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REVIEW ARTICLE

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PIK3CA and *PIK3R1* mutations in cancer: from the mechanism of activation to PI3K targeted therapies

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ABSTRACT

PIK3CA and *PIK3R1*, the genes that encode catalytic (p110α) and regulatory (p85α) subunits of PI3Kα kinase are frequently mutated in cancer patients, resulting in aberrant hyperactivation of the PI3K pathway. Due to its high clinical relevance, mutated PI3K proteins are attractive targets for anti-cancer therapy. To date, some PI3K inhibitors have displayed significant therapeutic effects. One of them, alpelisib, has been approved for the treatment of ER-positive, HER2-negative, and *PIK3CA*-mutated advanced or metastatic breast cancer. Below, we describe how *PIK3CA* and *PIK3R1* mutants influence PI3K activity. We also review the frequency of *PIK3CA* and *PIK3R1* mutations in cancers, diversity of these mutations, and PI3K therapeutic strategies.

Keywords: *PIK3CA*, *PIK3R1*, activating mutations, PI3K inhibitors, alpelisib

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Introduction

Since PI3K was identified as a lipid kinase associated with certain oncoproteins in 1988, the number of studies on its role has steadily increased [1]. The knowledge acquired during the past decades indicates that PI3K regulates many functions, including cell growth, protein synthesis, proliferation, metabolism, motility, and immune cell differentiation. The ability of PI3Ks to perform such diverse functions requires tight activity control mediated by several regulatory subunits. Abnormal regulation of PI3K signaling is closely associated with different human diseases, such as cancer, primary immunodeficiency, diabetes, and localized tissue overgrowth. According to a study from The Cancer Genome Atlas (TCGA), *PIK3CA* is the second most frequently mutated gene in human cancers (17.8%), whereas mutations in *PIK3R1* occur with 4.4% frequency [2]. Here, we review the current knowledge of PI3K activation in cancer, focusing on the role of mutations in these two genes.

Activation of PI3Kα by physiological factors

In response to growth factors, PI3Kα can be activated by receptor tyrosine kinases (RTKs) such as platelet-derived growth factor receptor (PDGFR) or non-receptor cytoplasmic tyrosine kinases such as Src-family kinases [3]. Tyrosine phosphorylation of these kinases, or their substrates, creates binding sites for the Src homology 2 domain (SH2) domains of PI3Kα regulatory subunits (p85, p55, and p50), resulting in PI3Kα membrane recruitment, stimulation of its enzymatic activity, and generation of the second messenger $PI(3,4,5)P_3$ (Fig. 1) [4]. In addition, direct binding of the RBD domain of the p110α catalytic subunit to activated Ras protein further stimulates PI3Kα activity. $PI(3,4,5)P_3$ provides docking sites for signaling proteins with pleckstrin-homology (PH) domains and recruits them to the plasma membrane. This includes the PH domain-containing protein kinase B (AKT) and its

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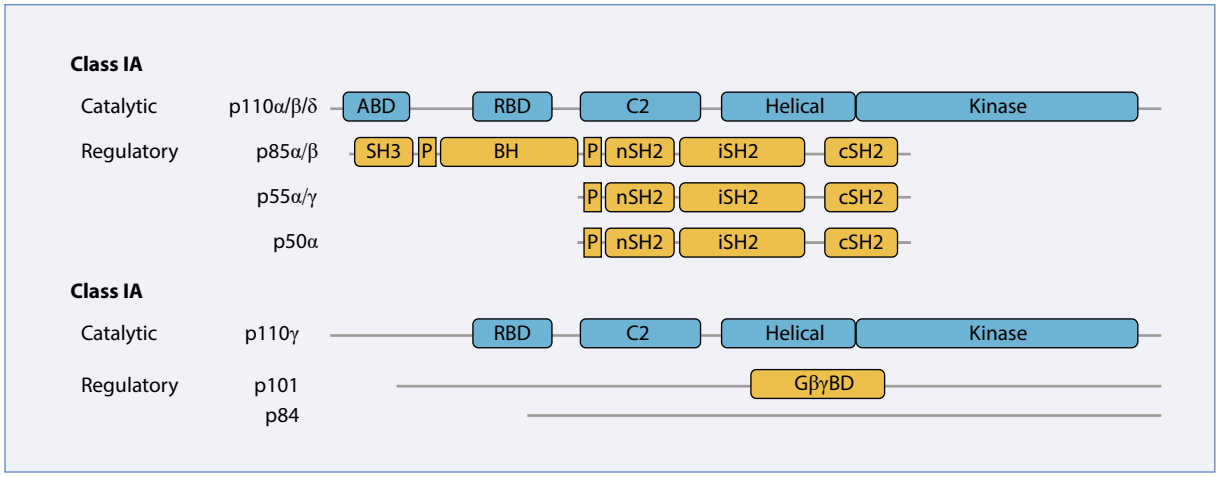

Figure 1. Domain architecture of class I PI3K catalytic and regulatory subunits. Class IA catalytic subunits (p110α, p110β, and p110δ) consist of an adaptor-binding domain (ABD), Ras binding domain (RBD), C2 domain, helical domain, and kinase domain. Class IA catalytic subunits associate with different regulatory subunits: p85α, p55α, p50α, p85β and p55γ. Class IA regulatory subunits are composed of two Src homology domains (nSH2 and cSH2) separated by an inter-SH2 domain (iSH2). The p85α and p85β subunits also contain an Src homology 3 (SH3) domain at their N-terminus, and a Bcr homology (BH) domain flanked by two proline-rich regions. The class IB catalytic subunit (p110γ) has the same structure as class IA except for the absence of an ABD domain. p110γ binds with either a p84 or a p101 regulatory subunit. p101 has a G-protein βγ dimer binding domain (GβγBD) that binds to βγ subunits of heterotrimeric G proteins following activation of GPCRs. p84 domain organization is unknown. The p110 catalytic isoforms (α, β, δ, and γ) are encoded by *PIK3CA*, *PIK3CB*, *PIK3CD*, and *PIK3CG*, respectively. p85α regulatory subunit (and its splice variants: p55α and p50α) are encoded by *PIK3R1*, p85β, and p55γ subunits by *PIK3R2* and *PIK3R3*, while p84 and p101 subunits are encoded by *PIK3R5* and *PIK3R6*, respectively

activator phosphoinositide-dependent kinase 1 (PDK1), TEC family kinases, and modulators of G protein activities such as guanine nucleotide exchange factors (GEFs) [5]. The AKT family kinases activated by PI3Ks in nearly all cells and tissues are particularly significant. Active AKTs translocate to the cytoplasm and nucleus, where they phosphorylate serine and threonine residues in many substrates, including tuberous sclerosis complex 2 (TSC2), forkhead family of transcription factors (FoxO), and glycogen synthase kinase 3 (GSK3), to regulate cell growth, survival, and metabolism [6]. Most of the known AKT substrates become inactivated by the phosphorylation events [7].

The termination of PI3K signaling by degradation of $PI(3,4,5)P_3$ can be mediated by lipid phosphatase PTEN, which hydrolyzes the phosphate at the 3-position of $PI(3,4,5)P_3$, converting it back to $PI(4,5)P_2$ [8].

In physiological conditions, PI3Kα is mainly in the autoinhibited state, in which the N-terminal SH2 domain (nSH2) interaction with the catalytic subunit occludes the phosphotyrosine binding site. The binding of the nSH2 domain to phosphorylated tyrosine on RTKs relieves this autoinhibition [9]. In PI3Kα, the extended coiled-coil inter-SH2 domain (iSH2) domain of p85α traverses the complex holding the regulatory and catalytic subunits together. This interaction brings the positively charged groove of the nSH2 domain near the two negatively charged residues of an exposed loop of the p110α helical domain, Glu542, and Glu545, which stabilizes the autoinhibited state [10]. Under physiological conditions, the kinetic barriers between the autoinhibited and active states are low and easy to overcome. During activation, the pYxxM motif of RTKs binds in the groove of nSH2 that in the heterodimer is occupied by a negatively charged exposed loop of the helical domain. Therefore, binding of nSH2 to the phosphotyrosine on RTKs and RTK adaptors removes nSH2 from the exposed loop of the helical domain and relieves p110α from autoinhibition [11].

Activation of PI3Kα by *PIK3CA* and *PIK3R1* mutations

PIK3CA somatic point mutations can result in a strong gain of function, promoting activation of PI3K-AKT signaling and tumorigenesis. *PIK3CA* is a commonly mutated oncogene with mutations mostly clustered at two hotspots in the kinase (H1047R) and helical (E542K and E545K) domains (Fig. 2) [12]. They act through different mechanisms. H1047R enhances the interaction of the kinase domain with the membrane, maximizing access to its substrate PIP_2, a membrane component. This mutant mimics the action of Ras [13]. It no longer requires binding to Ras-GTP, which is known to increase PI3K tethering to the cell membrane. In contrast,

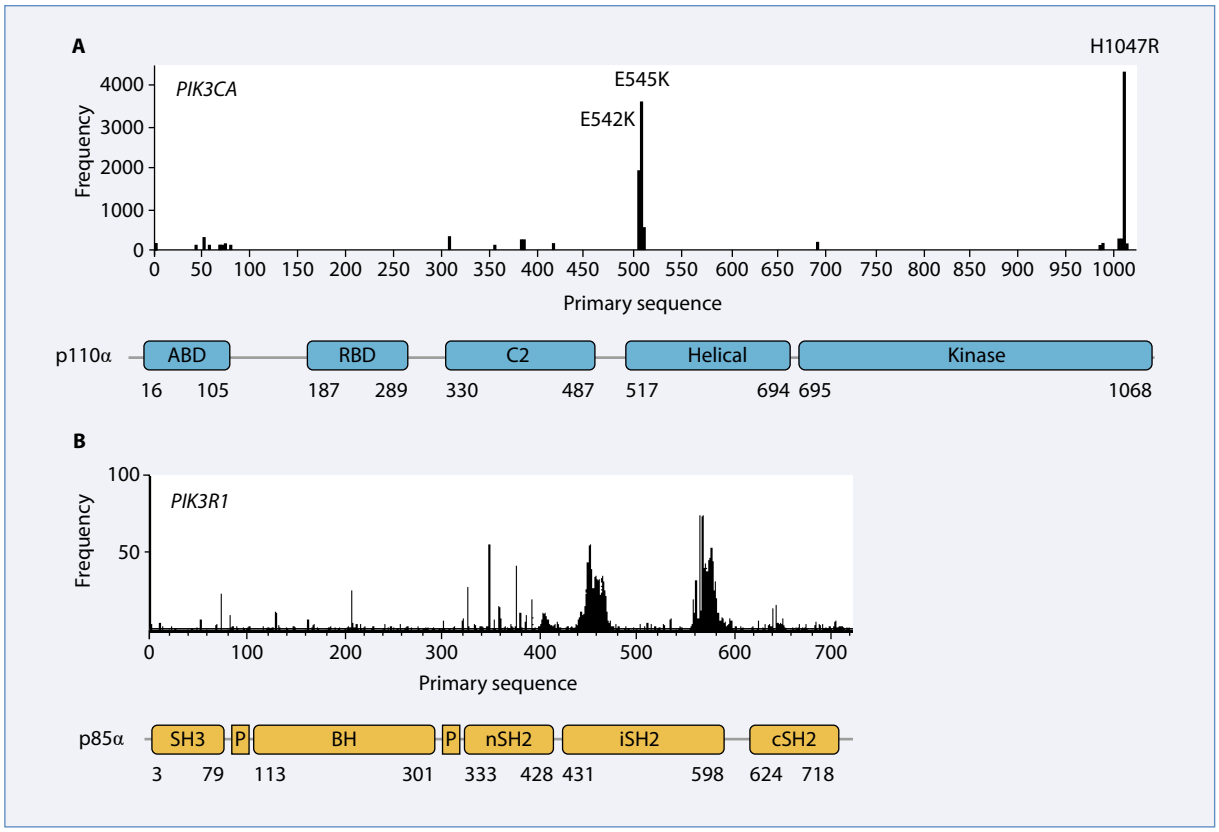

Figure 2. Frequency of *PIK3CA* and *PIK3R1* mutations in cancer. The frequencies and distribution of mutations in *PIK3CA* (**A**) and *PIK3R1* (**B**) in cancer (except for silent mutations) are shown on the primary sequence (adapted from the Cosmic database: http://cancer.sanger.ac.uk/cancergenome/projects/cosmic). The domains' positions in the amino acid sequence are indicated below; ABD — adaptor-binding domain; BH — Bcr homology; cSH2 — C-terminal SH2 domain; iSH2 — inter-SH2 domain; nSH2 —N-terminal SH2 domain; RBD — Ras binding domain; SH3 — Src homology 3 domain

E542K and E545K mutants disrupt the inhibitory contact between helical and nSH2 domains. Mutations at these positions mimic RTK's action. They release the autoinhibition such as that binding the RTK pYxxM motif to the nSH2 domain of the enzyme. In addition, there are numerous rare mutations located at the ABD (G106V), ABD-RBD linker (G118D), and C2 (N345K and C420R) domains that increase lipid kinase activity through disruption of the inhibitory interface between C2 and iSH2 domains along with movement of the ABD relative to the kinase domain [14]. These oncogenic mutations mimic conformational changes of the enzyme that are normally caused by membrane binding [11].

Loss of p85α, encoded by *PIK3R1*, leads to oncogenic transformation mediated by p110α, suggesting that *PIK3R1* acts as a tumor suppressor [15, 16]. Many *PIK3R1* mutations lie in the regulatory interfaces between the iSH2/nSH2 domains and the catalytic subunit [17]. They weaken the autoinhibitory interaction and retain the stabilizing interconnection between p85α and p110α, resulting in PI3K pathway activation [9]. The most frequent mutations (D560K and N564K/D) cluster in the iSH2 domain and disrupt the interaction with N345 of the p110α C2 domain, mimicking the N345K mutation [12]. Mutation in the nSH2 domain (K379E) of p85α disrupts the contact with E545 in the p110α helical domain and may have the same effect as the hotspot mutation E545K [11].

Several *PIK3R1* deletions and truncations at the C-terminus of iSH2 can mediate oncogenic transformation. These mutants can interact with p110 subunits and disrupt inhibitory contacts, increasing PI3K activity. Conversely, oncogenic truncations at the N-terminal to the iSH2 domain cannot bind the p110 subunit, and their activation mechanism has been proposed to be independent of PI3K catalytic activity [17]. These truncations affect structurally important domains and function by modulating free p85 interactions with binding partners [18, 19]. For instance, a truncation mutant in the BH domain (E160*) of p85α disrupts the p85-PTEN complex that is mediated by the BH domain, leading to a decreased PTEN level and activation of the downstream PI3K pathway [20]. Truncation mutants within the nSH2 domain (R348* and L370fs) directly bind Cdc42 and Rac1 and induce transformation via activation of JNK signaling [21].

PIK3CA and *PIK3R1* mutations in cancer

The Cancer Genome Atlas (TCGA) used to identify somatic variants across thousands of tumors from 12 cancer types demonstrated that the most frequently mutated gene is *TP53* (43%), followed by *PIK3CA* (17.8%) [2]. *PIK3CA* mutations occurred frequently (> 10%) in most cancer types except ovarian serous carcinoma, kidney renal clear cell carcinoma, and acute myeloid leukemia. *PIK3CA* mutations occur in endometrial carcinoma (52%), breast adenocarcinoma (33.6%), being specifically enriched in luminal subtype tumors, head and neck squamous cell carcinoma (20.6%), colon and rectal carcinoma (17.6%), bladder urothelial carcinoma (17.4%), lung squamous carcinoma (14.9%), and glioblastoma multiforme (11%). Tumors lacking *PIK3CA* mutations often had mutations in the *PIK3R1* gene. The frequency of *PIK3R1* mutations was lower than *PIK3CA* and amounted to 4.4% across all cancer types. The highest occurrence of *PIK3R1* mutations was observed in endometrial carcinoma (31%) and glioblastoma multiforme (11%).

Endometrial tumors most often exhibit *PIK3CA* mutations, which were detected in 52% of endometrioid endometrial cancer (EEC) and 33% of nonendometrioid endometrial cancers (NEEC) [22]. Interestingly, most of these mutations (72%) were found out of hotspot locations. *PIK3CA* amplifications (12%) and mutations were correlated with adverse clinicopathologic parameters of EEC [23]. Notably, *PIK3CA* mutations were associated with *PTEN* mutations, suggesting an additive effect of *PTEN* in these tumors' development. In addition, *PIK3R1* mutations were present in 43% of EECs and 12% of NEECs and were mutually exclusive with *PIK3CA* mutations [24].

In breast cancer, *PIK3CA* mutations were reported in 20–40% of cases, with most occurring within the helical and kinase domains. The incidence of mutations varied across different molecular subtypes and amounted to 18%, 22%, and 37% in the estrogen receptor (ER)-negative/ /human epidermal growth factor receptor 2 (HER2)- -negative, HER2-positive, and ER-positive/HER2-negative breast cancers, respectively [25]. *PIK3CA* mutations were associated with ER positivity, increasing age, lower grade, and smaller size but not with overall survival. Similar to uterine cancers, *PIK3CA* mutations frequently co-existed with *PTEN* mutations, which accelerate tumor development [26]. Mutations in *PIK3R1* are rare (2%) [27].

Head and neck squamous cell carcinoma (HNSCC) is a common cancer with frequent mutations in the PI3K pathway. Data from the TCGA indicate an overall *PIK3CA* mutation rate of 13.7% and an amplification rate of 16.5% [28, 29]. Mutations were located mainly in hotspots (65%) and were present in 8% of HPV-negative HNSCC tumors and 21% of HPV-positive tumors. In terms of prognosis, there was no significant relationship between *PIK3CA* mutational status and clinicopathological characteristics of tumors. Clinically, *PIK3CA* amplification was associated with a high risk of recurrence in HNSCC patients without lymph node metastasis [30].

In colorectal cancer (CRC), *PIK3CA* mutations were present in 21–28% of patients [2, 31]. *PIK3CA* mutations did not correlate with clinicopathological parameters such as disease stage or tumor differentiation, which indicates that they do not predict aggressive clinicopathological characteristics [32]. Cancers with *PIK3CA* mutations and *KRAS* wild type are observed in 12–14% of CRC [31]. A meta-analysis identified *PIK3CA* mutations as predictors of decreased response to anti-EGFR therapy in patients with metastatic CRC [33]. *PIK3CA* mutations frequently co-exist with *KRAS* mutations or microsatellite instability (MSI) [32]. In CRC, *PIK3R1* was mutated in 8% of cases, and 45% of *PIK3R1* mutant samples had *PIK3CA* mutations, suggesting that the p85α and p110α mutations are not always mutually exclusive in this tumor type [34].

Bladder tumors are a very heterogeneous disease characterized by a high prevalence of *FGFR3* mutations in superficial tumors and *TP53* mutations in muscle-invasive tumors. *PIK3CA* mutations occur with a frequency of 13–17% in bladder cancer [2, 35]. They are an early genetic alteration associated with *FGFR3* mutations in superficial papillary bladder tumors, which confirms that papillary and muscle-invasive tumors arise through different molecular pathways.

In lung cancer, the prevalence of *PIK3CA* mutations varies significantly, with higher frequency in squamous cell carcinoma (14.9%) in comparison with adenocarcinoma (4.4%) [2]. Similarly, *PIK3CA* copy number gains were more frequent in squamous cell carcinoma (33.1%) than in adenocarcinoma (6.2%) [36]. *PIK3CA* mutations were detected in 5.4–9% of non-small cell lung cancers and were associated with distant metastases and a poor prognosis [37, 38].

Glioblastoma (GBM) represents the most aggressive form of glioma with frequent alterations in the PI3K pathway. *PIK3CA* is either mutated (11%) or amplified (14%) in this tumor type [39]. Besides, there were also mutations in the *PIK3R1* gene (11%). *PIK3CA* activating mutations were associated with more disseminated disease at diagnosis, earlier recurrence, and shorter survival in adult GBM [40].

PI3K inhibitors

PI3K represents an attractive anticancer drug target since it is frequently activated in various cancer types. Numerous PI3K inhibitors (PI3Ki) have been developed and investigated in clinical trials during the last decades. Among these inhibitors, copanlisib, alpelisib, idelalisib, and duvelisib have been approved

by the Food and Drug Administration (FDA) for targeted therapy [41]. PI3Ki are divided into three groups: pan-PI3K inhibitors, isoform-specific inhibitors, and dual PI3K/mammalian target of rapamycin (mTOR) inhibitors.

Pan-PI3K inhibitors have activity against all four PI3K class I isoforms, PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ. They are frequently reported to cause adverse events such as rush, fatigue, nausea, dizziness, and vomiting. Copanlisib is an intravenous pan-PI3Ki, which was approved in 2017 by the FDA for the treatment of patients with relapsed follicular lymphoma (FL) and in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin lymphoma [42].

Isoform-specific PI3K inhibitors have been established to target only one or two PI3K isoforms. Compared to pan-PI3Ki, these drugs have a wider therapeutic index and a lesser off-target toxicologic effect due to different tissue distributions of PI3K isoforms [43]. Among isoform-specific PI3K inhibitors, three have been approved by the FDA: alpelisib, duvelisib, and idelalisib.

Alpelisib is an oral, highly specific inhibitor of PI3Kα isoform, which received FDA approval in 2019 [44]. This drug has demonstrated efficacy in combination with fulvestrant for postmenopausal women and men with hormone receptor (HR)-positive, HER2-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. This group of patients had significantly longer progression-free survival than the control group (11 months *vs.* 5.7 months) and the overall response rate (26.6% *vs.* 12.8%). The most frequent adverse events were hyperglycemia, rash, and diarrhea [45].

Inhibitors of PI3Kδ and PI3Kγ, like duvelisib and idelalisib, are restricted to patients with cancers of the immune system. Duvelisib is a dual inhibitor with targeted efficacy against PI3Kδ and PI3Kγ approved by the FDA in 2018 for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and in relapsed or refractory FL [46]. Idelalisib, a specific drug against PI3Kδ isoform approved by the FDA in 2014, has exhibited remarkable clinical benefits in combination with rituximab in CLL patients [47]. This drug has also been approved as monotherapy in patients with relapsed SLL and relapsed follicular B cell non-Hodgkin lymphoma [48].

Conclusions

Over the last few decades, significant progress has been made in our understanding of PI3Kα physiological activation and the mechanisms by which *PIK3CA* and *PIK3R1* mutations increase PI3Kα activity. Detailed molecular studies have evaluated the frequency and diversity of these mutations in a wide range of human cancers. Multiple PI3K inhibitors have been developed, and some have been approved for clinical use. In everyday practice, molecular assessment of *PIK3CA* hot spot mutations has predictive significance in breast cancer treatment with alpelisib, the PI3Kα inhibitor. Moreover, *PIK3CA* mutations were identified as predictors of decreased response to anti-EGFR therapy in patients with metastatic colorectal cancers. Considering that *PIK3CA* is the second most frequently mutated gene in cancers according to the TCGA study, many patients may obtain clinical benefits with molecular targeting of p110α mutant proteins. Continued examination of PI3Kα mutations and their functional consequences will be essential to identify mutant-specific inhibitors and define the most effective treatment for patients whose tumors harbor these genetic alterations.

Article Information and Declarations

Author contributions

I.K.R.: conceptualization, drafting the article, review and editing; A.T.: conceptualization, review and editing. Both authors have read and accepted the published version of the manuscript.

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Conflict of interest

Authors declare no conflict of interest.

Supplementary material

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