



# PI3K pathway in NSCLC

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The phosphatidylinositol 3-kinases (PI3Ks) are members of a family of intracellular lipid kinases that phosphorylate the 3'-hydroxyl group of phosphatidylinositol and phosphoinositides. PI3K regulate signaling pathways for neoplasia, including cell proliferation, adhesion, survival, and motility. Different classes of PI3K have distinct roles in cellular signal transduction. PI3K pathway is activated by several different mechanisms in cancers, including, somatic mutation and gene amplification. In this review, we examine the literature addressing PI3K mutation status and gene amplification, with an emphasis on non-small cell lung cancer.

**Keywords:** *PI3KCA*, NSCLC, mutations, gene amplification, copy number, p110 $\alpha$ , exon 9, exon 20

## PI3K CLASSIFICATION

The phosphatidylinositol 3-kinases (PI3Ks) are members of a family of intracellular lipid kinases that phosphorylate the 3'-hydroxyl group of phosphatidylinositol and phosphoinositides. This reaction leads to the activation of many intracellular signaling pathways that regulate functions such as cell proliferation, adhesion, survival, and motility (**Figure 1**).

Phosphatidylinositol 3-kinases are grouped into three classes (I, II, III) according to their substrate preference and sequence homology. Different classes of PI3K have distinct roles in cellular signal transduction, as do the different isoforms that can exist within each class (Engelman et al., 2006).

In mammals, numerous genes encode different isoforms of PI3Ks (Fruman et al., 1998).

### CLASS IA PI3K

This is the most clearly implicated class in human cancers (Yuan and Cantley, 2008). Class IA PI3K is a heterodimer that consists of a p85 regulatory subunit and a p110 catalytic subunit. Three genes, *PIK3R1*, *PIK3R2*, and *PIK3R3* encode the p85 $\alpha$ , p85 $\beta$ , and p55 $\gamma$  isoforms of the p85 regulatory subunit, respectively. The *PIK3R1* gene also gives rise to two shorter isoforms, p55 $\alpha$  and p50 $\alpha$ . The Class IA p85 regulatory isoforms have a common core structure consisting of a p110-binding domain [also called the inter-Src-homology 2 (inter-SH2) domain] flanked by two SH2 domains (Huang et al., 2007). The p85 regulatory subunit is crucial in mediating the activation of class IA PI3K by receptor tyrosine kinases (RTKs).

Three genes – *PIK3CA*, *PIK3CB*, and *PIK3CD* – encode the highly homologous p110 catalytic subunit isoforms p110 $\alpha$ , p110 $\beta$ , and p110 $\delta$ , respectively (Cantley, 2002). The p110 $\alpha$  subunit of PI3K $\alpha$  has five domains: an N-terminal domain called adaptor binding domain (ABD), that binds to p85 $\alpha$ , a Ras-binding domain (RBD), a domain called C2 that has been proposed to bind to cellular membranes, a helical domain, and a kinase catalytic domain

(Vanhaesebroeck and Waterfield, 1999; Cantley, 2002; Huang et al., 2007).

In mammals, class I PI3Ks are involved in cellular growing, proliferation, motility, cell survival, and intracellular traffic. Class I PI3K also regulates glucose homeostasis: insulin receptor substrate.

### CLASS IB PI3K

Class IB PI3K is a heterodimer consisting of a p101 regulatory subunit and a p110 $\gamma$  catalytic subunit. In 2005 two other regulatory subunits, p84 and p87 *PIKAP* (phosphoinositide 3-kinase gamma adapter protein of 87 kDa) were described.

### CLASS II PI3K

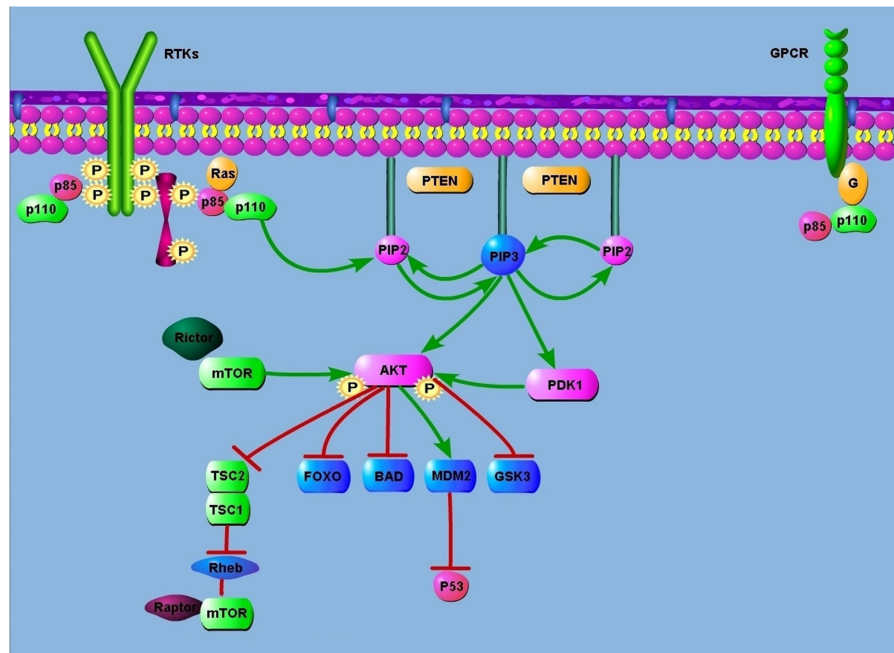
Class II PI3K consists of only a p110-like catalytic subunit. The three isoforms of class II-*PIK3C2 $\alpha$* , *PIK3C2 $\beta$* , and *PIK3C2 $\gamma$*  are encoded by distinct genes. Relatively little is known about the function of class II.

### CLASS III PI3K

Class III PI3Ks consist of a single member, *Vps34* (vacuolar sorting protein 34) which has been implicated in phagocytosis in the system immune and in traffic proteins and vesicles.

## PI3K SIGNALING CASCADE

All major elements of the PI3K pathway have been found mutated or amplified in a broad range of cancers. The axis of PI3K signaling in cancer begins with engagement of growth factors by receptor tyrosine kinases (RTKs). These RTKs are often mutated, amplified, or overexpressed, causing aberrant PI3K activation. For example, PI3K is activated by epithelial growth factor receptor (EGFR) in lung cancers harboring somatic activating mutations in EGFR (Skolnik et al., 1991; Engelman and Settleman, 2008). In this cancer, EGFR directly binds and activates PI3K. The regulatory subunit, p85, directly binds to phosphotyrosine residues on RTKs and/or adaptors (Carpenter et al., 1993). This binding relieves the



**FIGURE 1** | The phosphatidylinositol 3-kinase (PI3K) signaling cascade.

Class	Type	Vertebrates
Class IA	Catalytic	PIK3CA (p110 $\alpha$ )
		PIK3CB (p110 $\beta$ )
		PIK3CD (p110 $\delta$ )
	Regulatory	PIK3R1 (p85 $\alpha$ /55 $\alpha$ /p50 $\alpha$ )
		PIK3R2 (p85 $\beta$ )
Class IB	Catalytic	PIK3R3 (p55 $\gamma$ )
	Regulatory	PIK3CG (p110 $\gamma$ )
		PIK3R5 (p101)
Class II	Catalytic	p84
		PIK3R6 (p87PIKAP)
		PIK3C2 $\alpha$
		PIK3C2 $\beta$
Class III	Catalytic	PIK3C2 $\gamma$
	Regulatory	VP534
		PIK3R4 (p150)

intermolecular inhibition of the p110 catalytic subunit by p85 and localizes PI3K to the plasma membrane where its substrate, phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>), resides (Zhao and Vogt, 2008). PI3K can also be stimulated by activated Ras, which directly binds p110 (Shaw and Cantley, 2006). Additionally, the p110 $\beta$  catalytic subunit can be activated by G-protein coupled receptors (Katso et al., 2001).

Phosphatidylinositol 3-kinases is then recruited to plasma membrane-anchored receptors and is activated and phosphorylates PIP<sub>2</sub> on the 3'OH position to produce phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>). The tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (PTEN) negatively

regulates PI3K; dephosphorylates PIP<sub>3</sub> to PIP<sub>2</sub>, thereby terminating PI3K-dependent signaling (Courtney et al., 2010). PIP<sub>3</sub> propagates intracellular signaling by directly binding pleckstrin homology (PH) domains of various signaling proteins (Cantley, 2002). Phosphatidylinositol-3,4,5-trisphosphate (PIP<sub>3</sub>) propagates intracellular signaling as a second messenger activating many downstream molecules. The protein serine/threonine kinase AKT (also known as PKB) is a principal target of PIP<sub>3</sub> (Franke et al., 1997). Binding of PIP<sub>3</sub> to AKT leads to the membrane recruitment of AKT and subsequent phosphorylation by the mammalian target of rapamycin (mTOR)-ricor kinase complex and by 3-phosphoinositide-dependent kinase (PDK1; Sarbassou et al., 2005). The full activation of AKT phosphorylates many target proteins, such as forkhead (FOXO) family of transcription factors.

AKT promotes cell survival by inhibiting pro-apoptotic Bcl2 family members BAD and BAX (Cantley, 2002). AKT also can phosphorylate MDM2 leading to p53 degradation (Vivanco and Sawyers, 2002). AKT phosphorylates and inactivates the FOXO family of transcription factors. FOXO proteins promote the expression of pro-apoptotic genes, such as *Bim* and *Fas* and *p27Kip* and retinoblastoma-like2 (*RBL2*) to inhibit cell-cycle entry and cell survival.

AKT mediates cell metabolism by activating glycogen synthase through the inhibition of glycogen synthase kinase 3 (GSK3). AKT regulate protein synthesis by phosphorylating the tuberous sclerosis complex 2 (TSC2) protein tuberin, and therefore inhibits the GTPase-activating protein (GAP) activity of the TSC1–TSC2 complex toward Rheb. This allows GTP-bound Rheb to accumulate and activate the mTOR-raptor kinase complex, which in turn mediates phosphorylation of 4E-BP1 and p70, ultimately leading to increased protein synthesis (Richardson et al., 2004).

## IMPLICATIONS FOR DIABETES

The p85 regulatory subunit is required for the stabilization of p110 and for the activation of PI3K by the insulin receptor. A partial reduction in p85 levels leads to improved PI3K signaling and increased insulin sensitivity *in vivo*. PI3K signaling mediates different cellular responses depending on the tissue context, and defective PI3K signaling in many tissues contributes collectively to the complex metabolic defects associated with type-2 diabetes (Hansen et al., 1997; Barroso et al., 2003). Elevated levels of p85 have been observed in women with pregnancy-induced insulin resistance (Kirwan et al., 2004). Similarly, elevated levels of p85, but not p110, were observed in muscles of type-2 diabetic individuals, indicating that increased levels of p85 might contribute to muscle insulin resistance in diabetes.

## FREQUENCY OF MUTATIONS AND AMPLIFICATIONS IN THE PI3K PATHWAY IN NSCLC

Receptor tyrosine kinases upstream of PI3K, the p110 $\alpha$  catalytic subunit of PI3K, the downstream kinase, AKT, and the negative regulator, PTEN, are all frequently altered in cancer. The *PIK3CA* gene that encodes p110 $\alpha$  is also amplified at high frequencies in squamous cell lung carcinoma (Engelman et al., 2006). *PIK3CA* and *PIK3R1* are somatically mutated in cancers, and these mutations promote activation of the PI3K pathway (Ikenoue et al., 2005).

Huang et al. (2007) reported a 3.0-Å resolution structure of a complex between p110 $\alpha$  and a polypeptide containing the p110 $\alpha$ -binding domains of p85 $\alpha$ , a protein required for its enzymatic activity (Vanhaesebroeck and Waterfield, 1999). The structure showed that many of the mutations occurred at residues lying at the interfaces between p110 $\alpha$  and p85 $\alpha$  or between the kinase domain of p110 $\alpha$  and other domains within the catalytic subunit. The two most common genetic mutations that directly activate the PI3K signaling pathway are somatic activating mutations of p110 $\alpha$  (*PIK3CA*) and loss of the tumor suppressor PTEN.

Additionally, amplification of *PIK3CA* and AKT are occasionally observed in epithelial cancers (Engelman et al., 2006). In non-small cell lung cancer (NSCLC), mutations in *PIK3CA* and PTEN are uncommon, although there are reports demonstrating evidence for loss of PTEN protein expression and *PIK3CA* amplification (Massion et al., 2002; Marsit et al., 2005). Somatic mutations in *PIK3CA* have been identified in a variety of human tumors, including NSCLC. Most of these mutations in p110 $\alpha$  cluster to two hot spot regions in exons 9 and 20 (>75%). Exon 20 encodes the catalytic domain of p110 $\alpha$  (H1047R); exon 9 encodes the helical domain of p110 $\alpha$  (E545K; Samuels and Velculescu, 2004). A smaller cluster of mutations is also found in the N-terminal p85 interacting domain. While activating mutations in *PIK3CA* have been identified in NSCLC, no oncogenic mutations have been verified in p110 $\beta$ , p110 $\delta$ , or the class IB catalytic isoform p110 $\gamma$ . The expression of these p110 $\alpha$  mutants in cells confers AKT activation in the absence of growth factor stimulation (Samuels et al., 2005).

Samuels et al. (2004) sequenced PI3K genes in human cancers and corresponding normal tissue and identified 8 PI3K and 8 PI3K-like genes. Sequences containing the kinase domain of

identified PI3Ks were extracted from the Celera or Public draft human genome sequences. Primers for PCR amplification and sequencing were designed using the primer 3 program. They examined the sequences in a total of 396 tumors. Mutations in *PIK3CA* were identified in 1 (E545K) of 24 lung cancers (4%); and >75% of alterations occurred in two small clusters in the helical and kinase domains. Data suggest that mutant *PIK3CA* was likely to function as an oncogene in human cancers.

Lee et al. (2005) analyzed somatic mutations of *PIK3CA* gene (exons 9, 20) in the 668 tissue samples from gastric, breast, and hepatocellular carcinomas, acute leukemia, and NSCLC. The mutational analysis based on PCR, single-strand conformation polymorphism (SSCP) analysis, and sequencing analysis ensures the specificity of the results. They analyzed 229 NSCLC: 111 squamous cell carcinomas, 108 adenocarcinomas, and 10 large-cell carcinomas and detected *PIK3CA* somatic mutations in 3 of 229 NSCLC (1.3%). No significant correlation was found between *PIK3CA* mutations and the histologic subtypes of NSCLC. *PIK3CA* mutation hot spots, E545K, and H1047R, were detected in 50% of samples.

Gymnopoulos et al. (2007) suggested three groups of *PIK3CA* mutants, defined by their location in distinct functional domains of the protein. They hypothesized that these three groups could induce a gain in PI3K function by a different molecular mechanism. Kawano et al. (2006) genotyped the *PIK3CA* gene in Japanese lung cancer patients. The study included 235 lung cancer specimens obtained at lung cancer surgery at Nagoya Hospital from 1997 to 2003. The two *PIK3CA* mutation hot spots (exon 9, 20) were analyzed by real-time PCR, and then confirmed by direct sequencing. In exon 9, somatic mutations were found in eight patients (3 E542K, 3 E545K, 1 E542Q, 1 Q546K); in exon 20 there were no mutations. Around the eight mutations that objectified (8/235, 3.4%), two were adenocarcinomas, five were squamous cell carcinomas, and one adenosquamous carcinoma. *PIK3CA* mutation incidence was significantly lower in adenocarcinoma (2/135; 1.5%) than in squamous cell carcinoma (5/79; 6.5%,  $p = 0.0495$ ). Of the eight patients with *PIK3CA* mutation, three also harbored EGFR mutations. *PIK3CA* mutations did not correlate with gender, age, or smoking status. Overall, there was no significant difference in survival between patients with *PIK3CA* wild type ( $N = 227$ , 77 died) and patients with *PIK3CA* mutation ( $N = 8$ , 4 died).

The same group in 2007 investigated *PIK3CA* copy number in NSCLC (Kawano et al., 2007). They included 92 Japanese lung carcinoma patients who had undergone surgery at Nagoya Hospital. *PIK3CA* copy number was analyzed by quantitative real-time PCR; *PIK3CA* amplification (increased *PIK3CA* copy number) was defined as >3copies. Incidence of *PIK3CA* amplification was 12% (11/92). Among the 11 patients with *PIK3CA* amplification, 2 harbored *PIK3CA* mutations (E542Q, E545K). A correlation between *PIK3CA* amplification and *PIK3CA* mutation was not found ( $p = 0.7534$ ). Among the 11 patients with *PIK3CA* amplification, no EGFR mutation was found. *PIK3CA* amplification status was significantly different in regard to: gender (male 11/63 versus female 0/29;  $p = 0.040$ ), smoking history (current/former 11/59 versus never 0/33;  $p = 0.021$ ), histology

## SUMMARY

Bibliography	PI3KCA mut NSCLC	PI3KCA mut SCC	PI3KCA mut ADC	PI3KCA amplification	PI3KCA amp SCC	PI3KCA amp ADC
Samuels et al. (2004)	1/24 (4%)					
Lee et al. (2005)	3/229 (1, 3%)					
Kawano et al. (2006)	8/235 (3, 4%)	5/77 (6, 5%)	2/135 (1, 5%)			
Kawano et al. (2007)				11/92 (12%)	(36%)	(1, 6%)
Okudela et al. (2007)	5/139 (3, 6%)	1/35 (2, 9%)	2/85 (2, 5%)	21/115 (18, 3%)	(42, 9%)	(9, 6%)
Yamamoto et al. (2008)	11/691 (1, 6%)	5/249 (2%)	5/400 (1, 3%)	61/356 (17, 1%)	46/139 (33, 1%)	12/195 (6, 2%)
Angulo et al. (2011)	12/174 (6, 9%)	11/122 (9%)	1/49 (2%)		44/116 (38%)	
Carcereny et al. (2011)			6/118 (5, 1%)			
Ludovini et al. (2011)	6/145 (4, 1%)					

(squamous 10/28 versus adenocarcinoma 1/64;  $p = 0.0001$ ). Overall survival of 92 patients in regard to *PIK3CA* amplification status showed a significant difference in survival between patients with *PIK3CA* normal copy number ( $N = 81$ , 37 died) versus patients with *PIK3CA* amplification ( $N = 11$ , 9 died), Log-rank test  $p = 0.0045$ . Using cox regression model, only pathologic stage ( $p = 0.0337$ ) but not *PIK3CA* amplification ( $p = 0.2655$ ) was a prognostic factor.

Okudela et al. (2007) analyzed samples from 148 Japanese patients with lung cancer who were surgically treated at Hamamatsu Hospital and Mikatahara Hospital from 1997 to 2006. Fragments of PI3K were analyzed by PCR; DNA sequence was analyzed from 139 of the 148 tissues. *PIK3CA* mutations were found in 5/139 patients (3.6%). Copy number gains of *PIK3CA* locus were found in 21/115 patients by FISH (18.3%). No patients were found to harbor both *PI3KCA* mutation and alteration in copy number.

Yamamoto et al. (2008) analyzed 691 tumor samples from patients from Japan ( $N = 323$ ), Taiwan ( $N = 148$ ), USA ( $N = 150$ ), Australia ( $N = 70$ ) who underwent surgical resection. They identified *PIK3CA* mutations in 11/691 (1.6%). Mutations occurred in the following histological subtypes: 5 of 249 (2%) squamous cell carcinoma, 5 of 400 (1.3%) adenocarcinoma, and 1 of 42 (2.4%) other NSCLC. Sufficient DNA was available from 356 of these tumors for *PIK3CA* gene copy number analysis by real-time quantitative PCR which was detected in 61/356 (17.1%): squamous cell carcinoma 46/139 (33.1%) and adenocarcinoma 12/195 (6.2%).

Angulo et al. (2011) analyzed *PIK3CA* gene mutations (exon 9, 20) in 178 NSCLC: 123 squamous cell carcinoma, 51 adenocarcinoma, and 4 large-cell carcinoma. Screening *PIK3CA* gene mutation by PCR and direct sequencing was performed in 174. They identified 12 *PIK3CA* mutations (6.9%); in squamous cell carcinoma 11/122 (9%), and in adenocarcinoma 1/49 (2%). The analyses of *PIK3CA* gene amplification by FISH was limited

to squamous cell carcinoma and identified in 44 cases (38%). Tumors with *PI3KCA* mutation do not always display amplification of the gene; only 2.6% of the samples had both alterations concomitantly. These results would indicate a complementary relationship between *PIK3CA* amplification and mutations in NSCLC.

Carcereny et al. (2011) examined the presence and potential influence of *PIK3CA* mutations on outcome in 118 NSCLC patients with EGFR mutations treated with erlotinib. They detected six *PIK3CA* mutations (5.1%); 84% of patients had adenocarcinoma. The response rate was 50% for patients with *PIK3CA* mutation versus 70% for those with *PIK3CA* wild type ( $p = 0.03$ ). A non-significant trend toward shorter progression-free survival was observed in the six patients with *PIK3CA* mutations (9 versus 16 months;  $p = 0.59$ ).

Ludovini et al. (2011) realized a retrospective analysis to investigate the role of *PIK3CA*, EGFR, and KRAS gene mutations in predicting response and survival in 166 NSCLC patients treated with EGFR-TKIs. *PIK3CA* (exons 9, 20), EGFR, and KRAS mutations were analyzed using PCR. Of 166 patients, *PIK3CA* mutations were evaluated in 145 with 6 found to have *PIK3CA* mutations (4.1%). One adenocarcinoma patient with *PIK3CA* mutation (M10431) had EGFR mutation (selection 19). *PIK3CA* mutation correlated with shorter median time-to-progression (2.3 months in mutated versus 6 months in wild type, HR 2.9, CI 0.66–12.8;  $p = 0.01$ ), and worse overall survival (9.9 months in mutated versus 30.2 months in wild type, HR 4.76, CI 0.85–26.57;  $p < 0.001$ ). The authors suggested that *PIK3CA* seems to be an indicator of poor survival in patients with NSCLC treated with EGFR-TKIs.

In conclusion, several studies have analyzed the PI3K pathway in NSCLC and reported frequent alterations. At present ongoing studies are addressing the role of PI3K inhibitors in NSCLC in the hope that they may lead to targeted therapies in the not too distant future.

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