor types. Since p110 β may play a smaller role in insulin responses, it is possible that this class of compounds could show relatively few side effects.

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References and recommended reading

(Annotated references MUST be from the past two years, and the annotation should provide a brief description of the major findings and the importance of the study.)

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Figure 1.

Distinct roles for p110α and p110β in signaling.

p110α appears to be the major effector in classic RTK signaling whereas p110β responds to GPCRs. In a cell with equal amounts of the two enzymes, p110α carries the majority of the PI3K signal upon stimulation by EGF and IGF/insulin. Stronger signals such as PDGF are able to saturate AKT by activating either p110α or p110β.

EGF, epidermal growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor.

Figure 2.

p110 isoform-specific inhibition in treating tumors driven by oncogenic RTKs and Ras. Inhibitors of p110α and p110β will help block tumorigenesis induced by oncogenic RTKs (left part). A p110α-specific inhibitor will be useful to tumors driven by p110α mutants (not shown) and Ras (right part).

Figure 3.

p110 isoform-specific inhibition in treating PTEN-deficient tumors.

In a given tumor driven by PTEN loss, the p110 isoform dependence may be determined by input signals which are amplified by loss of PTEN. If these signals arise from a GPCR, then p110β will be the major isoform carrying the load. When the signals activating the PI3K pathway come from coexisting oncogenic components e.g. RTKs, Ras or activating mutants of p110α (*RTKs, *Ras, *p110α), then p110α takes command.