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The structural basis of PI3K cancer mutations: from mechanism to therapy

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Abstract

While genetic alteration in the p85α-p110α (PI3K) complex represent one of the most frequent driver mutations in cancer, the wild type complex is also required for driving cancer progression through mutations in related pathways. Understanding the mechanistic basis of the function of the PI3K is essential for designing optimal therapeutic targeting strategies.

Recent structural data of the p85α-p110α complex unraveled key insights into the molecular mechanisms of the activation of the complex and provided plausible explanations for the well-established biochemical data on p85-p110 dimer regulation. A wealth of biochemical and biological information supported by recent genetic findings provide a strong basis for additional p110-independent function of p85α in the regulation of cell survival. In this manuscript we review the structural, biochemical and biological mechanisms through which p85α regulates the cancer cell life cycle with an emphasis on the recently discovered genetic alterations in cancer. Since cancer progression is dependent on multiple biological processes, targeting key drivers such as the PI3K may be required for efficacious therapy of heterogeneous tumors typically present in patients with late stage disease.

Keywords

PI3K; P85; P110; Cancer; Structure

Introduction

The recent progress in our understanding of the genetic basis of cancer has made it clear that there is significant intra-tumour heterogeneity at the single nucleotide level. Single cell whole exome data from model tumours revealed previously unrecognized diversity of

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coding mutations. Such profound heterogeneity poses a challenge for designing successful targeted therapies for cancer patients and calls for novel strategies to circumvent this problem. One plausible approach is to target biological processes that are required for cancer progression. Such processes may be driven by mutations in key drivers but modulated and eventually implemented by a panel of proteins that directly contribute to an individual biological process. Here we review the mechanistic basis of the p110α (PIK3CA)/p85α (PIK3R1) phosphatidyl inositol 3 kinase function, a key modulator of several biological processes such as survival, proliferation, migration, invasion and metastasis and, therefore, an attractive target for therapy.

In 1985 Whitman et al., showed that the transforming ability of the polyoma virus middle-T antigen (PyMT), a membrane bound tyrosine kinase closely correlated with phosphatidylinositol (PI) kinase activity (1). This kinase activity was later found to phosphorylate the 3′ position on 4,5 diphosphorylated inositol phosphatidylinositol-4,5-bisphosphate (PtdIns(4,5)P2) to yield PtdIns(3,4,5)P3 (2). The generation of PtdIns(3,4,5)P3 results in activation of many intracellular signaling pathways including metabolism, proliferation, survival, motility and morphology. Although PyMT was later found to have independent oncogenic properties, its regulation of PI3K revealed that hyper-activation of this pathway can lead to uncontrolled proliferation, enhanced migration and adhesion-independent growth. Recent observations revealed further important insights into the mechanism of regulation and activation of the PI3K pathway in cancer.

PI3K activation occurs at the cell membrane

The p110α (PIK3CA)/p85α (PIK3R1) dimer receives regulatory stimuli from transmembrane receptors via tyrosine kinases. The protein tyrosine kinases involved can be the receptor itself, such as growth factor receptors (e.g. PDGFR, EGFR and IGFR) or kinases that are activated by direct or indirect association with the receptor (e.g. Src family of protein tyrosine kinases; Fyn and Lck). These tyrosine kinases are able to phosphorylate critical tyrosine residues within activation motifs, often located within the receptors themselves (e.g. autophosphorylation of the YXXM motif in PDGFR) or are present on protein adaptors (e.g. IRS, Shc, Grb, Gab and Cbl). As a multidomain-containing protein, the regulatory subunits of PI3K (p85, p55, p50) bind to the phosphorylated pYXXM motif via their SH2 domains (Figure 1A) resulting in PI3K membrane recruitment and generation of the second messenger PI (3,4,5) P3. In addition the RBD domain of p110α catalytic subunit (Figure 1A) is recruited to the plasma membrane through direct binding to the GTP-bound active form of membrane bound (myristylated) Ras.

PI3K initiates the intracellular signaling cascades by generating phospholipids. The production of second messenger phosphatidylinositol-3, 4, 5-trisphosphate (PtdIns(3,4,5)P3) leads to activation of a series of signaling pathways. The cellular level of PtdIns(3,4,5)P3 is tightly regulated by the opposing activity of PI3K and PtdIns(3,4,5)P3 phosphatases (PTEN, SHIP1 and SHIP2). PTEN is an important tumor suppressor, which functions as a lipid phosphatase that removes a phosphate group from position 3 of PtdIns(3,4,5)P3 and converts it back to PI(4,5) P2. PtdIns(3,4,5)P3 can also be dephosphorylated at position 5 by SHIP1 or SHIP2 to form PI(3,4) P2. PtdIns(3,4,5)P3 provides docking sites for signaling molecules with pleckstrinhomology (PH) domains and recruits them to cellular membranes (3). The most important effector of PI3K signaling is the PH domain-containing serine-threonine kinase AKT and its activator PDK1 (3-phosphoinositide-dependent kinase1). AKT is translocated to the plasma membrane by association with PtdIns(3,4,5)P3 and is activated by phosphorylation at S473 predominantly by the mammalian target of rapamycin complex (mTORC2) and at T308 by phosphatidylinositol-dependent kinase 1 (PDK1). AKT

phosphorylates a large number of downstream signaling molecules and subsequently regulates a wide range of cellular processes (3).

PI3K mutations in cancer cluster at activating hotspots

In 2004, Samuel *et al* first reported the analysis of eight PI3K and eight PI3K-like genes in 35 colorectal cancers, *PIK3CA* was the only gene that showed somatic mutations. More than 75% of all sequence alternations clustered at the helical and the kinase domains (Figure 1B). Ectopiclly expressed hot spot mutant H1047R was found to have higher lipid kinase activity than the wild-type kinase (4). Subsequent analysis of all coding exons of PIK3CA identified mutations in 74 of 234 colorectal cancers (32%), 4 of 15 glioblastomas (27%), 3 of 12 gastric cancers (25%), 1 of 12 breast cancers (8%) and 1 of 24 lung cancers (4). Hotspot mutations (E542K, E545K and H1047R) were subsequently reported to stimulate kinase activity and to exert strong oncogenic drive (5). In 224 tumour and normal pairs of colorectal cancers in The Cancer Genome Atlas (TCGA) genome-scale analysis, the PIK3CA was one of the 8 most frequently mutated genes (18% frequency of mutations) in the non-hypermutated tumor subgroup. There are also reports showing mutations of *PIK3CA*, in 52.4% of 42 endometrioid endometrial cancers (EEC), 33.3% of 66 non-endometrioid endometrial cancers (NEEC) (6).

In addition, mutations in the PI3K regulatory subunits have been described. *PIK3R1, PIK3R2 and PIK3R3*, encode p85α (which, through alternative transcription-initiation sites, encode two shorter isoforms p55α and p50α), p85β and p55γ regulatory subunits, respectively. *PIK3R1* was mutated in 9 of 108 colorectal (8%), 1 of 62 breast (2%), and 1 of 6 pancreatic (17%) tumor samples (7). In a TCGA cohort, 9 *PIK3R1 somatic* mutations were found in the 91 sequenced glioblastomas, and 8 out of 9 detected *PIK3R1* somatic mutations clustered at the iSH2 domain (Figure 1A-D) (8). A recent study of 42 EECs and 66 NEECs revealed an unusually high frequency of *PIK3R1* mutations. *PIK3R1* was somatically mutated in 43% of EECs and 12% of NEECs. The majority of mutations (93.3%) were localized at the p85α nSH2 and iSH2 domains (9). Therefore, many mutations would also affect the shorter isoforms p55α and p50α if those were expressed. In the recent TCGA analysis of 510 human breast tumors, 14 *PIK3R1* mutations were detected, and most of the mutations clustered in the iSH2 domain (particularly at amino acids 456-469 and 564-575) (10). Mutations in *PIK3R2* or *PIK3R3* are rare (8).

How p85 modulates the catalytic activity of p110

A wide variety of PI3K-activating cancer mutations occur at the interface between P110α and p85α (Figure 1B) suggesting that this interaction plays a key role in regulating the complex. In the absence of p85α, monomeric p110α is rapidly degraded (11) whereas coexpression of p85α stabilizes a low activity state of p110α (12). Strikingly the isolated iSH2 domain that binds to a large surface spanning the ABD domain and a groove formed by the helical, catalytic and C2 domain of p110α does not inhibit the p110α kinase. In contrast, inhibition of p110α by p85α requires the presence of the nSH2 domain. However, the nSH2 domain was not well defined in the p110α/p85α co-crystal structures and the interaction could only be modelled based on biochemical data. In the H1047R mutant p110α/p85α structure the nSH2 domain acts as a central scaffold binding to the interface formed by the kinase, helical, and C2 domains (Figure 1B). Biochemical data showed that phosphotyrosine peptides are capable of activating the niSH2/p110 complex but not the iSH2/p110 complex *in vitro* through their interaction with the nSH2 domain (Figure 1C). This suggests that the nSH2 domain is required for the inhibition of the p110 kinase and that modulation of its conformation may have a strong effect on modulating the p110 kinase activity (13-16). It is, therefore, thought that the main function of the iSH2 domain is to act

as a tether for p110, holding the p85/p110 subunits together, and that this interaction enables a second regulatory contact between the nSH2 and p110α that inhibits the p110 activity by inducing conformational change.

The p85 SH2 domains specifically bind to phosphotyrosine motifs (pYXXM) (17) via a charge interaction between an acidic patch on the phosphorylated motif and the basic residues on the surface of the nSH2 domain. Binding of p85α/p110α dimers to a number of tyrosine-phosphorylated proteins that are known to have two or more tyrosine phosphorylated YXXM motifs (e.g., PDRF-R, IRS-1) results in a two to three fold increase in enzyme activity *in vitro* (18). Binding of the nSH2 domain to phosphotyrosine peptides is thought to interfere with nSH2 binding to p110α and, therefore, relieves p110α from inhibition (Figure 1C).

The interaction of iSH2 with ABD/C2 domains of p110α provides a scope for allosteric regulation of the kinase

The ABD is in contact with the iSH2 coiled-coil domain of p85α at one extreme by face-to-face interaction, while the C2 domain provides an interaction site with the N-terminal helix of the iSH2 coiled coil structure (Figure 1B). The iSH2-ABD interface is large, with the concave face of the ABD β sheet interacting with at least seven helical turns in helix 1 and three turns of helix 2 of the iSH2 (13, 14). The C2 domain, which consists of two four-stranded antiparallel sheets that form a β sandwich, makes lateral contact with the iSH2 domain (13). The iSH2 interaction brings the nSH2 domain in close proximity with the helical domain of p110α. The predominately negatively charged p110α loop (residues 541-546) interacts with the positively charged nSH2 domain, and this makes this interface strong enough to position nSH2 in its inhibitory position (Figure 1B) (19).

Thus, it is important to note that there is relatively little direct interaction between the kinase domain of p110α and the niSH2 domains of p85α and this suggests that p85α regulation of p110α activity is predominantly allosteric in nature secondary to conformational changes in the non-catalytic domain.

The structural basis of activating PI3K mutations in cancer

As described above, tyrosine kinase receptors recruit the catalytic subunit of PI3K to the membrane through its associated regulatory subunit. After stimulation by receptor tyrosine kinases, the nSH2 domain moves away from the p110α helical domain to accommodate the binding of tyrosine-phosphorylated activators (e.g. PDGFR or IRS1). This allosteric regulatory mechanism brings p110α near its lipid substrates in the membrane and releases the inhibitory effect of p85α on p110α. Importantly, the p110 helical domain loop that contains sites of hotspot mutations (e.g. E542K and E545K) is located at the site where phosphotyrosine peptides bind to the nSH2 domain and potentially produce an electrostatic clash with lysine 379 of the nSH2 domain (Figure 1C). It is thought that the mutant p110 lysine residues occupy the space that, under physiological conditions, would only be occupied by phosphotyrosine partners and would therefore result in constitutive relief of inhibitory binding between nSH2 and p110 (Figure 1C). Interestingly, K379E nSH2 mutants inhibits the p110α-E545K oncogenic mutant, whereas the wild type p85 nSH2 does not, suggesting that the charge reversal reestablished the critical inhibitory interaction (14).

The structure of the common H1047R mutant in complex with p85α revealed some critical differences when compared with the structure of the wild type. In contrast to the wild type histidine residue the arginine residue does not interact with the activation loop leucine 596 but orients its side-chain away from the catalytic domain facilitating membrane recruitment.

The mutant structures is also in a region close to the C-terminus of p110α (residues 1050-1062) and induces structural changes in the loop spanning residues 864-874, both regions known to be important for the recruitment of the kinase complex to the plasma membrane. These structural changes may explain the observation that H1047R does not require binding to activated RAS which synergizes with the recruitment of the wild type kinase complex to the cell membrane (19). This explanation is consistent with the finding that H1047R mutants retain their transforming ability even if their interaction with RAS is abolished by mutating the RBD domain (20). Interestingly, both E542K and E545K mutants appear to require RAS binding to retain their transforming ability suggesting that the helical domain and kinase domain mutants activate the kinase through independent mechanisms (20).

The majority of hotspot mutants of p85α are clustered at the nSH2-iSH2 domains and many have been shown to induce a gain of PI3K enzymatic function, oncogenic cellular transformation, cellular proliferation, and enhance PI3K signaling (21). The structure of the p85/p110 complex suggests that these *PIK3R1* point mutations and insertions/deletions may disrupt the inhibitory effect of p85α on p110α.

Residues D560 and N564 of p85α are highly mutated in tumors. The structural data predict that the effect of mutating these residues would be similar to mutating N345 of the C2 domain of p110α (22). N345K is within hydrogen-bonding distance from D560 and N564 of iSH2 of p85α and mutations at these residues may disrupt the inhibitory interaction of the C2 domain with iSH2 (13). Consistent with this model, deletion of p85 after residue 571(p85ni-572^{stop}), or mutations of residues D560K/N564K, leads to constitutive PI3K activation (23). Analysis of the D560Y, N564D, D569Y/N564D, and DYQL579 mutants revealed that they retain the ability to bind to p110α, p110β and p110δ but that they have less inhibitor effect on the kinases leading to enhanced cell survival, AKT activation, anchorage-independent cell growth, and oncogenesis (7).

An analysis of the oncogenic activity of 9 mutants of p85 found in glioblastoma (24) and one engineered mutation K379E (14) was conducted and a comparison was made with the p110α mutant H1047R. When overexpressed in chicken embryo fibroblasts (CEFs), all mutants induced oncogenic cellular transformation, increased proliferation and enhanced downstream signaling. Among them, the most potent mutants, KS459delN and DKRMNS560del, showed specific transforming activity similar to the highly oncogenic p110α mutant H1047R. These two residues are located on equivalent positions of two alternate helices in the iSH2 domain, and are also in close proximity to the C2 domain of p110α. Mutations at these residues may disrupt the α-helical structure of the iSH2 domain and consequently may disrupt interactions with the C2 domain. In addition, the three C-termial iSH2 mutants (R574fs, T576del and W583del) all occur in the long α helix of the iSH2 domain and may, therefore, contribute to the abnormal interface between the iSH2 and the C2domains (21).

The GAP (also called BH) domain of p85α has been shown to harbor activating mutations in endometrial and other cancers (7, 9, 25). This mechanistic basis by which these mutations activate the PI3K pathway appear to be through modulating the interaction between p85α and PTEN or other p85α interaction partners rather than through a direct effect on p110α.

P110-independent regulation of cell survival by p85α

The BH domain (also called GAP domain, Figure 1A) of p85α bares conserved sequence homology to a large group of Rho GTPase-activating proteins (RhoGAPs). RhoGAPs catalyze the hydrolysis of GTP that is bound to small GTPases (Rho, Rac and Cdc42),

leading to their inactivation. In vitro studies showed that the p85α regulatory subunit can interact with the GTP-bound forms of the Cdc42 and Rac1. Ectopic expression of the BH domain containing forms of p85 (e.g. p85α), but not the BH deficient form p50, was found to decrease actin stress fibers and reduce focal adhesion complexes, resembling the Cdc42-dependent cytoskeletal changes induced by PDGF (26). In addition p85 can simultaneous bind to Cdc42 and Septin2 via the BH domain and a region around nSH2-iSH2, respectively. This subsequently regulates Cdc42 activity in cytokinesis and its localization at the cleavage furrow. Thus p85 contributes to the cell division during the later phases of cell cycle (27). P85α was found to posses GAP activity for Rab5 and Rab4 proteins that localizes on early endosomes and regulates vesicular fusion events (28). Because of the co-localization between p85 that is bound to PDGFR during receptor tyrosine kinase endocytosis and the early endosomal proteins Rab4 and Rab5, it is thought that the p85 regulates the GTP-bound state of Rab4 and Rab5 (28). Thus, at least in some model systems, the BH domain may posses GAP activity. In addition, the SH2 domains of p85α was found to interact with phosphorylated and activated STAT5 in leukemia cells and this resulted in activation of the PI3K pathway (29). Whether this interaction also modulates the transcriptional activity of STAT5 remains unknown.

In cells, the p85α subunit is about 30% more abundant than p110α. A model describing the balance between the two subunits of PI3K suggests that the extra 30% of p85 exists as a free monomer which is unable to transmit a RTK signal, but competes for binding to the phosphorylated insulin receptor substrate (IRS) proteins to inhibit signaling via the p85-p110 dimer. Heterozygous disruption of *PIK3R1* will only affect the monomer p85, but with little effetct on the p85-p110 dimer, which results in increased AKT activity and decreased apoptosis by insulin-like growth factor1 (IGF-1) through up-regulated PIP3 production. While complete depletion of p85, entirely losing the p110-binding ability, results in significantly increased apoptosis due to reduced PI3-kinase-dependent signaling (30).

Concluding remarks and future directions

The PI3K is a bright example of how studying human disease can significantly enhance the understanding of fundamental protein function. The discovery of hotspot mutations in cancer combined with a wealth of biochemical and structural data unraveled significant insights of the mechanistic basis of regulation of p110α catalytic activity. These insights underpinned the efforts to invent new diagnostic and therapeutic tools for targeting this complex in cancer and other diseases. Future directions will need to focus on two levels. At the molecular level, it is crucial that the role of the SH3 and the BH domains of p85α in regulating the activity of the kinase is investigated at the structural level to enable a full understanding of the intrinsic regulation of the PI3K activity. At the translational level, recent genetic discoveries of profound heterogeneity challenged the established dogma of therapeutic targeting of individual genetic alterations. Targeting a vital cancer process to prevent the evolution of the next generation of the cancer progeny is a plausible approach. Since the PI3K is a key component of many vital cellular processes, deeper understanding of its temporal role in regulating cancer progression is needed to allow its effective targeting.

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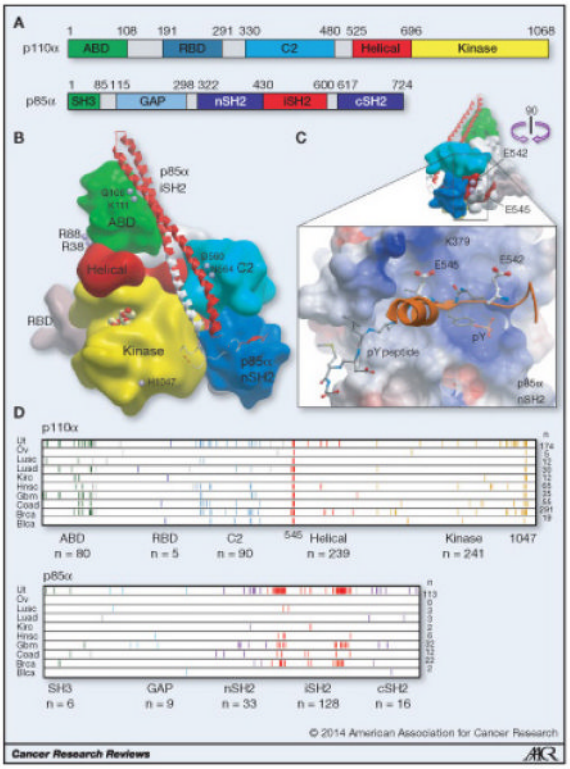

Figure 1.

Structural overview of the p85α/p110α complex: **A**: Schematic representations of the domain organization of both proteins. Boundaries were taken from Huang et al. The region of frequent mutation in p85 are indicated. **B**: Surface representation of the p85α/p110α complex. The p85a iSH2 domain is shown in ribbon representation. The region of deletions detected in cancer is highlighted in white. Cancer mutations are shown as sheres and are labeled. **C**: Rotated structure of the complex and details of the p85α nSH2 domain p110α interaction. A phosphopeptide binding to the SH2 domain is shown in ball and stick representation. **D:** Summary of TCGA data (8) showing the amino acid location of 884 exon mutations in p110α and p85α in 10 cancers. Vertical bars represent individual mutations. The number of mutations per tumour type and per domain is indicated. Ut: uterine endometrial cancer; Ov: ovarian cancer; Lusc: lung squamous cell carcinoma; Luad: lung adenocarcinoma; Kirc: kidney renal clear cell carcinoma; Hnsc: head & neck squamous cell carcinoma; Gbm: glioblastoma; Coad: colon and rectal adenocarcinomas; Brca: Breast cancer; Blca: Bladder cancer.

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