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Targeting the PI3K pathway for cancer therapy

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Abstract

The PI3K pathway plays an important role in key cellular functions such as cell growth, proliferation and survival. Genetic and epigenetic alterations in different pathway components lead to aberrant pathway activation and have been observed in high frequencies in various tumor types. Consequently, significant effort has been made to develop antineoplastic agents targeting different nodes in this pathway. Additionally, PI3K pathway status may have predictive and prognostic implications, and may contribute to drug resistance in tumor cells. This article provides an overview of our current knowledge of the PI3K pathway with an emphasis on its application in cancer treatment.

In the late 1980s, **PI3K** was discovered as a key enzyme required for oncogenic transformation of normal cells by oncoviruses [1–3]. Since then, extensive research on this kinase family has resulted not only in identification of its members and their function, but also in recognition of the PI3K pathway and its role in health and disease [4,5]. Specifically, the PI3K pathway plays a role in a wide range of key cellular functions such as cell growth, proliferation and survival. Additionally, aberrant activation of the PI3K pathway has been observed with high frequency in human malignancies and may result from somatic mutation, gene amplification or epigenetic alteration in various pathway elements [4]. These observations suggest a significant role for the PI3K pathway in tumorigenesis, cancer progression and treatment resistance. Consequently, significant efforts have been made to develop antineoplastic agents targeting different nodes in the pathway. In the past, similar strategies have improved clinical outcomes: for example, erlotinib in *EGFR*-mutated lung adenocarcinoma and trastuzumab in HER2/neu-positive breast cancer. Considering the high frequency of aberrant PI3K pathway activation in various tumor types, interventions targeting this pathway could be utilized in even larger patient populations and across a broad

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spectrum of malignancies. PI3K pathway status may also provide important predictive and prognostic information to guide therapy.

This article provides an overview of the structure and function of PI3Ks, key pathway components and aberrant pathway activation in cancer. PI3K isoforms, pathway status as a predictive and prognostic biomarker, and pathway molecular crosstalk are also discussed. Finally, a brief review of drugs targeting the PI3K pathway currently in clinical testing is provided.

Classification of PI3Ks

PI3Ks are a family of kinases that phosphorylate inositol-containing lipids (phosphatidylinositols; PIs) in the D-3 ring position. PI3Ks are classified, based on their structural features, into three classes. The different PI3K classes show distinct substrate preference *in vitro* and *in vivo* (Table 1) [6].

Class I PI3Ks are heterodimers with a regulatory and a catalytic subunit. They are traditionally divided into class IA and IB [4,7]. The catalytic subunit of class IA PI3K has a number of isoforms: p110α, p110β and p110δ. p37δ is a recently described isoform that results from alternative splicing of the *PIK3CD* gene transcript [8]. In contrast, p110γ is the only catalytic subunit isoform in class IB [4,9]. Normal tissues ubiquitously express p110α and p110β; p110δ and p110γ are highly expressed in leukocytes [10–12]. The most prominent role in cancer has thus far been attributed to p110α, encoded by the *PIK3CA* gene, which has been found to be amplified or mutated in a wide range of solid tumors.

The regulatory subunit in class IA includes p85α, p85β and p55γ. Alternative transcription initiation sites in the gene encoding p85α results in two other isoforms: p55α and p50α [4]. The regulatory subunits of PI3K class IB are p101 and p87 (also known as p84 or $p87^{PIKAP}$) [13,14].

Class II PI3Ks only have a catalytic subunit with significant sequence homology to that of PI3K class I (p110) [15]. This class appears to be involved in membrane trafficking and receptor internalization [16].

Class III consists of a single member, Vps34 catalytic subunit, which is regulated by p150 [17]. Vps34 is implicated in several key cellular functions including protein sorting [18], phagosome formation and maturation [19], regulation of mTOR in response to availability of amino acids [20,21] and autophagy [22,23].

Mechanism of PI3K class I activation

The three major mechanisms of activation of class I PI3Ks include **RTKs**, the GTPase Ras and G protein-coupled receptors (GPCRs).

RTKs

The regulatory subunit in class IA is composed of a p110-binding domain flanked by two SRC-homology 2 (SH2) domains. The SH2 domains of p85 bind to the phosphotyrosine

residues in the pY-xx-M context on activated RTKs, or the adaptor molecules. In turn, this relieves the inhibitory effect of p85 on p110 and results in its activation. There are other domains (e.g., SH3 and BCR homology domain) and distinct structural variations (e.g., N-terminal) in the regulatory subunit isoforms, which may provide alternate activation mechanisms [24].

Ras

Ras has a role in activation of both class IA and IB PI3Ks. All p110 isoforms contain a Ras-binding domain, which facilitates activation of the catalytic subunit [25–28], although the role of Ras in activation of p110β is controversial [27,29,30]. The ras–p110α interaction seems to be important for Ras-mediated tumorigenesis [25]. The p85 regulatory subunit can inhibit Ras-mediated activation [31]. Ras may also function as a coregulator of class IB PI3K [14].

GPCRs

GPCRs provide an important mechanism for PI3K activation. Directly, the Gβγ subunit activates p110β and p110γ isoforms [32,33]. GPCRs may also activate PI3K indirectly by activating tyrosine kinases and Ras.

Other mechanisms of PI3K activation, such as through small GTPases other than Ras, have been described and are the subject of ongoing research [24,34–36].

Once activated, p110 phosphorylates $PI(4,5)P_2$ to produce $PI(3,4,5)P_3$. This reaction is reversed by the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), which functions as a tumor suppressor. Phosphatidylinositols phosphate $(PIP)_3$ is the principal secondary messenger in the PI3K pathway. There is evidence that PI3K signaling through PIP_3 can be modulated by 5-phosphatases [37]. Recent data show that $PI(3,4)P_2$ may also have a role in signal transduction. PIP_2 is inhibited by inositol polyphosphate 4-phosphatase type II, which hydrolyzes $PI(3,4)P_2$ in the D-4 position [38–40].

PIP_3 recruits proteins with Pleckstrin homology domains, including PDK-1 and serine threonine kinase AKT (also known as PBK), to the cell membrane. PDK-1 phosphorylates AKT at its Thr-308 site. Phosphorylation of Ser-473 occurs through mTORC2 [41]. Activation of AKT results in a myriad of downstream signaling affecting cellular growth, proliferation and survival.

PI3K catalytic unit isoforms

Despite similar catalytic activity, p110 isoforms have nonredundant functions [42–45]. As an example, experiments in mice expressing a kinase-dead version of the endogenous PI3K p110α show an isoform-selective role for p110α in insulin signaling [46]. p110α and p110β catalytic units are expressed in all cells; however, p110δ and p110γ are highly expressed in leukocytes [10–12]. Loss of p110α and p110β in knock-out mice has been shown to be lethal during early embryonic phase [47,48]; in contrast, genetic inactivation of p110γ and p110δ results in defective immune responses [49–52].

It is not clear whether different regulatory and catalytic isoforms bind to each other preferentially. Although evidence suggests differential binding of regulatory subunits to receptors [53], recent data show that persistent inhibition of selected PI3K isoforms in normal cells can allow the remaining isoforms to couple to upstream signaling pathways in which they are not normally engaged [7,54].

p110α has been widely implicated in carcinogenesis, mainly due to frequent mutations and amplification of *PIK3CA* in different cancers (Table 2). Despite lack of such mutations among non-α p110s, there is emerging evidence of their role in a multitude of malignancies [11]. In a prostate cancer cell line, knockdown of p110β has been shown to suppress downstream effectors of the PI3K pathway [55]. Increased activity and expression of p110β has also been observed in tumor biopsies of human colon and bladder cancers [56]. Upregulation of p110γ and over-expression of p110δ has been reported in Chronic and acute myeloid leukemia, respectively [57,58].

Downstream effects of PI3K activation

Biological consequences of PI3K pathway activation can be divided into the following categories: cell growth and metabolism; cell survival; proliferation; angiogenesis; and invasion and metastasis (Figure1). Pathway functions independent of the catalytic activity of PI3K enzyme [24,46] and independent of AKT [59] have also been described and are beyond the scope of this review.

Cell growth & metabolism

Regulation of cell growth is mediated through AKT–mTOR interaction. Phosphorylation of TSC2 by AKT inhibits inactivation of rheb through the rheb-GTPase function of the TSC1–TSC2 complex. Rheb is the proximal activator of mTORC1 [60,61]. Downstream targets of mTORC1 include S6K and 4EBP1. S6K (p70 S6 kinase), which promotes protein synthesis and is activated by mTORC1. mTORC1 inhibits 4EBP1, a negative regulator of protein synthesis. The overall result of mTORC1 activation is increased protein synthesis and cell growth [62]. It should also be noted that S6K negatively regulates the PI3K pathway by inhibiting RTK-mediated pathway activation [63,64].

The PI3K pathway is also involved in mediation of insulin signal transduction. Specifically, AKT activation downstream of PI3K enhances cellular glucose uptake by promoting translocation of GLUT4 to the cell membrane [65]. Metabolic consequences of PI3K pathway inhibition, such as abnormal glucose homeostasis and hyperlipidemia, have been well documented in preclinical models and have been observed in human clinical studies [46,66,67].

Cell survival

Survival is mediated through several mechanisms: inhibition of FOXO (members of the winged helix or forkhead family of transcription factors) [68,69]; activation of NF-κB [69,70]; phosphorylation of MDM2, a negative regulator of p53 [71–73]; and inhibition of pro-apoptotic BCL-2 family protein, BAX [74]. BAD, another pro-apoptotic member of

BCL-2 family, was initially thought to be a key target of AKT [75,76], but subsequent studies did not support a major role for it [69,77,78].

Proliferation

Although AKT was originally recognized as a survival kinase, it also promotes cell proliferation. Cyclin D-1 is a cell cycle regulator and is involved in G1 to S phase progression. GSK3β phosphorylates cyclin D-1, resulting in its nuclear export and eventual degradation in the cytoplasm. AKT inhibits the kinase activity of GSK3β via phosphorylation, thereby promoting cell proliferation [79]. AKT also downregulates cyclin-dependent kinase inhibitors KIP1 and CIP1 (p27 and p21), thus promoting cell proliferation [80,81].

Angiogenesis

In animal models, the PI3K pathway has been shown to play a key role in physiologic and pathologic angiogenesis [82,83]. In tumors, pro-angiogenic effects of the PI3K pathway are conferred through HIF-1 and VEGF. HIF-1 is a heterodimer with α and β subunits and is an activator of VEGF transcription [84]. PI3K pathway activation results in HIF-1α upregulation and expression of VEGF [85]. Additionally, recent data suggest a HIF-1α-independent pathway for PI3K-mediated VEGF upregulation [86]. In preclinical studies, pathway inhibition by LY294002 (a PI3K inhibitor) or rapamycin (an mTOR inhibitor) has been shown to suppress HIF-1α and VEGF [82,85]. Reduction in eIF4E (a transcription factor downstream of mTOR) using antisense RNA to eIF4E has been shown to decrease VEGF expression in head and neck squamous cell cancer cell lines [87]. While these observations suggest that HIF-1α activation occurs downstream of mTOR and might be mediated through eIF4E, an mTOR-independent mechanism has also been suggested [88]. Phosphorylation and activation of endothelial nitric oxide synthase by AKT is another mechanism by which the PI3K pathway is involved in angiogenesis [89].

Invasion & metastasis

In cancer cell lines, activation of the PI3K pathway has been shown to promote invasion through upregulation of MMP-9 [90–92]. NF-κB is thought to mediate the effect of AKT activation on MMP-9 [90]. More recently, mTOR has been shown to play a regulatory role in migration, invasion and epithelial–mesenchymal transition in colon cancer through RhoA and Rac1 [93]. RhoA and Rac1 are small GTPases involved in actin cytoskeletal rearrangement and cell migration [94,95]. Early studies suggest that PI3K pathway inhibition at the level of AKT or mTOR could result in suppression of tumor migration and metastasis [93,96].

Aberrant pathway activation in cancer

Aberrant PI3K pathway activation has been shown in various malignancies. Pathway activation can arise from aberrant upstream signaling, such as *EGFR* mutations in non-small-cell lung cancer (NSCLC) [97]. Alternatively, somatic mutations, amplification or epigenetic alterations of various pathway components may also lead to pathway activation.

Gain-of-function mutations of *PIK3CA* are common in various malignancies. The majority (>80%) of these mutations are missense mutations that occur in three specific hotspots [98–100]. *PIK3CA* mutations have been observed with high frequency in breast (26%), endometrial (26%) and colon cancers (13%) [201]. Such activating mutations have not been observed in non-α isoforms. Over-expression of non-α isoforms in cell cultures, however, has been shown to induce oncogenic transformation [30]. It has been postulated that lack of cancer-specific mutations in the non-α p110s may reflect their inherent oncogenic potential [101]. Pathway activation may also result from *PIK3CA* gene amplification, an aberration observed with high frequency in squamous cell carcinoma of the lung (43% in one study [102]), as well as many other malignancies (Table 2).

Inactivation of PTEN leads to unopposed phosphorylation of PIP_2 to PIP_3 and downstream pathway activation. PTEN inactivation can be due to germ-line mutation (as occurs in Cowden syndrome), epigenetic silencing through promoter hypermethylation or loss of heterozygosity. Low PTEN expression has been reported in two-thirds of ERBB2 (HER2)-positive breast cancer through promoter hypermethylation [103]. Other pathway components such as *PIK3R1* and various isoforms of AKT and PDK1 have not been studied to the same extent as PTEN and *PIK3CA*; however, genetic aberrancy of these components has also been reported. Table 2 summarizes known PI3K pathway alterations in human cancers.

Significance of molecular crosstalk

There is a significant degree of molecular crosstalk between cellular signal transduction pathways. This crosstalk is a potential mechanism for resistance to therapies that target a single step in a specific pathway. While a detailed review of molecular crosstalk between PI3K and other pathways – such as MAPK [104], NOTCH [105,106], Wnt [106] and JNK [107] – is beyond the scope of this review, selected examples are provided to reflect its significance and clinical implications.

MAPK pathway

Crosstalk between MAPK and PI3K pathways can occur at different levels [104]. Ras activates both Raf and PI3K. In addition, TSC2 can be phosphorylated by either AKT in the PI3K pathway or ERK in the MAPK pathway, leading to activation of mTOR [108]. Therefore, inhibitors of the two pathways may have synergistic effects and minimize the risk of resistance; such strategies are currently under investigation in a Phase II trial (NCT01363232) [202].

Estrogen receptor

Crosstalk between the estrogen receptor and PI3K pathways is of particular importance in breast cancer. Ligand (estrogen)-independent activation of estrogen receptor α through the PI3K/AKT pathway may result in resistance to antiestrogen therapies [109,110]. Inhibition of mTOR, however, has been shown to restore sensitivity to hormonal therapy in breast cancer cell lines with AKT upregulation [111,112]. A Phase II study of the aromatase inhibitor letrozole with or without the mTOR inhibitor everolimus as neo-adjuvant treatment for hormone receptor-positive breast cancer has shown improvement in clinical responses

[113]. Further studies are required to establish the clinical benefit and to determine the optimal settings for application of such strategies.

PI3K pathway components as predictive & prognostic biomarkers

Over the past several years, significant effort has been made to identify biomarkers to guide cancer therapy. Predictive biomarkers provide information regarding treatment outcomes (e.g., umor response and toxicities). In comparison, prognostic biomarkers reflect the natural history of the disease and help to risk-stratify patients. Some biomarkers may be both prognostic and predictive, such as HER2/neu status in breast cancer and *KRAS* status in colorectal cancer. Because aberrant activation of the PI3K pathway occurs frequently in various malignancies, the value of PI3K pathway components as predictive and prognostic biomarkers has been a focus of multiple studies.

In HER2-positive breast cancer, activation of the PI3K pathway, determined by low PTEN expression or *PIK3CA* mutation, has been shown to be associated with resistance to the anti-HER2 monoclonal antibody, trastuzumab [114–116]. However, the effect of PTEN status on treatment outcomes with the EGFR/HER2 tyrosine kinase inhibitor lapatinib is less clear [117,118]. *PIK3CA* mutations have variable prognostic significance in breast cancer [119]. PTEN status has also been reported to predict disease recurrence in node-negative breast cancer [120]. In ovarian cancer, *PIK3CA* amplification has been associated with shorter survival [121] and resistance to cytotoxic chemotherapy [122]. *PIK3CA* amplification is also associated with poor prognosis in endometrial carcinoma [123]. Exon 20 *PIK3CA* mutation is a negative prognostic factor in stage III colon cancer patients [124]. Additionally, *PIK3CA* mutation has been associated with shorter overall survival and time to progression in stage IV NSCLC patients treated with EGFR tyrosine kinase inhibitors and may reflect resistance to therapy [125]. PTEN loss has been observed in *EGFR* mutated NSCLC and may confer resistance to erlotinib [126]. Genetic variation (single nucleotide polymorphisms) in several pathway components has been reported to predict toxicity and distant progression in patients with NSCLC treated with a platinum-based regimen [127]. It has been postulated that single nucleotide polymorphisms leading to downregulation of the pathway render normal cells more susceptible to chemotherapy and hence are associated with increased toxicities. Also, in NSCLC, AKT phosphorylation has been reported to be a poor prognostic factor [128]. PI3K pathway status may also have implications in radiation resistance [129].

Pathway interruption: the PI3K pathway as a drug target

Table 3 summarizes drugs targeting the PI3K pathway currently in clinical testing.

Pan-PI3K inhibitors

Inhibitors of PI3K enzymes can be isoform-specific or nonspecific. While pan-PI3K inhibitors may effectively block the pathway at the level of PI3K enzyme, such an approach may cause untoward side effects due to the impact on a wide range of physiologic cellular processes. A potential application for pan-PI3K inhibitors is when pathway activation is due to aberrant upstream signaling or PTEN inactivation. BKM120 (Novartis, Basel, Switzerland) is a pan-PI3K inhibitor; in the Phase I study of BKM120 in patients with

advanced solid tumors, dose-limiting toxicities were hyperglycemia, abdominal pain, skin rash and mood alterations [130]. Other side effects included decreased appetite, rash, diarrhea, nausea, fatigue, hyperglycemia, anxiety, depression and mucositis. While stable disease was the main clinical response (occurring in 26 patients – 58% of cases), two patients with breast cancer showed a partial response (one with *PIK3CA* mutation and one with mutated *KRAS* and *p53*).

Isoform-specific PI3K inhibitors

In contrast to pan-PI3K inhibitors, isoform-specific drugs can target the particular isoenzyme involved in the carcinogenic process and therefore may have a more favorable side-effect profile. Isoform-specific inhibitors of p110α and p110δ are currently in Phase I/II clinical trials. CAL-101 (Calistoga Pharmaceuticals, Seattle, WA, USA) is a p110δ isoform-specific inhibitor that has been studied as a monotherapy in a Phase I trial with 54 previously treated chronic lymphocytic leukemia patients [131]. CAL-101 resulted in a 26% response rate; median duration of response was not reached at the time of the report. Significant (grade ≥3) side effects included infection, cytopenias, neutropenic fever and transaminitis. Preliminary results of another Phase I study of CAL-101 suggest that it can safely be administered in combination with rituximab and/or bendamustine in pretreated patients with indolent non-Hodgkin's lymphoma [132].

Dual PI3K/mTOR inhibitors

mTOR and PI3K enzymes both belong to the phosphatidylinositol kinase-related family of kinases and have significant sequence homology in their active catalytic sites. Dual PI3K/mTOR inhibitors benefit from this structural similarity and inhibit PI3K, mTORC1 and mTORC2. This approach offers the advantage of interrupting the PI3K pathway at more than one node, resulting in more effective pathway suppression. Additionally, dual PI3K/mTOR inhibition can prevent the paradoxical upstream activation of AKT that can be seen with mTORC1 inhibitors [63]. LY294002 is an agent in this class [133]; however, poor pharmacokinetic properties have limited its clinical use. To improve solubility and tumor delivery, LY294002 has been conjugated to an integrin targeting peptide, to form the prodrug SF1126 (Semafore Pharmaceuticals, Westfield, IN, USA). Currently, there are many dual PI3K/mTOR inhibitors in clinical phase and preclinical development. BEZ235 (Novartis, Basel, Switzerland) is another example of this class; dose-limiting toxicities associated with BEZ235 were asthenia and thrombocytopenia. Common side effects included nausea, diarrhea, vomiting and fatigue [134].

mTOR inhibitors (rapalogs)

Rapamycin and its related compounds are mTOR inhibitors and have been in clinical use for many years. Rapamycin forms a complex with FKBP12, which binds to the FRB domain of mTOR to exert its inhibitory effect [135]. The FKBP12–rapamycin complex can bind to mTORC1 but not to mTORC2 [136,137]. Temsirolimus and everolimus are two drugs in this category that are approved by the US FDA for use in advanced renal cell carcinoma (both everolimus and temsirolimus) and advanced pancreatic neuroendocrine tumor (everolimus). Ridaforolimus (Ariad Pharmaceuticals, Cambridge, MA, USA) is a novel

rapalog in late stages of clinical development [138]. In a Phase III study of 711 pretreated patients with metastatic sarcomas (SUCCEED trial), ridaforolimus was shown to statistically improve progression-free survival compared with placebo (HR 0.72, $p = 0.0001$) [139]; the median progression-free survival was 17.7 versus 14.6 weeks for ridaforolimus and placebo, respectively. Clinical benefit rate (defined as complete response, partial response, or stable disease, lasting for 4 months or more), was significantly higher in the active treatment arm (40.6 vs 28.6%, $p= 0.0009$). Grade 3 adverse events were observed in 64% of patients receiving ridaforolimus. Significant side effects of any grade included stomatitis, infections, fatigue, cytopenias, diarrhea, cough, rash, dyslipidemia, hyperglycemia and pneumonitis. Overall, the side effect profile of ridaforolimus seems to be similar to that of other members of this family.

mTOR catalytic-site inhibitors

In contrast to the allosteric mechanism of rapalogs, which preferentially inhibits mTORC1, mTOR catalytic-site inhibitors block both mTORC1 and mTORC2. Inhibition of mTORC2 blocks AKT phosphorylation at the S473 residue, but not at T308 (site of phosphorylation by PDK1). Therefore, inhibition of mTORC1 and mTORC2 by these agents may mitigate rather than prevent the paradoxical upstream activation of AKT. OSI-027 is an example of this class; in Phase I studies of the compound in patients with advanced solid tumors, dose-limiting toxicities included decreased left ventricular ejection fraction and fatigue. Other potential drug-related toxicities were nausea and vomiting, pneumonia, asthenia, diarrhea, anorexia, elevated creatinine and reversible corrected QT interval prolongation [140].

AKT inhibitors

Drugs in this class inhibit AKT through various mechanisms such as competitive binding at the ATP-binding site, prevention of AKT localization to cell membrane and allosteric inhibition [141]. MK2206 (Merck, Whitehouse Station, NJ, USA) is an allosteric pan-AKT inhibitor with a long half-life that can be given in a weekly schedule. In a Phase I study of MK2206 in 70 patients with advanced solid tumors, dose-limiting toxicities were grade 3 rash and mucositis for an every-other-day schedule and rash for a weekly schedule. Other reported drug-related toxicities included rash, nausea, fatigue and hyperglycemia [142].

Future perspective

The PI3K pathway plays an important role in key physiologic and pathologic cellular functions. Numerous drugs targeting different nodes within the pathway have been developed and are currently under clinical testing. The optimal setting for use of PI3K pathway inhibitors remains to be defined. In theory, the highly varying prevalence of pathway activation among different tumor types may limit their application to selected patient populations. As single agents, inhibitors of the PI3K pathway may confer a meaningful clinical benefit when the tumor is essentially driven by aberrant pathway activation. However, involvement of more than one pathway in tumorigenesis and molecular crosstalk between various pathways limit the efficacy of PI3K pathway inhibitors as single agents and argues for their use in conjunction with other targeted therapies – such as inhibitors of the MAPK pathway – or cytotoxic agents. There may be a role for pathway

inhibitors in preventing/overcoming resistance to other antineoplastic agents. An armamentarium of multiple drugs that target the PI3K pathway at different nodes provides an exciting opportunity to personalize treatment based on molecular characteristics of an individual's tumor, comorbid conditions and toxicities. Finally, the PI3K pathway and its components may also serve as predictive and/or prognostic biomarkers. Further research is needed to better understand this intricate signal transduction network and to elucidate optimal strategies for the clinical use of drugs targeting this pathway.

Key Terms

PI3K	Family of enzymes involved in many key cellular functions
RTKs	Cell surface receptors for many hormones, growth factors and cytokines

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Executive summary

Background

- Extensive research on the PI3K family has resulted in identification of its members and their function, as well as recognition of the role of the PI3K pathway in health and disease.

Classification

- PI3Ks are classified based on their structural features into three classes; class I has been studied extensively, is involved in carcinogenesis and is the principal focus of this review.
- Class I PI3Ks are heterodimers with a regulatory subunit (p85) and a catalytic subunit (p110).

PI3K activation

- Class I PI3Ks can be activated through RTKs, the GTPase Ras and G-protein-coupled receptors.

PI3K isoforms

- Despite similar catalytic activity, p110 isoforms have nonredundant functions.

Downstream effects of PI3K activation

- PI3K pathway is involved in cell growth and metabolism, cell survival, proliferation, angiogenesis, and invasion and metastasis.

Pathway activation in cancer

- PI3K pathway activation occurs frequently in malignancies as a result of somatic mutations, amplification or epigenetic alterations of various pathway components, as well as aberrant upstream signaling.

Molecular crosstalk

- Molecular crosstalk between PI3K and other signal transduction pathways, such as MAPK, NOTCH, Wnt and JNK, is a potential mechanism for resistance to treatments and may have therapeutic implications.

Pathway components as biomarkers

- Early studies suggest that various PI3K pathway components, such as PTEN, may have predictive and/or prognostic value.

Pathway interruption

- Frequent pathway activation in cancer and the presence of multiple druggable pathway nodes have made the PI3K pathway a desirable target for cancer therapy. Numerous drugs (including pan-PI3K inhibitors, isoform-specific PI3K inhibitors, dual PI3K/mTOR inhibitors, rapalogs [mTORC1 inhibitors], mTOR

catalytic site inhibitors [mTORC1/2 inhibitors] and AKT inhibitors) are currently in clinical testing.

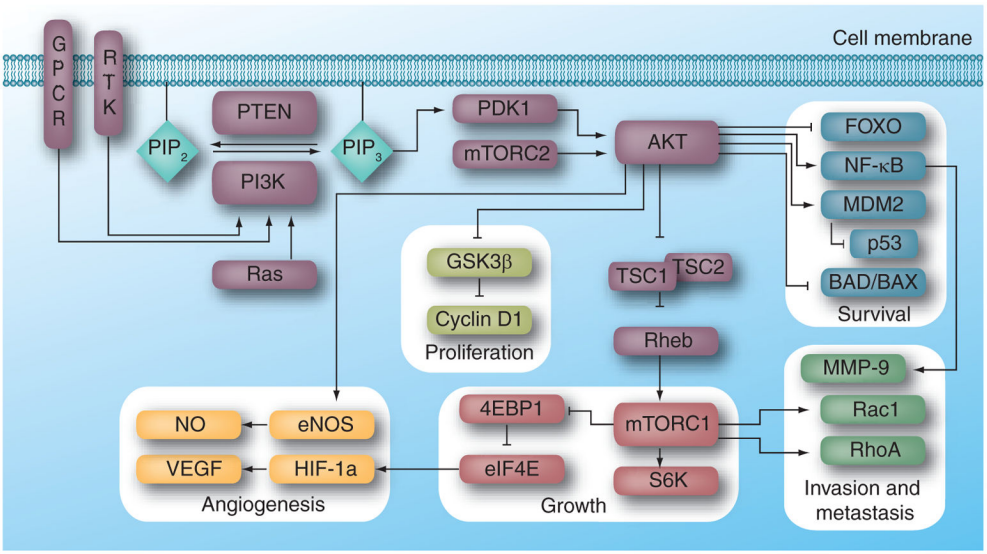

Figure 1. The PI3K pathway

eNOS: Endothelial nitric oxide synthase; GPCR: G protein-coupled receptor; NO: Nitric oxide; PIP: Phosphatidylinositols phosphate.

Table 1

Classification and characteristics of PI3Ks.

Class	Subunit	Protein	Gene	Tissue distribution	Substrate	Function
IA	Regulatory	p85α	*PIK3R1*	Ubiquitous; low in muscle [143,144]	PI, PI(4)P, PI(3,4)-P2	Cell growth, proliferation and survival (see text)
		p55α	*PIK3R1*	High in brain; low in muscle [143,144]		
		p50α	*PIK3R1*	High in liver; moderate in kidney and brain [143,144]		
		p85β	*PIK3R2*	Ubiquitous; lowest in striated muscle [144]		
		p55γ	*PIK3R3*	High in brain and testis; moderate to low in other tissues[144]		
	Catalytic	p101α	*PIK3CA*	Ubiquitous [47]		
		p101β	*PIK3CB*	Ubiquitous [145]		
		p101δ	*PIK3CD*	High in leukocytes; moderate to low in other tissues [12]		
		p37δ	*PIK3CD*	High expression in tumors [8]		
IB	Regulatory	p101	*PIK3R5*	High in leukocytes; moderate to low in other tissues [146]		
		p87 (p84, $p87^{PIKAP}$)	*PIK3R6*	High in leukocytes and heart [13]		
	Catalytic	p101γ	*PIK3CG*	High in leukocytes; moderate to low in other tissues [146]		
II	Catalytic	PI3KC2α	*PIK3C2A*	Ubiquitous; high in heart, placenta and ovary [147]	PI, PI(4)P	Membrane trafficking and receptor internalization
		PI3KC2β	*PIK3C2B*	Ubiquitous; high in thymus and placenta[148]		
		PI3KC2γ	*PIK3C2G*	Ubiquitous; high in liver and prostate [149]		
III	Regulatory	p150 (Vps15)	*PIK3R4*	Ubiquitous [150]	PI	Protein sorting, phagosome formation and maturation, regulation of mTOR in response to availability of amino acids and autophagy
	Catalytic	Vps34	*PIK3C3*	Ubiquitous [151]		

P: Phosphate; PI: Phosphatidylinositol.

Table 2

Aberrant activation of PI3K pathway.

Gene	Variation	Cancer type	Ref.
PIK3CA	Mutation	Breast (26%†)	[98,152–154]
		Colon (12%†)	[98]
		Endometrial (25%)	[155]
		Lung (3%†)	[102]
		CNS (5%†)	[98,156]
		Ovarian (9%†)	[153,157]
		Gastric (12%†)	[98]
	Amplification	SCCHN (37%)	[158]
		Lung (18% [43% in squamous])	[102,159]
		Cervical (69%)	[160]
		Gastric (36%)	[161]
		Esophageal (6%)	[162]
		Thyroid (8%)	[163]
		Ovarian (24.6%)	[157]
		Prostate (13%)	[164]
		Breast (21%)	[152]
PIK3R1	Mutation	CNS (4%†)	[165,166]
		Ovarian (2%†)	[167]
		Colon (5%†)	[167]
		Endometrial (26%†)	[168]
PTEN	Mutation	Cowden syndrome	[169]
		Endometrial (38%†)	[170]
		CNS (18%†)	[171]
		Prostate (14%†)	[171]
		Breast (5%†)	[171]
		Ovarian (6%†)	
	Promoter hypermethylation	Glioblastoma (9%)	[172]
		Prostate (56%)	[173]
		Breast (48%)	[103]
		Melanoma (60%)	[174,175]
		Gastric (39%)	[176]
		Colon (8%)	[177]
		Endometrial (19%)	[178]
		NSCLC (35%)	[179]
	LOH	Glioblastoma (69%)	[180]
		Prostate (32%)	[181]

Gene	Variation	Cancer type	Ref.
		Gastric (36%)	[161]
AKT1	Mutation	Breast (5%†)	[182,183]
		Colon (<1%†)	[182]
		Ovarian (1%)	[182]
		Lung (<1%†)	[184]
		Endometrial (2%†)	[185]
	Amplification	Gastric (20%)	[186]
AKT2	Mutation	Colon (1%)	[187]
	Amplification	SCCHN (30%)	[158]
		Pancreatic (10–20%)	[188,189]
		Ovarian (12–13%)	[190,191]
		Breast (3%)	[191]
		Colon (1%)	[187]
		Lymphoma (1%)	[192]
AKT3	Mutation	Melanoma (<1%)	[193]
PDK1	Mutation	Colon (1%)	[187]

LOH: Loss of heterozygosity; NSCLC: Non-small cell lung cancer; PIK3CA: Phosphoinositide-3-kinase catalytic isoform p110α; PIK3R1: Phosphoinositide-3-kinase regulatory subunit p85; SCCHN: Squamous cell carcinoma of the head and neck.

†Data taken from [201].

Table 3

Drugs targeting the PI3K pathway.

Drug	Description	Manufacturer	Study phase	Study setting
Pan-PI3K inhibitors				
BKM120	Oral	Novartis	I, I/II, II	Monotherapy: advanced solid tumors, prostate, leukemia, endometrial, lung and brain With chemotherapy: advanced solid tumors (carboplatin-paclitaxel or paclitaxel alone), colon (irinotecan) and breast (capecitabine) With other targeted agents: advanced solid tumors (GSK1120212† and MEK162†), GIST (imatinib), renal (bevacizumab), brain (bevacizumab) and breast (trastuzumab) With endocrine therapy: breast (fulvestrant and letrozole) With chemotherapy and other targeted agents: advanced solid tumors (paclitaxel and trastuzumab)
PX-866	Oral	Oncothyreon	I, I/II	Monotherapy: advanced solid tumors, prostate and brain With chemotherapy: NSCLC/SCCHN (docetaxel) With other targeted agents: colon/SCCHN (cetuximab)
XL147 (SAR245408)	Oral	Exelixis/Sanofi	I, I/II, II	Monotherapy: advanced solid tumors, lymphoma, endometrial and brain With chemotherapy: advanced solid tumors (carboplatin/paclitaxel) With other targeted agents: breast (trastuzumab), advanced solid tumors (erlotinib and MSC1936369B†) With chemotherapy and other targeted agents: breast (paclitaxel/trastuzumab) With endocrine therapy: breast (letrozole)
GDC-0941	Oral	Genentech	I	Monotherapy: advanced solid tumors and NHL With other targeted agents: advanced solid tumors (erlotinib and GDC-0973†) and breast (trastuzumab) With chemotherapy: NSCLC (carboplatin/paclitaxel) With chemotherapy and other targeted agents: breast (paclitaxel/bevacizumab), NSCLC (carboplatin/paclitaxel/bevacizumab) With endocrine therapy: breast (fulvestrant)

Drug	Description	Manufacturer	Study phase	Study setting
BAY80–6946	Intravenous	Bayer	I	Monotherapy: advanced solid tumors With other targeted agents: advanced solid tumors (BAY86–9766†) With chemotherapy: advanced solid tumors (gemcitabine, cisplatin/ gemcitabine and paclitaxel)
ZSTK474	Oral	Zenyaku Kogyo	I	Monotherapy: advanced solid tumors
GSK2126458	Oral	GlaxoSmithKline	I	Monotherapy: advanced solid tumors With other targeted agents: advanced solid tumors (GSK1120212†)
Isoform-specific PI3K inhibitors				
BYL719	Oral; PI3Kα inhibitor	Novartis	I, I/II	Monotherapy: advanced solid tumors With other targeted agents: advanced solid tumors (MEK162†)
CAL-101	Oral; PI3Kδ inhibitor	Calistoga	I, I/II, II	Monotherapy: hematologic malignancies With chemotherapy: NHL/CLL (bendamustine or fludarabine) With other targeted agents: NHL/CLL (rituximab and ofotumumab) With chemotherapy and other targeted agents: NHL/CLL (bendamustine and rituximab)
AMG 319	Oral; PI3Kδ inhibitor	Amgen	I	Monotherapy: lymphoid malignancies
INK1117	Oral; PI3Kα inhibitor	Intellikine	I	Monotherapy: advanced solid tumors
Dual PI3K-mTOR inhibitors				
SF1126	Intravenous	Semafore	I	Monotherapy: advanced solid tumors
PF-05212384 (PKI-587)	Intravenous	Pfizer	I, II	Monotherapy: advanced solid tumors and endometrial With chemotherapy: advanced solid tumors (irinotecan)
PF-04691502	Oral	Pfizer	I, II	Monotherapy: advanced solid tumors and endometrial With other targeted agents: advanced solid tumors (PD-0325901†) With chemotherapy: advanced solid tumors (irinotecan) With endocrine therapy: breast (letrozole)
XL765(SAR245409)	Oral	Exelixis/Sanofi	I, I/II	Monotherapy: advanced solid tumors, brain and lymphoma

Drug	Description	Manufacturer	Study phase	Study setting
				With other targeted agents: advanced solid tumors (erlotinib, MSC1936369B†) and NHL/CLL (rituximab)
				With chemotherapy: brain (temozolamide with or without radiation) and NHL/CLL (bendamustine)
				With chemotherapy and other targeted agents: NHL/CLL (bendamustine and rituximab)
				With endocrine therapy: breast (letrozole)
BEZ235	Oral	Novartis	I, I/II, II	Monotherapy: advanced solid tumors, kidney, endometrial and breast
				With other targeted agents: advanced solid tumors (MEK162†)
				With chemotherapy: advanced solid tumors (paclitaxel)
				With chemotherapy and other targeted agents: advanced solid tumors (paclitaxel/trastuzumab)
				With endocrine therapy: breast (letrozole)
BGT226	Oral	Novartis	I, I/II	Monotherapy: advanced solid tumors
DS-7423	Oral	Daiichi Sankyo	I	Monotherapy: advanced solid tumors
GDC-0980	Oral	Genentech	I, II	Monotherapy: advanced solid tumors/ NHL, endometrial and kidney
				With chemotherapy: breast (paclitaxel), advanced solid tumors (capecitabine and carboplatin/paclitaxel)
				With chemotherapy and other targeted agents: breast (paclitaxel and trastuzumab, paclitaxel and bevacizumab), advanced solid tumors (FOLFOX and bevacizumab, carboplatin/paclitaxel and bevacizumab)
				With endocrine therapy: breast (fulvestrant)
PWT33597	Oral	Pathway Therapeutics	I	Monotherapy: advanced solid tumors
MK-2206	Oral, allosteric inhibitor	Merck	I, II	Monotherapy: advanced solid tumors, lymphoma, ovarian/fallopian/peritoneal cancer, gastric/esophageal, breast, neuroendocrine, SCCHN, endometrial, kidney, liver and biliary
				With other targeted agents: advanced solid tumors (erlotinib and dalotuzumab), advanced solid tumors/ breast (trastuzumab, trastuzumab and lapatinib, and lapatinib), NSCLC (gefitinib and erlotinib), advanced solid tumors (AZD6422†) and colon (AZD6422†)

Drug	Description	Manufacturer	Study phase	Study setting
				With chemotherapy: advanced solid tumors (carboplatin and paclitaxel, docetaxel) and advanced solid tumors/ breast (paclitaxel) With chemotherapy and other targeted agents: CLL (bendamustine/rituximab) and breast (paclitaxel/trastuzumab) With endocrine therapy: breast (aromatase inhibitor or fulvestrant) and prostate (bicalutamide)
Perifosine (KRX-0401)	Oral, PH domain inhibitor	Keryx	I, II, III	Monotherapy: advanced solid tumors/ hematologic malignancies, pediatric advanced solid tumors, brain, CLL, NSCLC, sarcoma, renal, melanoma, prostate, SCCHN, breast and pancreatic With other targeted agents: advanced solid tumors (trastuzumab, sorafenib and sunitinib), pediatric advanced solid tumors (temsirolimus), GIST (imatinib), MM (bortezomib and UCN-01[‡]) and brain (temsirolimus) With chemotherapy: advanced solid tumors (gemcitabine, docetaxel and paclitaxel), colon (capecitabine), MM (lenalidomide) and ovarian (docetaxel) With endocrine therapy: breast (NS)
GSK2141795	Oral, ATP-competitive inhibitor	GlaxoSmithKline	I	Monotherapy: advanced solid tumors/ lymphoma With other targeted agents: advanced solid tumors (GSK1120212[†])
SR13668	Oral	SRI International	I	Monotherapy: healthy volunteers
VD-0002 (Triciribine, VQD-002, TCN-PM)	Oral	VioQuest	I	Monotherapy: advanced solid tumors/ advanced hematologic malignancies
mTOR catalytic-site inhibitors				
AZD8055	Oral	AstraZeneca	I, I/II	Monotherapy: advanced solid tumors, brain
OSI-027	Oral	Astellas	I	Monotherapy: advanced solid tumors/ lymphoma
INK128	Oral	Intellikine	I	Monotherapy: advanced solid tumors, MM/WM With chemotherapy: advanced solid tumors/breast (paclitaxel) With chemotherapy and other targeted agents: advanced solid tumors/breast (paclitaxel and trastuzumab)
Rapalogs				

Drug	Description	Manufacturer	Study phase	Study setting
Everolimus (Afinitor®, RAD001)	Oral	Novartis		US FDA approved for advanced renal cell carcinoma, advanced pancreatic neuroendocrine tumor and subependymal giant cell astrocytoma associated with tuberous sclerosis
Temsirolimus (Torisel®, CCI-779)	Intravenous	Wyeth		FDA approved for advanced renal cell carcinoma
Ridaforolimus (deforolimus, AP23573 and MK-8669)	Intravenous and oral	Ariad	I, II, III	Monotherapy: advanced solid tumors, pediatric advanced solid tumors, NSCLC, endometrial, sarcoma, hematologic malignancies, prostate and brain With other targeted agents: advanced solid tumors (MK-0752§, MK-2206, bevacizumab and dalotuzumab), breast (dalotuzumab and trastuzumab) and colon/NSCLC/SCCHN (cetuximab) With chemotherapy: sarcoma (doxorubicin alone, doxorubicin and ifosfamide, and gemcitabine and docetaxel), endometrial/ovarian (paclitaxel and carboplatin) and renal (vorinostat) With endocrine therapy: prostate (bicalutamide)

† MEK inhibitor

‡ Chk1-specific inhibitor

§ Gamma-secretase inhibitor.

CLL: Chronic lymphocytic lymphoma; GIST: Gastrointestinal stromal tumor; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; NS: Not specified; NSCLC: Non-small-cell lung cancer; PH: Pleckstrin homology domain; SCCHN: Squamous cell carcinoma of the head and neck; WM: Waldenstrom macroglobulinemia.

Data taken from [203].