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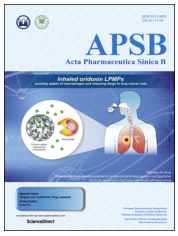

REVIEW

Class I phosphatidylinositol 3-kinase inhibitors for cancer therapy

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KEY WORDS

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Abstract The phosphatidylinositol 3-kinase (PI3K) pathway is frequently activated in human cancers. Class I PI3Ks are lipid kinases that phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) at the 3-OH of the inositol ring to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3), which in turn activates Akt and the downstream effectors like mammalian target of rapamycin (mTOR) to play key roles in carcinogenesis. Therefore, PI3K has become an important anticancer drug target, and currently there is very high interest in the pharmaceutical development of PI3K inhibitors. Idelalisib has been approved in USA and Europe as the first-in-class PI3K inhibitor for cancer therapy. Dozens of other PI3K inhibitors including BKM120 and ZSTK474 are being evaluated in clinical trials. Multifaceted studies on these PI3K inhibitors are being performed, such as single and combinational efficacy, resistance, biomarkers, etc. This review provides an introduction to PI3K and summarizes key advances in the development of PI3K inhibitors.

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1. Introduction

Phosphatidylinositol 3-kinases (PI3Ks) are a family of lipid kinases that phosphorylate the 3-OH of the inositol ring of phosphoinositides[1,2]. Class I PI3Ks (generally called PI3Ks) are lipid kinases that phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 serves as a second messenger that plays important roles in fundamental cellular responses such as cell growth, survival, migration and metabolism[3,4]. As a catalytic antagonist of PI3K, phosphatase and tensin homolog deleted on chromosome ten (PTEN) dephosphorylates PIP3 to PIP2 (Fig. 1). Since frequent gain-of-function mutations of PI3Ks and loss-of-function mutations of PTEN in human cancers suggest that PI3Ks are closely involved in tumorigenesis[5], inhibitors targeting PI3Ks are expected to be promising anticancer drug candidates. In the past decade, dozens of PI3K inhibitors have been developed as potential chemotherapeutic drugs. Many of these have successfully entered clinical trials. In particular, idelalisib (CAL-101) has been approved in the USA and Europe as the first-in-class PI3K inhibitor for cancer therapy.

In this review, we introduce PI3Ks and briefly describe the development of some representative PI3K inhibitors in clinical trials.

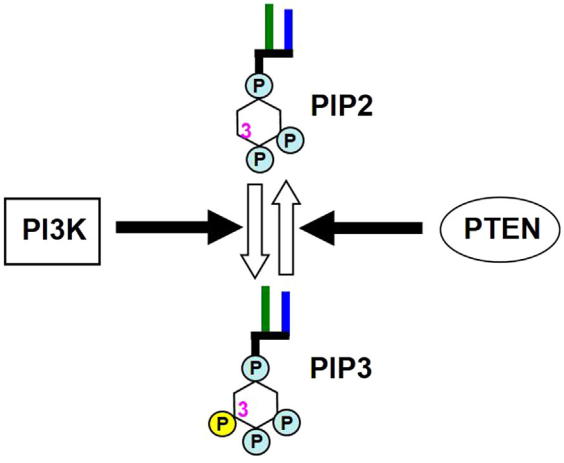

Figure 1 Schematic structures of PI3K and PTEN, and the related lipid reactions they catalyze. PI3K phosphorylates PIP2 at 3-OH to generate PIP3. As a counterpart of PI3K, PTEN dephosphorylates PIP3 to produce PIP2. PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate.

2. PI3K, critical element that is involved in carcinogenesis

PI3Ks belong to a family of lipid kinases that phosphorylate the 3-OH group of phosphoinositides[1,6,7]. Based on their primary structures and *in vitro* substrate specificity, PI3Ks are classified into three classes[8,9]. Class I PI3Ks, which preferentially catalyze the phosphorylation of PIP2 to generate PIP3, are heterodimeric kinases as complexes of a catalytic subunit p110 with a regulatory subunit p85, p101, or p84. Members of this class are generally called PI3Ks because they have been investigated far more than the other two classes. PI3K-related kinases (PIKKs), which sometimes are termed Class IV PI3Ks, are protein kinases with a similar structure to the catalytic subunits of PI3Ks. Examples of PIKKs include mTOR and DNA-dependent protein kinase (DNA-PK), which are known to be involved in protein synthesis or DNA repair[10]. Class I PI3Ks are further divided into subclasses IA and IB based on their regulatory subunit and upstream activator[7]. Class IA PI3Ks are mainly activated by various receptor tyrosine kinases (RTKs) and RAS[11]. There are three isoforms in Class IA including PI3Kα, PI3Kβ, and PI3Kδ, with the respective p110 catalytic subunit bound to the p85 regulatory subunit. Class IB PI3Kγ, which consists of catalytic subunit p110γ and a regulatory subunit p101 or p84, is mainly activated by G-protein-coupled receptors (GPCRs) such as chemokine receptors[12–14]. While the PI3Kα and PI3Kβ are expressed ubiquitously, PI3Kδ and PI3Kγ are mainly in hemopoietic cells[15]. In particular, PI3Kα is known to play an important role in tumorigenesis because a high frequency of gain-of-function mutations and amplification of *PIK3CA*, which encodes p110α; this isoform has been found in human cancers[16–20]. Additionally, PI3Kα was found to be involved in insulin signaling and glucose metabolism[21]. PI3Kβ was reported to activate platelets, suggesting a role in the development of thrombotic diseases[22]. Recently, various reports showed that PI3Kβ predominantly contributed to PIP3 production in PTEN negative cancers, suggesting the key role of PI3Kβ in tumorigenesis with PTEN inactivation[23,24]. PI3Kδ and/or γ inactivation leads to a severely impaired immune system[25,26], and blocks the recruitment of neutrophils to the sites of inflammation[27,28], suggesting that these two isoforms are involved in the immune system and inflammation. As the counterpart of PI3K, PTEN is also closely involved in cancer since frequent loss-of-function mutations were found in various human cancers[29]. In addition, *PI3K* mutation and PTEN inactivation were reported to cause resistance to cancer therapies targeting the RTKs[30]. Thus, PI3K is thought to be an attractive target for cancer chemotherapy.

PI3K pathway is closely involved in survival, growth, invasion of cancer cells and tumor angiogenesis. As shown in Fig. 2, after activation by RTK, GPCR or RAS, PI3K phosphorylates PIP2 to produce PIP3; this reaction is reversed by PTEN. PIP3 binds the pleckstrin homology (PH)-domain-containing protein kinases such as Akt and PDK1, to activate and recruit them to the plasma membrane. After recruitment by PIP3, Akt is activated by PDK1 and mTOR complex 2 (mTORC2)[3]. Activation of Akt promotes cell cycle progression by regulating glycogen synthesis kinase 3β (GSK3β) and the downstream cyclin D1. Akt also acts to maintain cell survival through inhibition of Bcl2-antagonist of cell death (BAD). Furthermore, Akt promotes cell growth by phosphorylation of the downstream mTOR complex 1 (mTORC1)[31], which translates mRNAs to protein *via* the p70S6K-S6 and 4E-BP1-eIF4E pathways[32]. In addition, hypoxia-inducible factor 1α (HIF-1α) was reported to be up-regulated downstream of mTORC1, and therefore promotes tumor angiogenesis by transcribing vascular endothelial growth factor (VEGF)[33]. By activating NF-κB and inducing secretion of matrix metalloproteinase (MMP), Akt also promotes cell invasion[34]. However, phosphorylation of S6K negatively regulates insulin receptor substrate (IRS), leading to a negative feedback loop[35–37]. Therefore, inhibition of mTORC1 may activate upstream proteins such as PI3K and Akt[38], and consequently reduces the inhibitory potency.

Development of novel PI3K inhibitors attracted a great deal of attention from both academia and industry, while classic PI3K inhibitors LY294002 and wortmannin did not reach clinical trials due to the toxicity and poor druggability. Among the PI3K inhibitors under active development, some are PI3K isoform specific inhibitors like idelalisib (CAL-101) and IPI-145, but most are pan-PI3K inhibitors (Table 1). Besides, some exhibit