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# A Review of Phosphocreatine 3 Kinase δ Subtype (PI3Kδ) and Its Inhibitors in Malignancy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
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Most cancer deaths are caused by metastasis. The phosphocreatine 3- kinase (PI3K) family includes the I-III classes, with class I divided into 4 subtypes (α, β, γ, δ); and PI3K signaling participates in the regulatory processes of cell proliferation, differentiation, apoptosis, and glucose transport. Moreover, PI3Ks are modulators of cellular membrane lipids involved in signaling and trafficking events. The PI3Kdelta isoform (PI3Kδ), which is not only specifically expressed in hematopoietic cells, but also in different tumor cell lines, is expressed extensively. The increase in PI3Kδ activity is often associated with a variety of cancers. Currently, the strategy of tumor therapy based on PI3Kδ and its related signaling pathway is developing. Besides its established role in controlling functions in autoimmunity and inflammation, the role of PI3Kδ in tumor and metastasis is not clearly elucidated, with the effects of inhibiting PI3Kδ in several types of tumors also remaining unexplored. In addition, the specific inhibitor of PI3Kδ in tumor progression and metastasis and its underlying mechanism need to be further studied. The purpose of this review is to rationalize the existing functions and mechanisms of PI3Kδ in tumor metastasis and the relationship with hematopoietic cells in cancers as well cross-talking with miRNA, which provides a new theoretical basis and potential therapeutic target for the drug therapy of tumor metastasis.

**Keywords:** PI3Kdelta • Hematopoietic Cells • miRNA • Cross-Talking • Tumor Metastasis

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## Background

Phosphocreatine 3 kinase δ subtype (PI3Kδ), a subtype of PI3Ks, is not only mainly expressed in leukocytes [1-2], but also mediated in neurons [3] and some transformed epithelial cells [4,5]. Its high expression in the hematopoietic system is related to a variety of immune functions, mainly manifested as adaptive immunity, which plays an important role in the function of B and T cells [6], and also has an influence on mast cells [7], neutrophils [8] and macrophages [9].

PI3K is divided into 3 categories: class I, class II, and class III. Class I PI3Ks have been extensively studied and consists of a catalytic subunit p110 and a regulatory subunit (p85 or p101 heterodimer). In view of the catalytic subunit p110, class I PI3K can also be divided into PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ, whose catalytic subunits are p110α, page 110 β, page 110 δ, and p110γ, respectively. In addition, the regulatory subunit α of PI3K, PI3K company β, and PI3K company δ are p85, belonging to the RTK family, and are activated by RTKs and RAS. However, only PI3Kγ, whose regulatory subunit is P101 heterodimer, belongs to the GPCR family [10].

Most cancer deaths are caused by metastasis. Increased PI3K activity and its pathways are often associated with multiple cancers [11,12]. It is well known that the high frequency of functional mutations and amplification of the PIK3CA (p110) gene plays an important role in tumorigenesis. Alpha has been observed in human tumors. In phosphatase and tension homologous (PTEN) negative cancers, PI3Kβ is primarily involved in the production of triphosphate (3,4,5) -triphosphate, suggesting that PTEN inactivation plays a key role in tumorigenesis [13,14]. PI3Kδ and PI3Kγ participate in the immune system and inflammatory response [15,16]. However, PI3Kδ-specific inhibitors have anti-tumor effects. In addition, edilaxil (CAL101) has become the first PI3K inhibitor to be approved for the treatment of patients with recurrent chronic lymphocytic leukemia [17]. In addition, Zhao et al showed that ZSTK474, the pan-PI3K inhibitor, exhibited anti-metastatic effects by blocking the migration of PC3 cells and inhibiting the secretion of matrix metalloproteinases [18]. The role of PI3Kδ in other types of cancer such as prostate cancer metastasis has been indicated by comparing differences in DU145 cell migration and invasion after PI3K inhibitor treatment in a study by Zhang et al [19].

Increasing clinical evidence suggests that PI3K inhibitors often perform poorly in clinical trials. Due to the adverse effects of blocking other isomers, patients should be given low doses of PI3K inhibitors, which can significantly limit the clinical efficacy of PI3K inhibitors [20-22]. In this case, elucidating the role of PI3K subtype in tumor metastasis is a necessary condition for the development of specific PI3K subtype inhibitors. In the present study, the existing functions of PI3K and somatic mutations of PI3Kδ in cancer and the cross-talk with PI3K-Akt are reviewed.

## Structure and Regulation of PI3Kδ

The catalytic subunit P110δPI3Kδhas an N-terminal regulatory subunit binding site, RAS-binding domain, C2 domain, and C-terminal kinase catalytic domain. The whole of class I PI3K have their regulatory subunit, P85, which includes 2 conserved Src homology-2 (SH2) domains that interplay with the phosphorylated tyrosine motif [23].

As a member of PI3K class Ia, PI3Kδ recognizes the phosphorylated tyrosine motif through the SH2 domain or is recruited into receptor complexes by targeting RAS-binding domain. The catalytic activity δ of PI3K is critical to its signal transduction and biological function [24]. While PI3Kδ is not activity, signal defects were observed in many types of cells, such as B cells, T cells, and mast cells. During signal transduction, PI3K typically responds to receptor activation that has tyrosine kinase activity. In particular, PI3Kδ also participates in the signal transduction of some GPCRs, for example, CXCR5 on B cells [25].

## PI3Kδ and Cells of Hematopoietic Lineage

NK cells are an important cell type of the innate immune system. However, the mechanisms underlying the potential role of NKs in tumor immune surveillance, protection, and inhibition have not been fully elucidated. The activity of PI3Kδ appears to be related to the development of NK cells. Developmentally deficient δs and PI3Kγ expression of NK cells were observed in PI3K-deficient mice. The changes in the number of NK cells in bone marrow and peripheral blood of PI3K patients and PI3Kγ double KO mice were significantly reduced, and a wide range of immature phenotypes were observed [26,27]. They are neither deficient in extravasation of tumor growth sites nor in cytotoxicity to tumor cells [28], an observation that clearly suggests that PI3Kδ can promote metastasis by protecting tumor cells from NK cell lysis. This leads to the production of cytokines and chemokines, such as transforming growth factor-β, and downregulating the expression of NKG2D inhibits the cytotoxicity of NK cells [29].

Myeloid cells, the main type of white blood cell, are the first line of defense. Infiltration of cells into the inflammatory site is a multi-step process in which cells roll along the endothelial cells of the vascular wall under the action of selectin, attach to the endothelial cells by integrin, leave the vessel by a process of endothelial stagflation, and finally migrate through the tissue by chemical attractants. Based on its high expression in





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leukocytes, PI3Kδ is also a target for hematological malignancies [30], including chronic lymphocytic leukemia [31]. Indeed, PI3Kδ appears to play an important role in the late phase of cell infiltration. In vivo studies showed decreased leukocyte emigration only after the prolonged CXCL2 and TNFα treatment on the condition of PI3Kδ deficiency [32]. Moreover, leukocyte emigration was associated with the tumor cells extravasation across the endothelial barrier to distant metastatic sites [33].

Neutrophil is responsible to inflammatory mediators or pathogens, which has a critical role in pathogen clearance, however, it can also lead to injury of tissue by chronic inflammation [34]. Both of PI3Kδ and PI3Kγ are involved in this process. PIP3 accumulation is induced by fMLP in TNF-activated human neutrophils, PI3Kγ in the early stage of PIP3 production no more than 10 s of stimulation, while PI3Kδ in the late phase of PIP3 occurs within minutes of the first phase [35]. Interactions between cancer cells and neutrophils are critical to disease progression, including neutrophils infiltrating the primary tumor, neutrophils interacting with circulating tumor cells (CTC), and their involvement in the formation of pre-metastatic niches [36,37]. Identification of the axis of CTCs/neutrophils/PI3Kδ may supply novel potential targets for preventing metastasis.

Macrophages are another type of myeloid cells involved in inflammatory response, and the tumor microenvironment (TME) is an important target of tumor therapy. However, detecting and destroying tumor-promoting TMEs is a huge challenge because TMEs can have beneficial or adverse effects on tumorigenesis [38]. Similarly, M1 macrophages are well known for their anti-tumor activity; however, under the action of immunosuppressive cytokines secreted by tumor tissue or TME, they often transform into a tumor-promoting M2 phenotype [39]. In addition, many studies have shown that the microenvironment has the ability to normalize tumor cells, suggesting that re-culturing stromal cells rather than targeting tumor cells may be an effective way to treat cancer [40]. Marwick et al showed that PI3Kδ expression was upregulated in macrophages in patients with chronic obstructive pulmonary disease (COPD) and that the PI3Kδ inhibitor IC87114 restored sensitivity to glucocorticoids [41]. Environmental triggers linked to chronic inflammation, such as tobacco smoke, are not surprisingly shown to modify the local environment of tissue and contribute to angiogenesis and metastasis. It is suggested that the enhancement of PI3Kδ activity may be a potential mechanism of tumor progression, and inhibition of PI3Kδ activity may be a new way to fight tumor metastasis.

As known, mast cells are produced by precursors of bone marrow and growth factors, and PI3Kδ may play a key role in mast cells differentiation by stimulating mast cells response to varied types of growth factors [42]. In treatment of IC87114 (PI3Kδ inhibitor) in PI3Kδ KD mice or mast cells, the cytokines, including TNF and IL-6, were significantly reduced [42]. In addition, IL-6 and TNFα are usually associated with bone and marrow metastasis [43]. Similarly, IL-6 is secreted by bone marrow stromal cells and has also been shown to promote osteolysis of osteoblasts, and osteoblasts [17] have also been reported to promote metastasis of neuroblastoma [44]. These data suggest that PI3Kδ may have a critical role in genesis and progression of tumors.

## PI3Kδ in Tumorigenesis and Immune Regulation

Angiogenesis is a complex, multi-step process that involves many synergistic pathways to generate stable blood vessels [45]. This process is necessary for the further growth of the primary tumor and also promotes distant metastasis and metastasis of cancer cells [46]. A series of studies have shown that targeted VEGF signaling [47,48] and the PI3K family [49] provide new prospects for angiogenesis and open up new strategies for the treatment of tumor metastasis. In particular, direct inhibition of vascular endothelial growth factor signaling [5] has proven to be very successful, but there are limitations [50,51]. PI3Ks inhibition are important for both VEGF signaling and angiogenesis, which is a potential alternative strategy [52]. Some studies have suggested that the PI3Kα subtype may play a role in tumorigenesis in cancer cells with (RAS) and PIK3CA [53-54] mutations, while the PI3Kα inhibitor BY719 and most pan-PI3K inhibitors have shown unsatisfactory results in clinical trials. Interestingly, the PI3Kδ inhibitor idelalisib, as the first specific PI3K inhibitor, has been approved by the FDA in 2014 and there is growing evidence that PI3Kδ is an attractive target for inhibition of tumor angiogenesis. PI3Kδ inhibitors negatively affected Akt and integrin b1, which are involved in cell migration and invasion [55-57] and might contribute to the anti-metastatic effect. Several PI3Kδ inhibitors, such as PI-3065 [58] and X-370 [59,60] are already in clinical trials. Above all, targeting PI3Kδ and its related pathway in endothelial cells might affect blood vessel stability and provide effective strategies for antiangiogenic therapy.

An increasing number of animal studies have shown that PI3Kδ subtype has the pharmacological effect of inhibiting tumor growth, which is not limited to hematological malignancies [61]. The explanation suggested is that these effects might be regulated by PI3Kδ in signaling pathways, which could protect tumors from immune attack [62]. Moreover, evidences from different solid tumor models indicated that the pharmacological inhibition of PI3Kδ significantly decreased metastasis [63]. These results suggested that PI3K inhibitor δ blocks blood-derived tumors and enhances the immune response to solid tumors [64].





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**Table 1.** The development status of PI3Kδ inhibitors.

| Inhibitor | Statement | Description |
|---|---|---|
| Idelalisib (CAL-101) | Launched | CLL, FL, SLL, etc. |
| Duvelisib (IPI-145) | Launched | CLL, FL, SLL, etc. |
| Umbralisib (TGR-1202) | Clinical phase III | CLL, FL |
| ME-401 (PWT-143) | Clinical phase III | FL, CLL |
| Parsaclisib (INCB050465) | Clinical phase II | Myelofibrosis, malignant lymphomas |
| Acalisib (GS-9820) | Clinical phase II | CLL and Lymphoma |
| AMG-319 | Clinical phase II | Inflammation, autoimmune diseases |
| Nemiralisib (GSK2269557) | Clinical phase II | COPD, asthma |
| IC87114 | Launched | PI3K inhibitor in COPD |
| PI-3065 | Launched | Restenosis |
| X-370 | In study | B cell acute lymphoblastic leukemia |

## PI3Kδ Inhibitors in Tumors

Despite significant efficacy in some solid cancers, the successful immune checkpoint blocking therapy (such as anti-PD-1) is limited by the developing mechanisms of immune resistance, such as tumor site invasion and functional CD8+ T cells development [65]. In addition, PI3Kδ inhibitors can solve these problems to inhibit immune-suppressed leukocytes, tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), for example [66].

On the other hand, there are many clinical cases of acute toxicity in patients treated with PI3Kδ inhibitors (idelalisib) [67]. In addition, PI3Kδ inhibitors may lead to side effects such as inflammation, neutropenia, a high risk of infection, and death [68]. In some cases, the targeted effects of the drug can elicit a highly reactive immune response. Therefore, the administration of selective PI3K isomers at the maximum tolerated dose, in combination with other therapies, may help to overcome complications and immune system suppression [69]. Indeed, IC87114 selectively inhibits PI3Kδ with the lower IC50 concentration compared with PI3Kα, PI3Kβ, and PI3Kγ [71]. On the basis of IC87114 modification, idelalisib (CAL101) has been produced with enhanced affinity to PI3Kδ and also higher selectivity than other PI3Ks isoforms [72]. GS-9820 and AMG319 are the other 2 selective PI3Kδ inhibitors currently in phase I clinical trials, and are used to treat malignant tumors of the lymphatic system [73,74]. It has been shown that PI3Kδ inhibitors reduce tumor survival/proliferation signals by blocking PI3K component signal transduction, including Akt and ERK1/2 phosphorylation [75]. In addition, PI3Kδ inhibitors may display anti-tumor activity by inducing apoptosis in the microenvironment [76]. At the same time, evidence of PI-3065 in the treatment of solid tumors suggests that PI3K inactivation inhibits tumor growth [77]. In addition, the details mechanism of PI3Kδ inhibitors in different tumor types treatment remains to be further elucidated (**Table 1**).

## PI3Kδ Cross-Talk with miRNAs

New evidence predicts that miRNAs regulate PI3Kδ in cancer and related signaling pathways [78,79]. MicroRNAs (miRNAs, miRs) are endogenous, non-coding RNAs, which are 18-20 nucleotides and have a role in regulating and modifying gene expression post-transcriptionally [80]. Generally, miRNAs are main and high regulators of cell behavior under normal and pathological conditions. The regulation of miRNAs can be involved in multiple stages of tumor cell diffusion from the primary site, including infiltration and exosmosis. Moreover, it is involved in tumor cell localization, tumor stromal cell interaction, dormancy and growth [81,82]. The conclusions above are supported by studies by Yuan et al on miR-26b direct targeting of PI3Kδ in human T-ALL cell lines. After treatment with PIK3CD shRNA or PIK3CD inhibitor (CAL-101), the growth of T-ALL cells was decreased and apoptosis was increased [83].

## Future Challenges in PI3Kδ Research

Understanding the molecular mechanisms of PI3K δ activation of tumor progression and metastasis may provide a promising avenue for new therapeutic approaches. PI3Kδ-associated signal transduction pathways are activated in tumor cells by PI3K, and they may be cooperatively processed in the solid tumor microenvironment, resulting in reduced tumor growth. On the other hand, we need a method based on precision medicine to overcome the drug resistance mechanism of cancer cells and minimize the adverse effects and interference with blood cell homeostasis. With the development of next-generation





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sequencing technologies and precise drugs in clinical trials, a growing number of biomarkers predicting PI3Kδ efficacy are expected to be validated for PI3Kδ-specific tumor inhibitors.

## Conclusions

In summary, the new generation of PI3Kδ provide opportunities and challenges in precision medicine and development of cancer treatments and inhibitors. As PI3Kδ advances in the cancer field each year, more and more patients will benefit from PI3Kδ-based inhibitors in the future.

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**Conflicts of Interest**

None.





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