Review Article



# Regulation of PI3K signaling in cancer metabolism and PI3K-targeting therapy

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**Abstract:** The phosphatidylinositol-3-kinase (PI3K) signaling plays a key role in various cellular functions and is frequently activated in cancer, making it an attractive therapeutic target. The PI3K signaling pathway influencing glucose metabolism, lipid synthesis, nucleotide production, and protein synthesis, all of which contribute to cancer cell proliferation and survival. It enhances glucose uptake through the activation of glucose transporters and glycolysis, while also promoting lipid synthesis via downstream factors like mTORC1. This pathway boosts nucleotide synthesis by regulating transcription factors like MYC, activating key enzymes for purine and pyrimidine production. Additionally, due to its essential role in cancer cell growth, the PI3K pathway is a key target for anticancer therapies. However, treatment using PI3K inhibitors alone has limitations, including drug resistance and significant side effects such as hyperglycemia, fatigue, and liver dysfunction. Clinical trials have led to the development of isoform-specific PI3K inhibitors to reduce toxicity. Combining PI3K inhibitors with other treatments, such as hormone therapy or surgery, may improve efficacy and minimize side effects. Further research is needed to fully understand the mechanisms of PI3K inhibitors and improve individualized treatment approaches. In this review, we introduce the characteristic of three classes of PI3Ks, discuss the regulation of cancer metabolism including the control of glucose uptake, glycolysis, *de novo* lipid synthesis, nucleotide synthesis and protein synthesis, and review the current statuses of different PI3K inhibitors therapy.

**Keywords:** Phosphatidylinositol-3-kinase (PI3K); cancer; metabolism; target therapy; PI3K inhibitor

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## Introduction

The phosphatidylinositol-3-kinase (PI3K) signaling pathway is a crucial intracellular mechanism that regulates various cellular functions, including growth, metabolism, movement, survival, and angiogenesis. The activation of the PI3K/AKT/mTOR pathway is crucial in driving tumor progression, as well as other physiological and pathophysiological functions. After PI3K activation, PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to form phosphatidylinositol-3,4,5-trisphosphate (PIP3), leading to the translocation and activation of protein kinase B (AKT) on the cell membrane. AKT belongs to the serine/threonine-specific protein kinase family and exists in three main isoforms: Akt1, Akt2, and Akt3. AKT can phosphorylate various intracellular substrates such as

glycogen synthase kinase 3 beta (GSK-3β), Bcl-2-associated death promoter (BAD), and forkhead box O (FOXO) transcription factors, thereby regulating multiple biological functions of cells including metabolism, proliferation, survival, and metastasis.

Under physiological conditions, the activation of the PI3K/AKT signaling pathway begins with the binding of growth factors, hormones, and other extracellular signals to receptor tyrosine kinases (RTKs), regulating organismal metabolism. This pathway plays a crucial role in maintaining normal cell growth, proliferation, and survival. However, dysregulation of the PI3K/AKT pathway is common in various cancers, leading to metabolic reprogramming of cells. This results in the overactivation of cellular processes that enhance cell survival, growth, and metabolism, promoting tumorigenesis to meet the synthetic demands of tumor cells.

The PI3K/AKT signaling pathway plays a critical role in regulating cellular metabolism by various mechanisms, including direct modulation of metabolism-associated proteins, indirect regulation of metabolism through transcription factors, acute metabolic changes mediated by phosphorylation of metabolic enzymes, and long-term metabolic effects through the regulation of gene expression programs. These regulatory mechanisms enable the PI3K/AKT pathway to exert key roles in cell growth, proliferation, and survival.

Therefore, targeting the PI3K/AKT signaling pathway has become an attractive strategy for cancer treatment. This is because the pathway plays crucial roles in cell growth, metabolism, and survival. In cancer cells, the PI3K/AKT pathway is often aberrantly activated, leading to abnormal proliferation and survival. By inhibiting this pathway, it is possible to reprogram the metabolic processes of cancer cells, inducing apoptosis (programmed cell death) or senescence (loss of cellular function), thereby preventing further proliferation and spread of cancer cells.

Numerous inhibitors have been developed to target the PI3K signaling pathway, with some approved for clinical therapy, leading to improvements in the survival rates of cancer patients. However, there are still numerous issues related to side effects and drug resistance that need to be addressed. Despite some successes in clinical use, PI3K inhibitors are still plagued by concerns regarding side effects and drug resistance. Side effects may include hyperglycemia, rash, fatigue, among others, while resistance issues may lead to decreased drug efficacy. Therefore, systematic exploration of the mechanisms of action of PI3K inhibitors and the formulation of individualized treatment decisions are crucial for further enhancing the clinical effectiveness of PI3K inhibitors.

## Overview of the PI3K

PI3K is a group of enzymes associated with the plasma membrane, primarily involved in regulating essential biological processes such as cell growth, survival, proliferation, and metabolism. Its function involves the synthesis of PIP3 in signaling pathways, thereby activating a cascade of downstream signaling molecules, including AKT and mammalian target of rapamycin (mTOR), to influence cellular physiology and pathology (1).

PI3K can be divided into three main classes: I, II, and III, each composed of specific subunits, including a regulatory subunit and a catalytic subunit. These classes have distinct substrate specificities and functions, regulating cellular signaling and metabolic pathways differently (2).

The PI3K pathway plays a critical role in regulating tumor cell metabolism, particularly in glycolysis and fatty acid synthesis. It promotes glucose uptake and utilization, enhancing energy storage by influencing AKT and mTOR signaling. Additionally, the PI3K pathway stimulates cell growth and proliferation through the activation of AKT and mTOR. Studies have shown that this pathway is not only vital for the growth of normal cells but is also aberrantly activated in various cancers, driving tumor cell growth and survival, and closely associated with tumor invasion and metastasis. Moreover, the PI3K pathway integrates signals from multiple growth factors and cytokines, allowing cells to adapt to environmental changes and promote growth and survival. In cancer treatment, the abnormal activation of the PI3K pathway is often linked to treatment resistance. Understanding the modern mechanisms of this pathway can help develop new therapeutic strategies to overcome resistance. Furthermore, the PI3K pathway interacts with other signaling pathways in the tumor microenvironment, such as the MAPK and Wnt pathways, influencing tumor growth, metastasis, and response to treatment. Therefore, PI3K has become an important target in cancer therapy, and inhibitors targeting this pathway have been extensively researched and used in clinical trials, offering new hope for cancer patients' treatment (3).

### *Class I PI3Ks*

Class I PI3Ks are a crucial group of cellular signaling enzymes involved in regulating key biological processes

such as cell growth, survival, proliferation, and metabolism. Class I PI3Ks include PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, with their catalytic subunits encoded by PIK3CA, PIK3CB, PIK3CG, or PIK3CD genes. They catalyze the conversion of PIP2 on the cell membrane to PIP3. Class I PI3Ks are further divided into two subclasses based on their structure, substrate specificity, and regulation: IA and IB. Class IA PI3Ks are activated by RTKs and consist of a regulatory subunit (p85) and a catalytic subunit (p110) (4). The p85 subunit has five variants (p85α, p55α, p50α, p85β, and p55γ), while p110 has three isoforms (p110α, p110β, and p110δ). Class IA PI3Ks can bind to intracellular signals from proteins like Rho, SHP1, and protein kinase C, and activate downstream signaling molecules through the p110 subunit (5). Class IB PI3Ks include a catalytic subunit (p110γ) and a regulatory subunit (p101 or p84) and are typically activated by G protein-coupled receptor (GPCR) Gβγ subunits. In summary, Class I PI3Ks are critical regulators of cell growth, metabolism, and survival. Class IA and IB subtypes play distinct roles in cellular signaling pathways, and their dysregulation is associated with various diseases, making them important targets for therapeutic research.

### *Class II PI3Ks*

Class II PI3Ks are a class of relatively complex enzymes characterized prominently by their C-terminal C2 domain. This domain lacks critical aspartic acid residues necessary for binding Ca2+, indicating that Class II PI3Ks can interact with lipids independently of Ca2+. Class II PI3Ks comprise three subtypes: PI3K-C2α, PI3K-C2β, and PI3K-C2γ. PI3K-C2α and PI3K-C2β are widely expressed, whereas PI3K-C2γ is expressed predominantly in the liver, breast, prostate, salivary glands, and exocrine pancreas. They can synthesize two distinct products, phosphatidylinositol-3-phosphate (PI(3)P) and phosphatidylinositol-3,4-bisphosphate (PI(3,4)P2), depending on substrate specificity (6).

Compared to Class I PI3Ks, Class II PI3Ks have been relatively overlooked in research, especially in the field of cancer. However, recent studies suggest their potential significant roles in cancer development and progression. Class II PI3Ks primarily regulate intracellular dynamics and membrane trafficking rather than functioning in signal transduction. Specifically, PI3K-C2α regulates cancer cell death and mitosis by controlling spindle stability. In contrast, PI3K-C2β is involved in cancer cell migration and invasion, potentially influencing proliferation through the regulation of cyclin B1 expression. However, our understanding of the role of PI3K-C2γ in cancer is still limited (7).

Due to their regulation of crucial membrane-related processes such as endocytosis, lysosomal activity, and cell adhesion, Class II PI3Ks may play either promotive or inhibitory roles in tumor growth, invasion, and metastasis. Therefore, gaining a deeper understanding of the functions and regulatory mechanisms of Class II PI3Ks is essential for developing more effective cancer treatment strategies. Future research should further explore the roles of Class II PI3Ks in the tumor microenvironment and the development of targeted drugs against these enzymes, aiming to provide more personalized and efficient treatment options for cancer patients (8).

### *Class III PI3Ks*

Class III PI3Ks are heterodimeric enzymes consisting of a regulatory subunit (VPS15) and a catalytic subunit (VPS34), which have been found to be involved in the regulation of autophagy. VPS34 phosphorylates phosphatidylinositol (PI) to generate PI(3)P. VPS34, the smallest PI3K catalytic core, forms two tetrameric complexes—complex I and complex II, which play roles in autophagy and endocytosis, respectively. Complex I is involved in the recruitment of the endoplasmic reticulum (ER), crucial for the formation and elongation of autophagosomes, while complex II regulates endosome maturation and promotes fusion between autophagosomes and late endosomes/lysosomes.

Research on VPS34 in cancer has revealed its role in promoting cell survival and proliferation through inducing autophagy. For instance, studies have shown that VPS34 expression correlates with the oncogenic activity of human breast cancer cells. VPS34 enhances the binding of PKC-δ to p62, leading to its phosphorylation at serine 349, thereby positively reinforcing Nrf2-dependent transcription of oncogenes and promoting tumor growth. Additionally, inhibitors of VPS34 significantly enhance the sensitivity of breast cancer cells to tyrosine kinase inhibitors by suppressing autophagy. Therefore, VPS34 represents a promising therapeutic target for combination therapies in breast cancer (9).

## Key regulation of cancer metabolism

Metabolic reprogramming, including lipid dysfunctions, is a key characteristic of cancer cells. It leads to changes

in metabolic enzymes and pathways that impact the development, progression, and metastasis of cancer. The activity of upstream oncogenes of PI3K is increased in cancer cells, resulting in altered nutrient transporters and metabolic enzymes. This alteration in metabolism meets the anabolic needs of abnormal cells and contributes to cancer progression.

### *Control of glucose metabolism (glucose uptake and glycolysis)*

One of the most common metabolic characteristics that distinguish tumor cells from normal cells is altered glucose metabolism. This metabolic feature is known as aerobic glycolysis, also referred to as the Warburg effect. Aerobic glycolysis refers to the tendency of tumor cells to convert glucose to lactate through glycolysis, even in the presence of sufficient oxygen, rather than producing energy through mitochondrial oxidative phosphorylation. This process is characterized by increased glucose uptake and lactate production; tumor cells exhibit a higher rate of glucose uptake and predominantly convert glucose to lactate, even in an oxygen-rich environment (10). Glycolysis not only generates adenosine triphosphate (ATP) but also provides metabolic intermediates necessary for biosynthetic processes, including the synthesis of proteins, lipids, and nucleotides, which are essential for cell growth and proliferation (11). Aerobic glycolysis also helps maintain redox balance within the cell by regenerating NAD+ through the primary conversion of pyruvate to lactate.

The PI3K/AKT pathway promotes glycolysis through various mechanisms, including increasing glucose uptake, activating key glycolytic enzymes, regulating the expression of glycolysis-related genes, and modulating the utilization of metabolic products (12). This pathway plays a critical role in cellular energy metabolism and growth, with a particularly significant impact in tumor cells, enabling them to grow rapidly even under adverse conditions (13).

The PI3K/AKT pathway plays a significant role in regulating anabolic metabolism through directly phosphorylating mechanisms. The pathway directly regulates glucose uptake and glycolysis through glucose transporters (GLUTs), with AKT promoting glucose uptake via both GLUT1 and GLUT4 (14-17). AKT promotes the translocation of the glucose transporter GLUT4 by phosphorylation, facilitating its movement from intracellular vesicles to the cell membrane, thereby increasing cellular glucose uptake (18). Additionally, upon AKT activation, FoxO1 and FoxO3a are phosphorylated and translocated from the nucleus to the cytoplasm, leading to the suppression of thioredoxin-interacting protein (TXNIP) expression. TXNIP is a protein that promotes the endocytosis of GLUT1 and GLUT4, thereby inhibiting glucose uptake (19,20). Furthermore, the AKT signaling pathway enhances the metabolic activation of glucose by directly phosphorylating and activating hexokinase 2 (HK2), a key enzyme in the glycolytic pathway. HK2 catalyzes the conversion of glucose to glucose-6-phosphate, which is the first step in glycolysis and a critical rate-controlling step. HK2 is highly expressed in many cancer cells and associates with the outer mitochondrial membrane, contributing to the high glycolytic activity of cancer cells. AKT phosphorylates HK2 directly, increasing its enzymatic activity and mitochondrial localization. This process facilitates HK2 to more efficiently perform its catalytic function within the cell, thereby enhancing glycolytic efficiency (21,22).

PI3K activation has also been found to promotes glycolytic flux in an AKT-independent manner, except for PI3K-initiated AKT activation. Aldolase is a key glycolytic enzyme responsible for catalyzing the breakdown of fructose-1,6-bisphosphate (F1,6BP) into glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP). This step is the fourth in the glycolytic pathway and is crucial because it splits the six-carbon molecule into two three-carbon molecules, allowing the metabolic process to continue. Stimulation of PI3K by growth factors and insulin prompts the release of the glycolytic enzyme aldolase A bound to filamentous actin, and a subsequent rise in aldolase activity, which leads to heightened glycolytic flux (23). Increased levels of aldolase A in cancer are linked to adverse patient prognosis. Inhibition of aldolase A has been demonstrated to reduce tumor growth in xenograft models (24). Therefore, inhibiting the PI3K pathway to reduce the activity of aldolase A and consequently suppress tumor growth may represent a promising therapeutic approach.

Furthermore, the PI3K/AKT pathway indirectly regulates glycolysis and other metabolic pathways through downstream transcription factors such as FOXO, HIF1 (hypoxia-inducible factor 1), MYC, and ATF4 (activating transcription factor 4) (25-27). These transcription factors oversee the regulation of gene expression related to glucose transporter production and glycolytic enzyme activity (28).

Those studies indicate that PI3K signaling is crucial in facilitating glucose uptake and glycolysis, in both normal and cancerous cells. In the context of oncogenic PI3K

signaling, the aforementioned regulatory mechanisms collectively contribute to the persistent activation of aerobic glycolysis. This metabolic trait, commonly observed in cancer cells, enables metabolic intermediates to be utilized by metabolic pathways branching off glycolysis, ultimately contributing to the biosynthesis of cellular macromolecules.

### *Control of de novo lipid synthesis*

The PI3K/AKT signaling pathway is essential for the regulation of various cellular processes, including cell survival, growth, and metabolism. One of the metabolic processes regulated by this pathway is *de novo* lipid synthesis. Lipid synthesis is necessary for membrane biogenesis, signal transduction, and energy storage, and plays a crucial role in regulating normal cellular function. Nevertheless, irregularities in lipid synthesis have been associated with the development of cancer (29). The production of fatty acids and sterols from cytosolic acetyl-CoA through *de novo* lipid synthesis can be initiated in two ways: either from citrate with the involvement of ATP citrate lyase (ACLY), or from acetate via acetyl-CoA synthetase. Extensive research has demonstrated that PI3K signaling can activate multiple enzymes involved in lipid synthesis and promote this process through various mechanisms, including transcriptional regulation and post-translational modifications (30,31).

By directly phosphorylating ACLY, the PI3K/AKT pathway can activate *de novo* lipid synthesis, leading to heightened production of cytosolic acetyl-CoA, which is then utilized in the synthesis of fatty acids and sterols (32,33). In addition, this pathway can also contribute to protein acetylation reactions. Studies have shown that the AKT-ACLY axis plays a pivotal role in tumor growth and histone acetylation (34). ACLY is frequently often observed to be upregulated in different human cancer types, and inhibiting this enzyme has demonstrated efficacy in decreasing cancer cell proliferation in both laboratory and animal models, indicating its promise as a therapeutic target for cancer treatment (35).

The activation of the PI3K/AKT pathway can also promote the synthesis of fatty acids and cholesterol by activating the sterol regulatory element-binding protein (SREBP) family of transcription factors, which regulate the expression of genes related to lipid biosynthesis. Studies have shown that tumors can increase glucose uptake through the PI3K/AKT/mTOR signaling pathway, thereby driving the N-glycosylation of SREBP cleavage-activating protein (SCAP), which in turn activates SREBP. The N-glycosylation of SCAP is crucial for its transport and activation. The precursor protein of SREBP is bound to the ER membrane in an inactive form. Its activation is inhibited by the ER-resident protein Insig, which prevents the translocation and nuclear activation of SREBP. For SREBP to become an active transcription factor, it needs to be transported to the Golgi apparatus for proteolytic cleavage. Once cleaved, it can then enter the nucleus to regulate the expression of target genes. Insig binds to SCAP, and glucose-mediated N-glycosylation promotes the dissociation of SCAP from Insig, forming the SCAP/SREBP complex and facilitating its transport from the ER to the Golgi apparatus. In the Golgi, the precursor protein of SREBP is proteolytically cleaved, and the active form of SREBP translocates to the nucleus. Once in the nucleus, it binds to the sterol regulatory elements (SRE) of target gene promoters, upregulating the transcription of genes involved in lipid biosynthesis. These genes encode enzymes such as acetyl-CoA carboxylase and fatty acid synthase for fatty acid synthesis, as well as HMG-CoA reductase for cholesterol synthesis (36,37). SREBP family induce the expression of a wide range of enzymes involved in the synthesis of sterols and fatty acids, including SLC25A1, ACLY, ACSS2, ACC, FASN and SCD1 (38). In addition to promoting the processing and nuclear translocation of SREBP, the PI3K/AKT/mTORC1 signaling pathway can also activate SREBP through other pathways, resulting in the upregulation of lipogenic gene expression and increased *de novo* lipid synthesis. For example, SREBP can be phosphorylated by synthase kinase-3 (GSK3) at either Ser-73 or Arg-96, facilitating its dissociation from the SREBP-1c-SCAP complex and subsequent GSK-3-dependent proteasomal degradation via the ubiquitin ligase pathway. And AKT can inhibit glycogen GSK3, thereby enhancing the stability of active SREBP and preventing its degradation via ubiquitination (39-42). Hence, AKT signaling can potentially boost SREBP processing by activating mTORC1 and maintain the stability of activated SREBP by inhibiting GSK3 activity. Moreover, recent studies have unveiled a collaborative role of MYC with SREBP in fostering lipogenesis and promoting cancer progression (43,44).

In addition, mTORC1 affects lipid synthesis through the phosphorylation and activation of S6 kinase 1 (S6K1). S6K1 is one of the downstream effector proteins of mTORC1, playing a critical role in protein synthesis, cell growth, and metabolic regulation. S6K1 enhances ribosomal translation activity by phosphorylating and regulating multiple translation initiation and post-translational

 

modification factors, leading to increased synthesis and activity of enzymes involved in lipid synthesis. Specifically, activated S6K1 can directly phosphorylate SR protein kinase 2 (SRPK2), enabling its regulatory role in RNA splicing within the nucleus, impacting the transcription and translation levels of genes related to lipid synthesis, thus influencing lipid biosynthesis and metabolism (45). Moreover, numerous *de novo* lipid synthesis enzymes have been found to be upregulated in diverse cancer types, encompassing SREBPs, SRPK2, and the lipogenic enzymes activated by SREBP family. These constituents continue to be regarded as promising targets for cancer therapy (46,47).

### *Control of nucleotide synthesis*

Nucleotides play a crucial role in the synthesis of nucleic acids and the facilitation of diverse cellular processes, comprising purines and pyrimidines. In cancer cells, there's a significant increase in the generation of new nucleotides, vital for driving their rapid growth and proliferation—a departure from the behavior of healthy cells (48).

Various metabolic pathways play crucial roles in nucleotide synthesis, including the pentose phosphate pathway (PPP), which provides ribose-5-phosphate necessary for nucleotide synthesis. Serine and glycine are essential precursors for pyrimidine and purine synthesis, participating in one-carbon unit transfer. One-carbon metabolism, which includes the folate cycle and methionine cycle, supplies one-carbon units required for the synthesis of purines and pyrimidines. Glutamine is converted into glutamate and ammonia in cells and further participates in the tricarboxylic acid (TCA) cycle, providing the nitrogen and carbon skeletons needed for nucleotide synthesis. The TCA cycle provides precursor molecules for nucleotide synthesis, such as oxaloacetate, which can be converted to aspartate and contribute to pyrimidine and purine synthesis (49,50). Therefore, it's evident that AKT signaling regulates nucleotide synthesis through multiple mechanisms, thereby impacting metabolism.

The activation of the PI3K/AKT/mTORC1 signaling pathway can enhance the metabolic flux of glucose carbon into the PPP, facilitating the production of ribose essential for nucleotide synthesis (51). The PI3K/AKT/mTORC1 pathway enhances the metabolic flux of the oxidative PPP by upregulating the expression of its key enzyme, glucose-6-phosphate dehydrogenase (G6PD). G6PD catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconolactone while reducing NADP+ to NADPH. This reaction is the first step in the oxidative PPP and serves as the rate-controlling step for this pathway. Glucose-6-phosphate gains entry into the oxidative arm of the PPP through the activity of glucose-6-phosphate dehydrogenase, resulting in the generation of ribose-5-phosphate and bypassing glycolysis (52,53). Additionally, research has shown that AKT can directly activate transketolase (TKT), a key enzyme in the non-oxidative phase of the PPP (54). Evidence shows that the PI3K/AKT signal crosstalks with PPP branching metabolic pathways to promote PPP metabolism by stabilizing G6PD protein and inhibiting G6PD E3 ligase TIRM21, while PPP metabolites reinforce AKT activation and promote cancer metabolic reprogramming (51). In breast cancer cells, metabolic enzymes in both oxidative and non-oxidative PPP are upregulated, therefore, inhibiting them can reduces tumor proliferation; After treatment with PI3K inhibitors, the metabolic flux through the non-oxidative PPP in breast cancer cells is significantly reduced (55,56), indicating a greater dependency of tumors on this metabolic pathway (57). Hence, investigating PPP metabolic enzymes or targeting PI3K holds considerable significance and can offer more tailored and individualized approaches to cancer treatment.

AKT can regulate nucleotide synthesis by modulating the transcription of MYC. Additionally, MYC directly regulates the expression of enzymes involved in the pyrimidine and purine synthesis pathways. For example, phosphoribosyl pyrophosphate (PRPP) is essential for nucleotide synthesis, and MYC controls the synthesis of PRPP by regulating phosphoribosyl pyrophosphate synthase 2 (PRPS2) at both the transcriptional and translational levels (58-60). Moreover, glutamine is a crucial primary nitrogen donor for synthesizing pyrimidine and purine bases. MYC can promote both the synthesis and uptake pathways of glutamine. MYC regulates the transcription of several key enzymes involved in glutamine synthesis, such as glutamate-cysteine ligase (GCLC), glutamate kinase (GK), and glutamate dehydrogenase (GDH). MYC also upregulates the expression of transporters SLC1A5 and LAT1, thereby increasing the rate of cellular glutamine uptake (61,62).

The PI3K/AKT/mTORC1 signaling pathway influences nucleotide synthesis through various mechanisms, including the regulation of both pyrimidine and purine synthesis. In pyrimidine synthesis, growth factor signaling activates the PI3K/AKT pathway, subsequently activating mTORC1. mTORC1 then phosphorylates and activates the primary rate-limiting enzyme in the pyrimidine synthesis pathway,

thereby promoting pyrimidine synthesis (63). In addition to pyrimidine synthesis, mTORC1 triggers purine resynthesis through transcriptional mechanisms. Moreover, mTORC1 activates ATF4, increasing the expression of enzymes involved in serine synthesis and its conversion to formate, providing one-carbon units for purine ring formation. Through these mechanisms, the PI3K/AKT/mTORC1 signaling pathway coordinates nucleotide cellular metabolism to ensure an adequate supply of pyrimidines and purines, supporting nucleotide synthesis and the rapid proliferation and growth of cells (64).

Therefore, the PI3K/AKT/mTORC1 signaling network is pivotal in governing *de novo* nucleotide synthesis by its capacity to regulate both post-translational and transcriptional mechanisms. This is accomplished through the activation of key enzymes involved in both pyrimidine and purine synthesis pathways, including CAD (cytosolic carbamoyl-phosphate synthetase II, aspartate transcarbamylase and dihydroorotase), and through the induction of specific metabolic enzymes and the injection of metabolites into purine synthesis pathways. These discoveries underscore the significance of mTORC1 as a central figure in cellular metabolism and propose that directing interventions toward this pathway could present a promising therapeutic approach for addressing specific diseases, such as cancer, that are characterized by dysregulated nucleotide synthesis.

### *Control of protein synthesis*

Protein synthesis is a complex and resource-intensive process, and the PI3K/AKT/mTORC1 signaling pathway plays a crucial regulatory role in this process. mTORC1 regulates protein synthesis by phosphorylating multiple downstream substrates. Two key downstream substrates are S6K1 and eIF4E binding protein (4E-BP) (65). mTORC1 phosphorylates and activates S6K1, which further promotes protein synthmTORC1 activates S6K1 by directly phosphorylating it at multiple sites (such as T389). Activated S6K1 further phosphorylates ribosomal protein S6 and the translation initiation factor eIF4B, thereby enhancing the initiation of translation and the ribosome biogenesis function, promoting protein synthesis. For 4E-BP1, in its unphosphorylated state, it binds to eIF4E and inhibits the initiation of translation. Once phosphorylated, 4E-BP1 releases eIF4E, allowing it to bind with eIF4G, forming the active translation initiation complex eIF4F (66). In addition to 4E-BP, the phosphorylation of La-related protein 1 (LARP1) downstream of mTORC1 is also involved in selectively inducing the translation of 5'-TOP mRNAs (67). Both AKT and S6K1 can phosphorylate LARP1, facilitating its dissociation from the 5' UTRs and thus relieving the inhibition on translation, promoting 5' cap-dependent translation initiation (68). Additionally, S6K1 activates eIF4B, a positive regulator of translation initiation, and facilitates the degradation of the eIF4A inhibitor PDCD4, further promoting the initiation of translation.

Additionally, the PI3K/AKT/mTORC1 signaling pathway regulates protein synthesis by enhancing rRNA transcription. mTORC1, through its downstream effectors like S6K1, phosphorylates and activates nucleolar transcription factors such as UBF and transcription initiation factor 1A (TIF-1A). TIF-1A and UBF work together to promote the binding and activation of RNA polymerase I at the rDNA promoter (69). This upregulates the transcription of rRNA, promoting ribosome biogenesis. Through these mechanisms, the cell's capacity for protein synthesis is significantly enhanced. This pathway plays a crucial role in regulating proliferation and cell growth.

## Targeting PI3K signal therapy in cancer

### *Pan-PI3K inhibitors*

Pan-PI3K inhibitors are primarily designed to target the p110 subunits of class IA PI3Ks, as these subunits are closely associated with the development and progression of tumors. Several small-molecule pan-PI3K inhibitors, such as buparlisib (BKM120), pictilisib (GDC-0941) and pilaralisib (XL147), have been developed as potential cancer therapies.

The thienopyrimidine derivative GDC-0941 was the first pan-class I PI3K inhibitor to undergo clinical trials. It exhibits potent inhibitory activity against p110α and p110δ enzymes, as well as inhibiting p110β and p110γ at nanomolar concentrations in kinase assays. Research has shown that GDC-0941 exhibits significant anti-tumor activity in patients, mouse xenograft models, and *in vitro* models, whether used alone or in combination with other therapeutic methods (70-72).

BKM120 (buparlisib) is a potent inhibitor of class I PI3Ks, which targets the p110-α/β/δ/γ isoforms with IC50 values of 5, 27, 7, and 14 nM, respectively, in cell-free assays. It has exhibited significant anti-cancer effects across various solid cancer models (73). At tolerated doses, buparlisib displays substantial antitumor activity in human tumor xenograft models and possesses favorable oral

bioavailability *in vivo* (74). In a phase II study (EPOC1303) involving patients with advanced esophageal squamous cell carcinoma (ESCC), including those previously treated for the disease, BKM120 demonstrated promising efficacy (75). Additionally, a derivative of BKM120, known as PQR309, has been developed. This compound differentiates the microtubule inhibitory activity of BKM120 from its PI3K inhibitory activity, providing enhanced safety and flexibility for combination therapies (76). The phase I clinical trial of PQR309 (NCT01940133) has shown promising efficacy and PI3K inhibition, and a phase II clinical trial is currently in progress (77).

XL147 is a class I PI3K inhibitor that exhibits high specificity towards class I PI3Ks (α, β, γ, and δ). *In vitro* assays have demonstrated the effective inhibition of PIP3 formation in cell membranes by XL147, along with the phosphorylation of downstream kinases such as AKT, p70S6K (the 70 kDa ribosomal protein S6 kinase), and ribosomal protein S6 in various tumor cell lines. This inhibition leads to a broad spectrum of potencies in impeding cell proliferation. Following oral administration, XL147 has shown to sustain inhibition of Akt, p70S6K, and S6 phosphorylation in multiple human xenograft models for at least 24 hours. Subsequent administration of XL147 has resulted in significant suppression of tumor growth with manageable toxicity profiles (78). In a phase I study involving patients with advanced solid tumors, the maximum tolerated dose of pilaralisib was determined to be 600 mg once daily. The administration of pilaralisib tablets was associated with favorable safety outcomes and exhibited preliminary antitumor efficacy (79). Furthermore, pilaralisib was evaluated in a phase II study involving patients with advanced or recurrent endometrial carcinoma, demonstrating a favorable safety profile and limited antitumor activity in this patient cohort (80). Clinical trials have indicated that combining XL147 with other therapeutic modalities enhances its antitumor efficacy compared to its monotherapy use (81).

### *PI3K isoform-specific inhibitors*

PI3K inhibitors with specificity for certain isoforms have been shown to have fewer toxic side effects and off-target toxicity than pan-inhibitors. Consequently, isotype-specific inhibitors are considered more efficacious and can be administered at higher doses. Alpelisib (BYL-719), inavolisib (GDC-0077), idelalisib (GS-1101/CAL-101), GDC-0326 and taselisib (GDC-0032) are exemplars of isoform-specific inhibitors.

The first oral specific inhibitor targeting class I p110α PI3K is BYL-719 (alpelisib) (82). Clinical trial findings from a phase I study of alpelisib showcased its efficacy as a monotherapy in managing patients with solid tumors harboring PI3KCA mutations (83). In a subsequent Phase 1b clinical trial, the combination of BYL-719 and fulvestrant demonstrated a manageable safety profile among patients with estrogen receptor-positive advanced breast cancer, irrespective of PIK3CA alterations. Initial data indicate a potentially enhanced clinical activity of this combination in tumors with PIK3CA alterations compared to those lacking such mutations (84). Furthermore, in the SOLAR-1 trial, the efficacy of alpelisib combined with fulvestrant was assessed in patients both with and without PIK3CA mutations. The findings revealed a significant improvement in progression-free survival (PFS) with the addition of alpelisib to fulvestrant in patients with PIK3CA-mutated, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (85,86).

A novel PI3Kα inhibitor, inavolisib, has been discovered in recent years. PIK3CA mutations occur in approximately 40% of HR+ breast cancer cases globally, making targeted therapies for these mutations clinically significant. Inavolisib has emerged as a promising treatment for PIK3CA-mutated HR+/HER2– advanced breast cancer. It selectively induces degradation of the mutant p110α protein, the catalytic subunit of PI3Kα, with a selectivity for PI3Kα that is 300 times greater than for other PI3K subunits (87). Inavolisib has advanced to phase III clinical trials (NCT04191499), showing significant efficacy in combination therapies for endocrine-resistant populations with PIK3CA mutations, with good safety and tolerability profiles. It offers a new and more effective treatment option for patients with PIK3CA-mutated breast cancer and is poised to become a first-line therapy for this patient population (88).

Idelalisib was granted Food and Drug Administration (FDA) approval as the initial PI3K inhibitor for managing relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (89). A randomized, double-blind, placebo-controlled phase 3 trial was conducted to assess the efficacy of combining idelalisib with bendamustine and rituximab in relapsed or refractory chronic lymphocytic leukemia patients. The findings indicated that this combination therapy led to enhanced progression-free survival compared to bendamustine plus rituximab monotherapy. Nonetheless, the idelalisib-treated group exhibited a heightened risk of

infections (90). Another phase III clinical trial compared the outcomes of idelalisib plus rituximab versus placebo plus rituximab in relapsed CLL patients, revealing that the idelalisib and rituximab combination therapy significantly improved both progression-free survival and overall survival compared to rituximab monotherapy (91).

In addition, GDC-0326, another p110α-selective inhibitor, has been identified (92,93). It has demonstrated promising efficacy in a mouse model of pancreatic neuroendocrine tumors (PanNETs), showing advantages in reducing angiogenesis and decreasing lymph node metastasis (94). Taselisib is also a selective PI3K inhibitor designed to target p110α rather than p110β (95). However, it also exhibits inhibitory effects on the p110δ and p110γ isoforms, and this off-target inhibition may be a key factor contributing to its suboptimal performance in clinical trials (96).

### *Dual PI3K and mTOR inhibitors*

Inhibitors targeting both the PI3K and mTOR signaling pathways, known as PI3K/mTOR inhibitors, have been developed. Despite lacking FDA approval for cancer treatment currently, they are anticipated to yield improved therapeutic outcomes by concurrently suppressing both signaling pathways. This is because PI3K and mTOR share a structurally similar p110 subunit. The current pan-PI3K/mTOR inhibitors available for clinical use include apitolisib, gedatolisib, SF1126, voxtalisib, omipalisib, samotolisib, bimiralisib, paxalisib, and GSK1059615 (97-104). Although PI3K/mTOR inhibitors exhibit lower specificity compared to isotype-specific inhibitors, they have shown promise in the treatment of various types of tumors.

Apitolisib, also referred to as GDC-0980, serves as a potent inhibitor targeting class I PI3K, displaying notable potency against the p110-α/β/δ/γ isoforms with IC50 values of 5, 27, 7, and 14 nM, respectively, as observed in cell-free assays. Beyond its primary impact on PI3K, apitolisib also engages with the mTOR signaling pathway. Preclinical studies have revealed apitolisib's capacity to induce cytotoxicity and apoptosis in glioma cell lines in a dose- and time-dependent manner (105). In a randomized open-label phase II trial, the safety and efficacy of apitolisib were compared with everolimus in patients diagnosed with metastatic renal cell carcinoma. Results indicated that apitolisib exhibited inferior efficacy compared to everolimus, likely attributed to multiple on-target adverse events stemming from the complete blockade of PI3K/mTOR signaling (106).

Several dual PI3K/mTOR inhibitors have been studied in clinical trials to evaluate their efficacy and pharmacokinetic properties. Among them, gedatolisib (PKI-587) is an effective dual inhibitor targeting PI3Kα/γ and mTOR, demonstrating high efficacy in cell-free assays with IC50 values of 0.4 nM, 5.4 nM, and 1.6 nM for PI3Kα/γ and mTOR, respectively (107). SF1126, developed by SignalRx, is a small molecule conjugate selectively inhibiting all PI3K class IA isoforms as well as other members of the PI3K superfamily, including DNA-PK and mTOR. Voxtalisib (XL765), developed by Sanofi, is also an effective inhibitor targeting the PI3K p110γ, DNA-PK, and mTOR pathways. Omipalisib (GSK458) is a selective, pan-PI3K ATP-competitive inhibitor that also targets the mTOR pathway, with a Ki for the catalytic p110α subunit in the subnanomolar range. These dual PI3K/mTOR inhibitors have demonstrated promising therapeutic effects in research studies.

### *Adverse reactions and management of toxicity of PI3K inhibitors*

At present, various PI3K inhibitors have been developed, and they have shown good efficacy in experimental models or clinical trials. However, the toxicity caused by the on-target and off-target effects of PI3K inhibitors presents a major challenge, impacting the effectiveness of treatment. For example, in pan-PI3K inhibitors, common adverse effects include hyperglycemia with BKM120, rash with XL147, and neutropenia with GDC-0941. Additionally, pan-PI3K inhibitors are associated with neuropsychiatric effects (confusion, depression, anxiety), hepatotoxicity, and diarrhea. Among PI3K p110α isoform inhibitors, BYL719's common adverse effect is hyperglycemia, while GDC-0032 commonly causes rash, along with diarrhea and pneumonitis. For dual PI3K and mTOR inhibitors, voxtalisib may cause stomatitis, SF1126 frequently leads to hyperglycemia, and GSK1059615 often causes immunosuppression (108,109).

Managing the toxicity of PI3K inhibitors requires a comprehensive approach that includes considering the drug dosage, adjusting treatment regimens, and symptomatic management. First, it is advisable to choose more selective PI3K inhibitors. For instance, early pan-PI3K inhibitors, due to their broad targeting and higher toxicity, did not gain wide clinical use. In contrast, alpelisib, with its α-isoform specificity, has demonstrated significant antitumor activity with manageable toxicity in HR+, HER2– advanced breast

cancer patients, making it a preferred option. Additionally, close monitoring of patient safety data and symptomatic management of adverse effects is essential. Appropriate symptomatic treatments, such as using insulin to control hyperglycemia, topical corticosteroids for skin issues, and antidiarrheal agents for diarrhea, can help reduce adverse events and prolong treatment duration. Furthermore, besides PIK3CA mutations, other potential biomarkers that may affect the efficacy of PI3K inhibitors in advanced breast cancer warrant further clinical investigation. Identifying these markers could support the development of combination therapies to simultaneously target multiple pathways, helping to prevent the development of resistance (110).

## Conclusions

The PI3K signaling pathway plays a critical role in tumor metabolism, involving regulation in various aspects including glucose metabolism, lipid synthesis, nucleotide metabolism, and protein synthesis. This pathway enhances the uptake and utilization of glucose, augmenting the dependency of tumor cells on glucose. This process primarily occurs through increased expression of glucose transporters, activation of glycolysis pathways, and promoting glucose conversion to pyruvate. Additionally, the PI3K pathway promotes lipid synthesis pathways by activating downstream factors like mTORC1, leading to increased lipid synthesis and accumulation, thereby facilitating the growth and proliferation of tumor cells. Moreover, PI3K signaling enhances nucleotide synthesis by regulating the activity of transcription factors such as MYC, which involves pathways for both pyrimidine and purine synthesis. This process entails the activation of several key enzymes like PRPS2 and thymidylate synthase. Furthermore, the PI3K pathway boosts protein synthesis by activating downstream factors like mTORC1, facilitating translation initiation, and increasing translation rates. This supports the rapid proliferation of tumor cells by meeting the demand for protein synthesis. Overall, the PI3K signaling pathway orchestrates a metabolic reprogramming in cancer cells, favoring anabolic processes such as glycolysis, lipogenesis, nucleotide biosynthesis, and protein synthesis to sustain their rapid proliferation and survival.

Targeting the PI3K signaling pathway is highly appealing for anticancer therapy because of its essential role in cell growth, proliferation, and survival. Clinical trials with dual PI3K/mTOR and pan-PI3K inhibitors have reported high rates of side effects, prompting the creation of isoform-specific PI3K inhibitors with better specificity and lower toxicity.

However, the efficacy of using PI3K inhibitors alone for treatment is limited, which is associated with drug resistance, a narrow therapeutic window, and medication side effects. Therefore, combining them with other treatment modalities, such as hormone therapy, surgery and other anticancer drugs, may enhance effectiveness and reduce side effects. Common adverse reactions include hyperglycemia, vomiting, fatigue, rash, nausea, loss of appetite, diarrhea and abnormal liver function. It is also important to closely monitor medication side effects and provide corresponding symptomatic treatment when using PI3K inhibitors.

To date, the precise mechanism of action of PI3K inhibitors remains incompletely established, necessitating further extensive and systematic exploration. This endeavor will facilitate the monitoring of therapeutic efficacy during PI3K inhibition therapy, optimize the management of adverse effects, and enable the development of more individualized treatment regimens.

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## Footnote

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