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Review

Targeting PI3K signaling in cancer: Challenges and advances

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ABSTRACT

The key role of phosphoinositide 3-kinase (PI3K) pathway in different cellular processes and several disorders, together with the presence of targetable proteins, opened the way to promising studies for the development of small molecule inhibitors. Despite the high expectation, the shift of PI3K inhibitors to the clinic met several limitations due to the emergence of dose-limiting, on-target adverse effects. In this review, we will summarize the main issues and recent advances in PI3K inhibitors clinical trials. The effort to develop isoform-specific inhibitors, together with novel therapeutic strategies aimed at reducing the toxicity and adverse effects, opened a new promising era for PI3K inhibitors. In addition, we will focus on the recent emergence of class II and III PI3K inhibitors, which helped to define their class I non-redundant role.

1. Introduction

The phosphoinositide 3-kinases (PI3Ks) are a large family of lipid enzymes that phosphorylate the 3'-OH group of phosphatidylinositols (PI) at the plasma membrane (Fig. 1). > 30 years of discoveries acknowledged a fundamental role for the PI3Ks axis in several cellular processes including inflammation, metabolism, motility, cell proliferation and survival [1–3]. This plethora of functions and implication in different diseases promoted a great effort in the development of compounds targeting the PI3K signaling pathway. At present, a significant number of PI3K inhibitors are under clinical investigation for cancer treatment, including pan-PI3K inhibitors, isoform-selective and dual PI3K/mTOR inhibitors.

1.1. Class I PI3K structure and function

The class I PI3Ks are subdivided into class IA and IB enzymes, based on the differences in regulatory subunits. The class IA is composed by three catalytic subunits p110α, p110β and p110δ encoded by the genes PIK3CA, PIK3CB and PIK3CD. In association to these three catalytic subunits, five different p85-like regulatory subunits (p85α, p85β, p50α, p55α and p55γ), encoded by the genes PIK3R1, PIK3R2 and PIK3R3, activate and associate with class IA [4,5]. Functionally, the p85 regulatory subunit contains two Src homology 2 domains, nSH2 and cSH2, that mediates binding to p110. Once activated downstream of phosphorylated receptors and their adaptors, the inhibitory nSH2/cSH2 interactions are lost, resulting in PI3K activation [6]. Class IB includes the catalytic subunit p110γ, encoded by the gene PIK3CG, and associates with either p84 (PIK3R5) or p101 (PIK3R6) regulatory subunits, which do not have known domains [4,7]. Class IB is activated exclusively by Gβγ subunits downstream of GPCRs. The class IA p110β is also activated by GPCRs through Gβγ heterodimer [8,9].

While p110α and p110β are widely expressed in all tissues [10,11], p110δ and p110γ expression is mainly restricted to leukocytes [12]. Receptor tyrosine kinase (RTK) or GPCRs activation recruits class I PI3Ks to the plasma membrane, where the p85-mediated inhibition of p110 is relieved and p110 directly phosphorylates PI(4,5)P2 to produce PI(3,4,5)P3. This lipid thus acts as a second messenger activating membrane-localized signaling proteins such as AKT, involved in cell growth and survival [13]. Interestingly, class IB has a non canonical kinase-independent function, acting as an adaptor for phosphodiesterase 3b (PDE3B) or as a scaffolding protein sequestering leucine methyl transferase (LCMT1), an activator of protein phosphatase 2A (PP2A). These protein complexes are key regulators of cAMP levels and cardiac contractility [14,15].

Activating and inactivating mutations have been frequently described for class IA PI3K in a variety of human diseases, including overgrowth syndrome and cancer [16]. The *PIK3CA* gene, which encodes for p110α, is one of the most frequently mutated genes in cancer. The majority of *PIK3CA* mutations are heterozygous non-random (hotspot) gain-of-function missense mutations present in the helical domain (E542K, E545K) and the regulatory arch of the kinase domain

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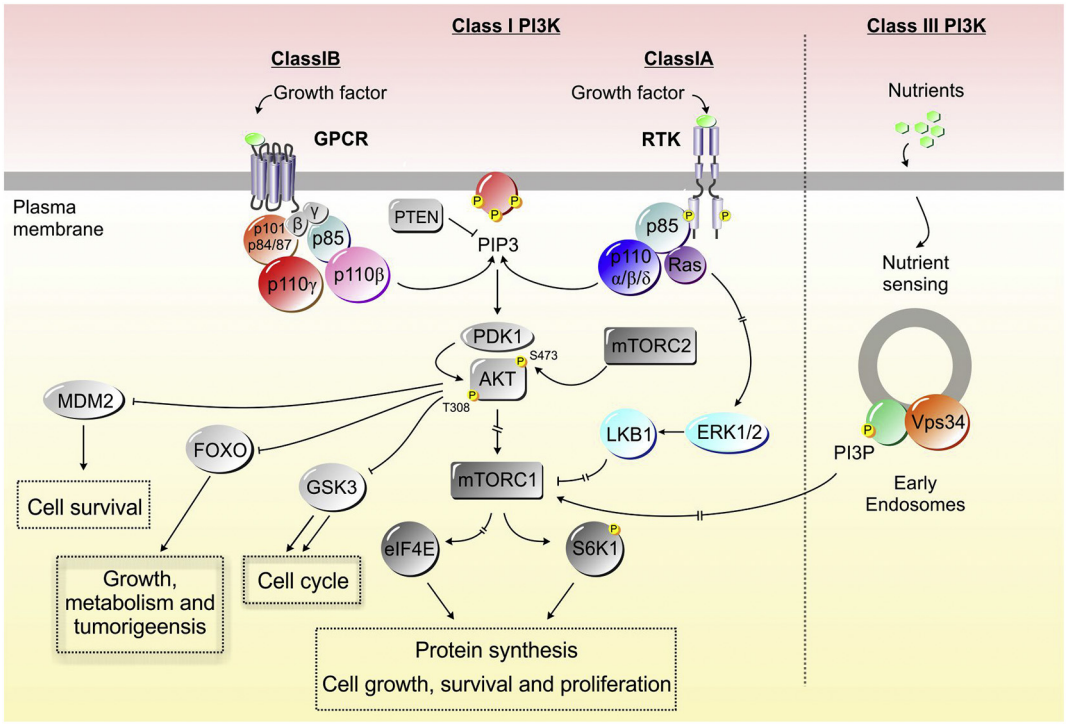

Fig. 1. Schematic representation of PI3K/AKT/mTOR signaling pathway.

(H1047R) [13,17]. While helical mutants are no longer sensitive to the by pY phosphopeptides activation but still require Ras to promote cell transformation, the H1047R mutation results in increased association with membranes, thus allowing p110α^{H1047K} to be independent to the presence of Ras in cell transformation [6]. Other rare mutations associated with cancer in p110α are mainly located in the ABD (R38H, R88Q) and C2 domain (D560Y, N564D and N564K) [6].

Unlike p110α, the p110β catalytic subunit mutations are not commonly described in cancer. However, its activity has been linked to tumorigenesis in combination with the loss of the phosphatases PTEN, which converts PI(3,4,5)P3 to PI(4,5)P2 [11,18]. Somatic activating mutation also occur in the regulatory subunit p85α (R380*) by impairing the association of p85α to p110, both in cancer and overgrowth syndrome [19].

Differently from p110α and p110β which are ubiquitously expressed, p110δ has a more specific pattern of expression, being highly enriched in leukocytes. In fact the characterization of p110δ PI3K pathway has attracted more attention for its role in immune disease. Mutations in the p110δ isoform have been reported in activated PI3K delta syndrome (APDS1), a primary immunodeficiency disease [20], and p110δ protein was found to be the predominant isoform expressed in human primary breast carcinoma [21].

The frequent aberrant activation of the class I PI3K pathway in human cancer, immune and inflammatory diseases, has led to intense efforts to develop PI3K pathway inhibitors. Thanks to the high resolution structures obtained for class I PI3K, isoform-selective ATP competitive PI3K inhibitors have been developed. The first p110δ selective PI3K inhibitor has been recently approved for leukemias treatment [22], and > 80 clinical trials are currently ongoing for other anti-PI3K drugs [13]. The characteristics and selectivity of the most frequently used and novel PI3K inhibitors are listed in Table 1.

1.2. Class II and III PI3K structure and function

Class II PI3Ks include three different isoforms (PI3K-C2α, PI3K-C2β and PI3K-C2γ), sharing with class I PI3Ks a common domain organization composed of a C2-helical-kinase core (Fig. 1). Differently from class I, the class II PI3Ks have a C-terminal region comprising a C2-PX domain that mediates the association of the enzymes with PI(4,5)P2 at the plasma membrane [23,24]. PI3K-C2α and PI3K-C2β also present longer N-terminus domain compared to class I PI3Ks and this region is responsible for the association of the enzymes with clathrin during endocytosis [25] and cell division [26]. While PI3K-C2α and PI3K-C2β show almost ubiquitous expression [27], PI3K-C2γ expression is generally observed to hepatic and pancreatic parenchyma as well as breast, prostate and small intestine [28,29]. A general consensus regarding the phosphoinositide generated by class II PI3Ks is still missing, however, at least in vitro, they can produce both PI(3)P and PI(3,4)P2 [25,27,30].

Recently low-affinity and partially selective inhibitors targeting PI3K-C2β and PI3K-C2γ have been developed [31,32] (Table 2). Inhibition of PI3K-C2β was achieved by using the compound named PI701 that showed significant reduction in PI3K-C2β activity in an in vitro lipid kinase assay. The half maximal inhibitory concentration (IC50) values for specific inhibition of the enzymatic activity of PI3K-C2β were 528 nM for PI701 while values above 10 μM were observed for the other PI3K isoforms. Interestingly, in a panel of acute myeloid leukemia, brain tumors and neuroendocrine tumors overexpressing PI3K-C2β, the treatment with PI701 significantly reduces cell proliferation and survival [31]. Similarly, two compounds targeting PI3K-C2γ were developed with IC_{50} in the range of 3.5 μM compared to > 40 μM over PI3K-C2β/PI3K-C2α [32]. Until now, no data showing a biological relevance for the inhibition of PI3K-C2γ has been reported.

The Class III PI3K, also known as vacuolar protein sorting 34 (Vps34), is the ancestral member of the PI3K family and it is present in all eukariotes [33]. The Vps34 converts PI in PI(3)P, a second lipid messenger which is important in several vesicle sorting pathways to lysosomes, including autophagy and phagocytosis. Similar to class I PI3K, Vps34 contains a C2, an helical and a kinase domain, however the C2 domain has a different role compared to class I PI3K (Fig. 1). In fact, class I C2 domain is required for membrane recruitment, while Vps34 C2 domain has a scaffold function, mediating the association with the regulatory subunits. Class III PI3K is present in two different functional complexes, Complex I and Complex II, interacting with e following subunits: Vps15 (encoded by PIK3R4), Vps30 (BECN1) and either

Table 1
Representative Pan and Selective Class I PI3K Inhibitors under Clinical Investigation.

Target	Inhibitor	Trial Phase	p110α	p110β	p110γ	p110δ	Reference
Pan-PI3K	Buparlisib (BKM120)	III	52	166	262	116	[37,46,47,53]
p110α	Alpelisib (BLY719)	II	5	1200	290	250	[68]
p110α	Taselisib	III	0.29*	9.1*	0.12*	0.97*	[58,59]
p110δ	Idelalisib (CAL-101)	FDA approved	820	565	89	2.5	[50,52,55]
Pan-PI3K/mTOR	PQR309	II	33	661	708	451	[43]
Pan-PI3K/mTOR	Dactolisib (BEZ235)	II	4	75	5	7	[48,49,54]

Class I IC_{50} values (nM). *K_i.

Vps38 (UVRAG) or Atg14 (ATG14L). Complex I is characterized by the presence of aAg14 and NRBF2 components whereas complex II contains UVRAG protein. Although both complexes share a similar v-shaped conformation, Complex I has reduced activity on flat membranes compared to complex II, differing in the way of lipid substrate interaction [33].

The development of selective vps34 inhibitors [34,35] (Table 3) led to the definition of the role of vps34 in vesicle trafficking and autophagy. In addition, the pharmacological inhibition of class III PI3K resulted beneficial for the metabolic homeostasis in mice [36].

2. Failure of class I PI3K inhibitors

The PI3K family is one of the major altered pathways in several diseases, making it a promising therapeutic candidate for different disorders as cancer, immune diseases and inflammatory conditions [37]. However limiting success was reached, mainly because of a number of concerns about severe and occasionally fatal side effects of PI3K inhibitors.

One cause of class I PI3K inhibitors failure is the adaptive resistance and activation of compensatory pathways, independent from genomic changes [38]. Among these compensatory mechanisms, there is the reactivation of other critical signaling effectors such as tyrosine kinase receptors (HER2, HER3, IGFR1 and insulin receptor), Wnt-β-catenin, mTORC, NOTCH and ERK pathway.

The concomitant inhibition of class I PI3K and parallel compensatory pathways increased the therapeutic efficacy. For example, PIK3CA mutant BC cell lines treated with alpelisib, a p110α selective inhibitor, developed resistance to mTOR hyperactivation, which was reverted by the combination with everolimus [39]. One of the mechanism of resistance to p110α inhibition has been identified in the aberrant activation of PDK1 or SGK1 in PIK3CA mutant breast cancer cells [40].

Another mechanism which may prevent the success of PI3K inhibitors is the intrinsic or acquired resistance due to mutations in regulatory genes or increased genes encoding RTKs. Amplification of c-myc is a common mechanism of resistance but the direct targeting of this oncogene is still an unmet need [41]. Similarly, the prediction of which specific RTK, among a wide panel, confers resistance to PI3K inhibition is challenging.

Finally, clinical trials of pan-PI3K inhibitors as single agents have reached modest results due to off-target toxicity, as hyperglycaemia, gastrointestinal intolerance (anorexia, nausea, vomiting, diarrhea) and stomatitis [42,43]. The emergence of isoform-specific PI3K inhibitors provided a way to achieve maximal inhibitory doses while avoiding excessive off-target toxicity [44]. Nonetheless, PI3K isoform switching is a well-known mechanism of resistance to isoform-selective PI3K inhibitors [45].

For example, the phase I/II trial study on the PI3Kα/δ inhibitor Pictilisib in combination with cisplatin was stopped by the company due to excessive toxicities and lack of efficacy (clinicaltrials.gov). On the other hand, the reduced doses in order to prevent toxicities caused insufficient target of tumor tissue, i.e. the use of Buparlisib and taselisib in PI3KCA-mutant breast cancer patients was not approved by FDA, due to their modest effects [37]. Although some of these toxic effects are 'off-target', others may be directly related to mechanisms of action of the drug. A significant limit to clinical application of PI3K pathway inhibitors is the development of inflammatory conditions.

The BELLE series of clinical trials had a discontinuous story, due to frequency in adverse events as elevation of liver transaminases as a dose-limiting toxicity. The pan-PI3K inhibitor Buparlisib was effective in combination with various drugs in patients with estrogen receptor positive (ER+) and HER2 negative (HER2-) breast cancer [46,47]. Regrettably, Buparlisip (BKM120) showed off-target effects due to intrinsic tubulin-binding activity, therefore a novel selective analog, PQR309, has been selected for early clinical trials [43]. In addition, phase 1 trial of BEZ235, a dual PI3K/mTOR inhibitor, in advanced renal cell carcinoma [48] and pancreatic neuroendocrine tumors was prematurely terminated because of dose-limiting toxicities in absence of objective responses [49]. Similar results were described for the use of Idelalisib, a selective p110δ inhibitor approved for Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin lymphoma (NHL), in combination with rituximab. Trial discontinuation was due to main adverse autoimmune effects as increased transaminase for liver inflammation, pneumonitis and pneumonia, diarrhea and colitis. The toxicities of this drug seem to be directly correlated to its mechanism of action. In fact, the inhibition of PI3Kδ results in the depletion of Treg and consequent increase in T cell response, contributing to immune stimulation [50–52]. Similarly, in phase I studies, mucositis was reported in patients treated with Buparlisib or the dual PI3K/mTOR inhibitor, BEZ235 [53] [48,54]. Nevertheless, this pro-inflammatory effect can be potentially beneficial for cancer immunotherapy. A proposed strategy was the combination of class I PI3K inhibitors with tumor stroma immunomodulators in CLL and B-cell malignancies [55,56].

Besides inflammatory effects, a major complication of class I PI3K inhibitors is the reactivation of the PI3K-mTOR signaling pathway, with the consequent hyperactivation of the insulin pathway. P110α inhibitors paradoxically activates AKT signaling and glucose uptake in many tumors, as pancreatic cancer. The acute hyperglycemia sensed by the pancreas induces a massive release of insulin in the blood. This degree of hyperinsulinemia can reactivate PI3K signaling. This was in

Table 2
Representative Class II PI3K Inhibitors.

Target	Inhibitor	PI3K-C2α	PI3K-C2β	PI3K-C2γ	Class I	Company, Reference
PI3K-C2β	PI701	N.D.	530 nM	N.D.	> 10 μM	[31]
PI3K-C2γ	Compound 26	> 10 μM	23 μM	340	> 10 μM	[32]

Class II isoforms IC_{50} values.

Table 3
Representative Class III PI3K Inhibitors.

Target	Inhibitor	Vps34	p110α	p110β	p110γ	p110δ	Company, Reference
PI3K-C3 (vps34)	SAR405	1.2 nM	> 10 μM	> 10 μM	> 10 μM	> 10 μM	[35]
PI3K-C3 (vps34)	PIK-III	18 nM	3960 nM	> 9.1 μM	1200 nM	3040	[34]
PI3K-C3 (vps34)	VPS34-IN1	25 nM	> 10 μM	> 10 μM	> 10 μM	> 10 μM	[40]

Class III isoforms IC_{50} values.

part avoided combining isoform specific inhibitors with pharmaceutical or dietary suppression of insulin feedback [57].

3. Advances in PI3K inhibitors

Considerable efforts have been devoted toward the inhibitors targeting PI3K to improve clinical efficacy and to reduce adverse effects. The generation of isoform-selective PI3K inhibitors may reduce the intrinsic toxicity associated with pan-PI3K inhibition, allowing the exploration of combination therapies. In addition, the development of molecules that can selectively inhibit p110α mutants has nearly been achieved [13].

In line with the evidence for isoform specific-PI3K targeting in preclinical models, pivotal clinical trials indicate new opportunities for p110α-selective inhibition in selected patient populations. A phase I dose-escalation trial reported improved activity of Taselisib (tested at lowest dose) in patients with PIK3CA-mutant tumors versus tumors without PIK3CA mutations (hotspots) [58]. In contrast, an open-label phase II study reported responses in patients with both PIK3CA-mutated and PIK3CA-wt, when treated with Taselisib plus fulvestrant [59]. Currently, the phase 3 SOLAR-1 is evaluating the effects of Taselisib or placebo plus fulvestrant in two separate breast cancer cohorts characterized by patients with wt or mutated PIK3CA (https://clinicaltrials.gov/ct2/show/NCT02437318). This large study will establish whether Taselisib has higher antitumor activity in PIK3CA-mutated versus PIK3CA-wt tumors when combined with fulvestrant. Importantly, this specific activity against PIK3CA mutants is due to taselisib's unique mechanism of action, targeting the degradation of mutant PIK3CA H1047R [60].

In particular, these preclinical studies indicate that taselisib, which has the ability to trigger degradation of mutant p110a protein, can suppress more effectively the PI3K signaling pathway, resulting in greater anti-tumor activity and improved therapeutic index.

Similar results were observed with the α-selective inhibitor Alpelisib in combination with letrozole (http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.e12527) in patients displaying PIK3CA mutations. Importantly, the combination Alpelisib + letrozole showed superior safety profile compared to that of Buparlisib plus fulvestrant in the BELLE-2 and 3 trials. Patients that manifested mild hyperglycemia were successfully managed with metformin treatment. In addition, combination of Alpelisib plus fulvestrant in PIK3CA mutant/ER^+ patients showed significantly increased progression-free survival compared to wild type PIK3CA [61].

New generation of isoform-selective PI3K inhibitors shows great promise in combination with CDK4/6 inhibitor Palbociclib in preclinical models of breast cancer, NSCLC and pancreatic cancer [62,63].

Another important advance in the field is represented by new treatment schemes and drug administration, broadening the therapeutic window for PI3K inhibitors. Innovative treatment schemes can reduce systemic feedback through elevated glucose and insulin in order to raise safety profiles of anti-PI3K drugs. To prevent severe side-effects due to systemic administration of PI3K inhibitors, alternative delivery routes have been explored. Recently Campa et al. developed a new highly selective and potent pan-PI3K class I inhibitor, CL27c [64] (patent registered WO/2012/073184) for inhaled therapy. In contrast to conventional PI3K inhibitors, CL27c is designed as a biologically inactive membrane-permeable pro-drug optimized for aerosol delivery. CL27c is hydrolyzed into the active moiety once inside the epithelial cellular lining of the airways. As such, CL27c can minimize the systemic toxic effects of pan-PI3K inhibitor (typically hyperglycemia/hyperinsulinemia), efficiently target the pulmonary tissue, and lower phospho-AKT levels in lungs [64]. CL27c reverts the growth of pulmonary fibroblasts in a model of a cancer-like disorder such as idiopathic pulmonary fibrosis [65]. These findings provide a justification for further studies of this novel drug administration system, to increase treatment efficacy and reduce systemic adverse effects. Although clinical trials with rapalogs and dual PI3K/mTOR inhibitors showed limited efficacy in cancer treatment, several diseases outside of oncology (including tuberous sclerosis, Cowden and overgrowth syndromes) substantially benefit from PI3K/mTOR inhibitors [13]. These diseases share a common etiology characterized by an aberrant PI3K signaling and a partial pathway inhibition is sufficient to extend life- and healthspan of these patients.

4. Conclusions

The failure of many clinical trials confirmed that that the toxicity of broad PI3K pathway inhibition is the major limit to optimal therapeutic efficacy. Currently, multiple compounds targeting PI3K pathway are in clinical trials showing great promise for PI3K-mutated tumors [66,67]. It is now emerging that different strategies aimed at reducing the toxicity and adverse effects are required. Besides new treatment schemes and chemical modifications, broadening the therapeutic window for pan-PI3K inhibitors is necessary. Studies like those reviewed here give us important clues as to which specific genomic alterations are critical for proper patient stratification and successful development of next generation inhibitors.

In addition, PI3K inhibitors are associated with statistically significant increased risk of high-grade hyperglycaemia. While most of the side effects may be easily managed, education of healthcare professionals is crucial to guarantee patient safety. Lastly, PI3K inhibitors have also immunomodulatory activity on angiogenesis and tumor microenvironment. Besides its direct effect on cancer cells, emerging evidence indicates that PI3K inhibitors may restore the immune response to tumors and improve responsiveness to checkpoint blockade treatment. Therefore, PI3K inhibitors may offer an improved therapeutic opportunity to treat also non-resolving inflammatory pathologies. Eventually, the recent development of specific class II/IIIPI3Ks will help to define the role of these new isoforms as “cancer genes” with non-redundant class I functions.

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Declarations of interest

EH is co-founder of Kither Biotech, a company involved in the development of PI3K inhibitors. The other authors declare no conflict of interest.

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