PI3King the right partner: unique interactions and signaling by p110β

Hashem A. Dbouk
Department of Pharmacology, University of Texas Southwestern Medical Center, 6001 Forest Park Rd, ND7.202, Dallas, TX 75390
Email: hashem.dbouk@utsouthwestern.edu

Abstract
Phosphoinositide 3-kinases (PI3Ks) are central regulators of cellular responses to extracellular stimuli, and are involved in growth, proliferation, migration, and metabolism. The Class I PI3Ks are activated by Receptor Tyrosine Kinases (RTKs) or G Protein-Coupled Receptors (GPCRs), and their signaling is commonly deregulated in disease conditions. Among the class I PI3Ks, the p110β isoform is unique in being activated by both RTKs and GPCRs, and its ability to bind Rho-GTPases and Rab5. Recent studies have characterized these p110β interacting partners, defining the binding mechanisms and regulation, and thus provide insight into the function of this kinase in physiology and disease. This review summarizes the developments in p110β research, focusing on the interacting partners and their role in p110β-mediated signaling.
Keywords : PI3K, p110β, RTKs, GPCRs, Rho-GTPases, Rab5

PI3Ks are a family of lipid kinases that are central in cellular signaling, mediating responses to growth factors and extracellular stimuli, as well as regulating a wide variety of intracellular processes [1, 2]. PI3Ks are divided into 3 classes based on sequence homology between catalytic subunits and substrate specificity (Table 1) [3, 4]. The class I PI3Ks is further subdivided into two subclasses based on their regulatory subunits, with class IA consisting of three catalytic subunits (p110α, β, and δ) which associate as obligate heterodimers with one of five different regulatory subunits (p85α, p55α, p50α, p85β, and p55γ) collectively referred to as p85 [5, 6], while the class IB consists of a single catalytic subunit, p110γ, that can associate with either of two regulatory subunits, p87 and p101, which can mediate different signaling inputs [2, 7-9].

The class I PI3Ks use $PI(4,5)P_2$ as a substrate to generate the product $PI(3,4,5)P_3$ which initiates major signaling pathways downstream [1]. While the sequence, domain composition, and structures of the class I PI3K catalytic isoform are to a large extent similar and homologous, the main differences in function amount from tissue-specific distribution of the catalytic subunits, as well as an array of common and unique interacting partners that modulate intracellular distribution, responses and functions of the isoforms. The identification of these interacting partners and characterization of their effects on different catalytic subunits is paramount for our understanding of these enzymes and our ability to target their unique and overlapping functions.

Class	Catalytic Subunit(s)	Regulatory Subunit(s)	Substrate	Product
I A	p110α, β, δ	p85α, p55α, p50α p85β, p55γ	$PI(4,5)P_2$	$PI(3,4,5)P_3$
I B	p110γ	p101/p87	$PI(4,5)P_2$	$PI(3,4,5)P_3$
II	PIK3C2α, β, γ	-	PI, PI(4)P	PI(3)P, $PI(3,4)P_2$
III	vps34	vps15	PI	PI(3)P

Table 1. PI3K classes, subunits, substrates, and products

The signaling downstream of PI3Ks and the generation of $PI(3,4,5)P_3$ is mediated through the recruitment of Pleckstrin homology (PH)-domain containing proteins which can bind to $PI(3,4,5)P_3$ [10, 11]. Among PH-containing proteins, Akt, which was first discovered as the cellular homolog of the transforming retroviral oncogene v-Akt [12, 13], represents the canonical signaling pathway downstream of PI3Ks [14]. Akt is recruited to the membrane by its PH domain following PI3K activation where it is activated by phosphorylation on two residues: T308 in the kinase domain is phosphorylated by another PH-containing protein, phosphoinositide-dependent kinase 1 (PDK1) [15], and S473 in the hydrophobic motif which is phosphorylated by the mammalian target of Rapamycin complex 2 (mTORC2) [16]. Akt has multiple downstream substrates with a common consensus motif for phosphorylation [17], and can lead to regulation of various pathways, most prominently activation of mTORC1 via phosphorylation and inhibition of Tuberous Sclerosis Complex 2 (TSC2) which, together with TSC1, form a GTPase-activating protein (GAP) complex for Ras homolog enriched in brain (Rheb) [18-20]. Rheb can position the mTORC1 at the late endosome/lysosome where it is active [21], and therefore release of TSC1/2-mediated inhibition of Rheb by Akt results in activation of the mTORC1 pathway. In turn, mTORC1 modulates ribosomal biogenesis, protein translation, and increased cell size and growth through multiple targets, including ribosomal p70 S6 kinase and the eIF4E binding proteins (4E-BP 1 and 2) [22]. Other Akt targets include Glycogen Synthase Kinase 3 (GSK3) which is inhibited by Akt phosphorylation [23], Akt Substrate of 160 kDa (AS160) whose phosphorylation by Akt allows the membrane translocation of the insulin-dependent glucose transporter 4 (GLUT4) [24, 25], the pro-apoptotic Bcl2-antagonist of cell death (BAD) leading to decreased cell death [26], Forkhead Box O (FOXO) transcription factors leading to 14-3-3 binding and cytosolic sequestration to prevent their transcription of pro-apoptotic genes [27, 28], as well as modulation of Nuclear Factor Kappa B (NFκB) function and activity through various mechanisms [29-31]. The net outcome of class I PI3K pathway activation is the induction of cell growth and proliferation, coupled to inhibition of apoptosis, and thus this pathway is of great importance in development and is commonly hijacked in cancer and other diseases.

The division of class I PI3Ks into two subclasses was for a long time in conjunction with their responses to distinct signaling inputs: While both subclasses were generally shown to signal downstream of Ras [32], the class IA catalytic subunits with the SH2-domain containing p85 regulatory subunits signal downstream of RTKs, while the class IB subunit p110γ/p101 can bind to Gβγ subunits and signal downstream of GPCRs [2]. However, recent data has increased the complexity of the signaling by both subclasses, with the class IA p110β subunit shown to be activated by GPCRs [33-37] and p110γ being activated following RTK and Toll-like receptor stimulation in myeloid cells [38]. In addition, recent data has shown the ability of p110β to interact with Rab5 [39, 40] as well as with small GTPases Rac and cdc42 but not with Ras [41], suggesting that this isoform is unique among class I PI3Ks in terms of its interactions and regulation. Interestingly, among the PI3Ks, while p110α knockout causes mid-gestational embryonic lethality [42] and p110δ or p110γ knockout mice are viable [43, 44], p110β knockout causes lethality by embryonic day 3.5 [45], a very early time point highlighting the extreme significance of p110β and the major roles it plays in development, thereby necessitating further study and understanding of this isoform.

Disruption of PI3K signaling is a hallmark of many diseases, in particular cancer [46], where a large number of mutations in the pathway have been observed, with major mutational hotspots in p110α and p85 [47-49], while the Phosphatase and Tensin Homolog deleted from chromosome 10 (PTEN), which antagonizes PI3K signaling and dephosphorylates $PI(3,4,5)P_3$ back to $PI(4,5)P_2$, is commonly mutated or deleted in tumors [50, 51]. Interestingly, mutations in other class I catalytic subunits are rare [52, 53], with only one

p110β mutation having been described and characterized [53], while some amplifications of p110β and p110δ have been documented [54, 55]. The reason behind the accumulation of oncogenic mutations in the p110α subunit and not other class I catalytic isoforms is because, at least *in vitro*, p110α is only transforming when mutated while the other subunits are all transforming when over-expressed in the wild-type state [56]. A major recent finding was the requirement of p110β as the driving PI3K subunit in PTEN-null driven prostate tumors [57], although this is not a general case for all PTEN-deficient cancers as another study suggested that the specific catalytic subunit driving PTEN-null tumors may also be dependent on the tissue of origin of the tumor [58]. Furthermore, p110β signaling has been implicated in the pathogenesis of other tumors such as ErbB2-driven or H-Ras driven tumors [59, 60]. In addition, p110β has been implicated in a variety of other diseases and physiological processes including male fertility, thrombosis, metabolism, lung fibrosis, and Fragile X-syndrome [41, 59-65]. These studies have increased the interest in p110β and necessitated the understanding of p110β regulation by interacting partners and characterizing its many functions.

p110β interactions and their impact on p110β regulation

p110α and p110β are both ubiquitously expressed [66, 67], and yet display major differences in their modes of regulation and their signaling, particularly as seen by the ability of wild-type p110β to transform cells while p110α does not [56]. p110β is distinct among the class I PI3Ks in the diversity of its interacting partners (**Fig. 1**), and these allow multiple signaling inputs to control the activity, localization, and signaling of p110β in cells. In addition to different interacting partners, p110β displays unique contacts with the p85 subunit, which is a common regulator of all class IA subunits, while it does not interact with Ras, which is an activator of all other class I PI3Ks. The presence of unique interactions as well as the lack or divergence in mechanisms of interactions shared with other PI3K catalytic subunits make the understanding of p110β interactions crucial for deciphering its regulation and many functions, and how these can be disrupted in disease conditions.

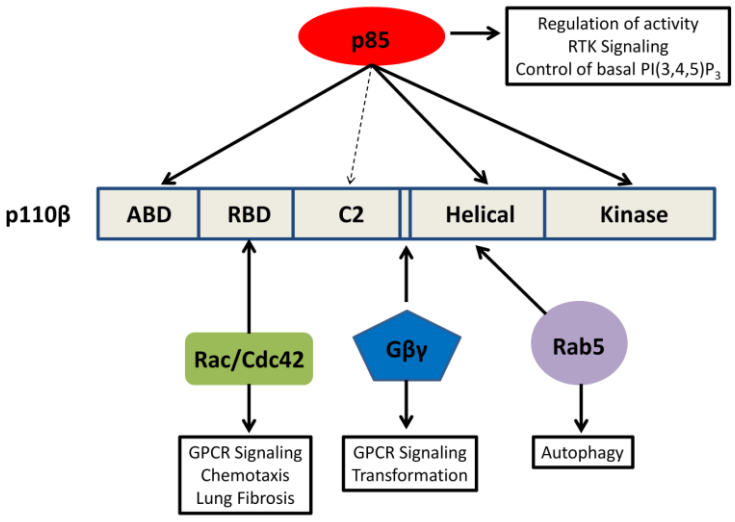

Figure 1. Domain structure of p110β and regions of interactions. The p110β catalytic subunit consists of 5 domains: Adaptor-binding domain (ABD), Ras-binding domain (RBD), C2, helical and kinase domains. p110β can interact with p85 through its ABD, C2, helical and kinase domains, although the C2-iSH2

contact is diminished or absent (dashed line) when compared to other class IA catalytic subunits. p110β can also interact with Rac and cdc42 through the RBD domain, with Gβγ subunits binding p110β at the linker region between the C2 and helical domains, and with Rab5 at the helical domain. These different interactions mediate the many functions of p110β in maintaining basal PI(3,4,5)P_3 levels, signaling from receptors, autophagy, and are deregulated in tumors and disease conditions.

p110β regulation by the p85 regulatory subunits

The class IA PI3K catalytic subunits are obligate heterodimers with p85 regulatory subunits [5], requiring this interaction for thermal stability of the p110 subunit [68]. Furthermore, p85 binding to p110 subunits results in inhibition of the basal activity of p110s and allows their activation following RTK stimulation via recruitment to activated receptors through the two SH2 domains within p85 [68-71]. The p85 subunit was shown to form multiple contacts with the p110α subunit, with the inter-SH2 (iSH2) coiled coil making contacts with the Adaptor Binding Domain (ABD) and the C2 domain of p110α, while the N-terminal SH2 domain (nSH2) formed contacts with the C2, helical, and kinase domains of p110α [48, 69, 72-75]. The interaction with the ABD is essential for the stabilization of the p110 molecule, whereas the other contacts have been shown to mediate the inhibition of basal activity and regulate the activation by phosphopeptides.

Consistent with the importance of these p85-p110 contacts in regulation of activity and signaling by class IA PI3Ks, these contact sites between the C2, helical or kinase domains of p110α and the iSH2 and nSH2 of p85 are hotspots for oncogenic mutations [47, 48, 69]. Interestingly, mutations in p85 subunits have been suggested to work mainly through p110α, not p110β [76, 77]. Analysis of the p85-p110β contact residues suggested a possible mechanism for the p110β-independent mechanism of p85 mutations: A contact residue mediating the p110 C2-p85 iSH2 contact and inhibition in p110α is not conserved in p110β. Rather, the analogous residue in p110β is similar to an oncogenic p110α mutation, leading to disruption of the C2-iSH2 contact between p110β and p85, and subsequently decreased inhibition of p110β basal activity [77, 78]. This is supported by Hydrogen-Deuterium exchange data showing that the C2-iSH2 interface between p110β and p85 is more exposed and dynamic compared to that of p110α or p110δ, consistent with decreased inhibition of p110β at that interface [79]. This diminished inhibitory contact between the C2 and iSH2 domains would lead to a higher basal activity in p110β. The importance of p110β basal activity is further suggested by studies in PC-3 cells, which are PTEN null prostate cancer cells, showing that basal PI(3,4,5)P_3 level in cells is p110β-dependent [80]. The connection between p110β basal activity and PTEN-deficient tumors is more intriguing due to the presence of PTEN in a complex with p85 and p110β [81]. This provides a model for the requirement of p110β in PTEN$^{-/-}$ tumors whereby p85-p110β-PTEN complex normally maintains the low threshold of PI(3,4,5)P_3 levels in cells through a constant cycle of high p110β basal activity countered by the associated PTEN, and this delicate balance is disrupted in tumors driven by loss of PTEN function [78].

In contrast to the loss of an inhibitory interface between p110β and p85 at the C2-iSH2 contact region, crystallization of p110β with the icSH2 domains of p85 revealed surprising new inhibitory contacts between the kinase domain of p110β and the C-terminal SH2 domain (cSH2) of p85 [82, 83]. Unlike the inhibitory interaction between the nSH2 domain and the helical domain which maintains the phosphopeptide binding region of the SH2 covered, the cSH2-kinase domain contacts do not block the phosphopeptide binding region. The mechanism of release of inhibition requires a longer peptide following the phosphotyrosine residue, compared to the nSH2, and such a longer peptide can disrupt the inhibitory contacts between the cSH2 and kinase domain. This

allows for the possibility to target the cSH2 to block the binding of phosphotyrosine-containing peptides without affecting the inhibitory contacts with the kinase domain [84], paving the way for peptide-mimetics to specifically block cSH2-mediated activation of p110 kinases.

p110β interaction with Rac and cdc42

The assumption that all class I PI3Ks are activated similarly by Ras [8, 85-90] was recently shattered by a study carefully looking at the interaction of p110β and Ras-GTP but found no regulation of that catalytic subunit by Ras [41]. Instead, the work by Hirsch and colleagues revealed novel interactions of the p110β RBD domain with Rac1 and cdc42, and to a much weaker level with RhoA and RhoG [41]. The interactions of Rac and cdc42 with p110β can directly stimulate the kinase activity of p110β, but more importantly can also regulate the activation of p110β downstream of GPCRs, via the Rac-GEF DOCK180/ELMO1-mediated pathway [41, 91]. According to the model, p110β can directly bind to Gβγ subunits and get activated to near maximal level, while simultaneously DOCK180/Elmo1 are recruited by direct binding to Gβγ subunits as well, activating Rac and placing in close proximity to p110β, whereby Rac interaction with p110β leads to full activation of p110β downstream of GPCRs [41, 92]. This interaction with Rac was shown to be important for LPA-mediated fibroblast chemotaxis *in vitro* and in an *in vivo* model of lung fibrosis [41], and thus targeting this specific interaction could have important benefits in some inflammatory syndromes or other GPCR-mediated diseases [93-95]. The extent of the contribution of Rac/cdc42 interaction with p110β to the overall response to GPCR stimulation is still not clearly defined relative to the effect of direct Gβγ binding, in particular whether these events occur concurrently or are spatially and/or temporally segregated with respect to the overall p110β response to GPCRs.

p110β activation by Gβγ subunits downstream of GPCRs

As mentioned in the section above, there are two mechanisms or steps for p110β activation downstream of GPCRs: 1) The major mechanism for p110β activation following GPCR stimulation is direct binding of p110β to Gβγ subunits, accounting for the majority of the p110β activity; 2) The second mechanism which adds to the Gβγ-mediated stimulation to reach maximal p110β activity is via the DOCK180/Elmo1-Rac mediated pathway. The direct activation of p110β downstream of GPCRs and interaction with Gβγ subunits was first shown more than a decade ago [33-35] and later shown to be the major pathway activating p110β, whereas overall RTK-stimulated PI3K activity was unaltered upon loss or inhibition of p110β [36, 59, 60].

Unlike characterization of p110-p85 interactions, defining the p110β-Gβγ interaction was more difficult due to the transient nature of the interaction and the lack of a unique motif amongst Gβγ interacting proteins. A dual approach to identify the p110β-Gβγ interaction interface using sequence alignments between class IA p110 subunits and hydrogen-deuterium exchange mass spectrometry (HDX-MS) identified the linker loop between the C2 and helical domains (C2-helical linker) as the region required for interaction with Gβγ subunits [37]. Further sequence alignment to define conserved p110β residues in this C2-helical linker identified two Lysine (KK) at residues 532-533 as central in this interaction [37], and analogous residues within p110γ were later shown to be required for the interaction with Gβγ subunits [96]. The interaction with Gβγ was shown to affect p110β in both kinase-dependent and kinase-independent mechanisms, with the localization of p110β to plasma membrane playing an important role in Gβγ-mediated functions of p110 [37]. These data point towards a scaffolding function of p110β that is still uncharacterized and could have a significant role on signaling independent of the lipid kinase activity. Interestingly, the HDX-MS study also revealed a novel interface on the Gβγ subunit for interaction with effector proteins. The interaction with p110β was shown to involve both the classical interface that coincided with

the region of interaction of many other Gβγ effectors as well as novel interface that was unique to p110β [37]. This provides a mechanism to target the p110β-Gβγ interface specifically, without altering the interaction of Gβγ subunits with other proteins, and preliminary analyses suggested the feasibility of such an approach [37].

The importance of the Gβγ interaction and the function of p110β downstream of GPCRs is highlighted by studies showing the impact of blocking both Gβγ-mediated direct activation and the DOCK180/Elmo1-Rac-mediated complementary activation of p110β on disease [37, 41]. Mutation of the residues required for p110β-Gβγ interaction decreased invasion towards GPCR ligands in different cell lines and also decreased migration of tumor cells specifically lacking PTEN [37]. This is consistent with a requirement for p110β in PTEN-deficient tumors [57], and suggests that the input of GPCRs to p110β is of central importance in the development and progression of these tumors. The ability to target the p110β-Gβγ interface with minimal side effects and cross-reactivity with other PI3K isoforms or Gβγ effectors could prove highly beneficial for the treatment of many tumors dependent on this pathway.

p110β interaction with Rab5

p110β has been shown to bind to Rab5-GTP, possibly on clathrin-coated vesicles, [39, 97], and was suggested by yeast two-hybrid to bind via two sections of p110β: a part of the ABD-RBD linker and RBD domain (residues 136-270) and a section of the helical and kinase domains (residues 658-759) [39]. This interaction of p110β with Rab5 has no effect on the kinase activity of p110β [41]. To accurately identify the residues of p110β required for Rab5 interaction, Backer and colleagues performed sequence analysis coupled with analysis of the crystal structure of p110β [82] to identify potential interaction sites, and subsequently identified two residues (Q596 and I597) in the helical domain as necessary and sufficient for interaction with Rab5 [98].

This interaction with Rab5, which has well-studied roles in endocytosis and early-endosomal maturation via interaction with the class III PI3K vps34 [99, 100], supported evidence for a possible kinase-independent role of p110β in endocytosis and trafficking [59, 60]. The p110β mouse knockout studies showed a defect in clathrin-mediated endocytosis, with decreased EGF and transferrin uptake, as well as decreased clathrin staining beneath the plasma membrane without change in the perinuclear clathrin levels, and a surprising complete loss of EEA1 staining, all of which can be rescued with the expression of kinase-dead p110β at physiological levels [59, 60]. The role of p110β in endocytosis has not been further characterized, and requires more studies to analyze the exact mechanism of any potential role for p110β in this process, as well as define the timing or stage of this process in which p110β is required.

Interestingly, a recent study identified p110β as a positive regulator of autophagy, a function which was mediated through association with the vps34/vps15-Beclin-1 Atg14L complex [101]. The interaction of p110β with the vps34 complex suggested a potential link through Rab5, and this was confirmed using point mutants of p110β that abrogated Rab5 binding to show a requirement for the interaction in autophagy [40]. The role of p110β in autophagy was shown to be downstream of growth factor limitation and not nutrient deprivation. The mechanism of action of p110β under growth factor-poor conditions is through the increase of Rab5-GTP levels by protecting the Rab5-GTP from the Rab-GAP activity of p85 [40, 102]. In turn, the increased Rab5-GTP can increase vps34 activity and drive autophagy. In contrast, under growth factor-replete conditions, p110β is recruited away from Rab5 to the plasma membranes and receptors, leaving Rab5 to be mostly in the GDP-bound state due to the Rab-GAP activity of p85, which leads to low levels of autophagy [40].

The p110β-Rab5 interaction has defined roles in autophagy, but its impact on endocytosis or the activation kinetics of p110β has not been studied. The interaction with Rab5 could recruit p110β to early endosomes, from which signaling

could still occur. A similar situation has been shown for p110γ which is activated by Gβγ subunits at Rab11a-positive endosomes, and this is required for proper Akt signaling [103]. One point to highlight is the relative proximity in the p110β crystal structure of the Gβγ and the Rab5 binding interfaces, opening the possibility for the interactions being cooperative or mutually exclusive, or even provide a model for a spatial and temporal regulation of the interactions to control the time course of p110β stimulation, activity, and localization. Whether p110β signaling occurs, at least partially, from the early endosome is still untested, and could suggest a role for Rab5 in localization of p110β to allow and enhance its signaling from specific compartment or allow for a kinase-independent scaffolding role at the endosome limited to or extending beyond vps34.

Concluding remarks

The recent emergence of p110β as a major player in development and tumorigenesis [59, 60] has spurred research into this catalytic isoform of PI3Ks. Understanding the regulation of the different class I PI3Ks is crucial for proper targeting of this pathway in disease conditions, particularly in P#K-driven cancers. The frequency of activation of the PI3K pathway in tumors makes it an attractive target for therapeutics, however this has proven more complicated than anticipated. While p110α is the most commonly mutated isoform in a variety of tumors, studies are still ongoing on the efficacy of isoform-specific inhibitors vs pan-PI3K inhibitors [104], although mutation-specific inhibitors could provide a valuable approach [105]. In fact, isoform-specific inhibitors, while useful tools for *in vitro* studies, have not translated to beneficial therapeutics for malignancies and disease. Several ATP-competitive inhibitors of p110β have been generated and tested for their effects on p110β-dependent processes such as PTEN-null tumor growth and platelet activation [62, 106-109], but their efficacy in the clinic has not been tested. With respect to p110β, the targeting of different interactions may be useful and has been recently discussed [84], and the major target is blocking the interaction with Gβγ subunits which is the major activating mechanism for p110β and regulates both kinase-dependent and –independent functions of p110β such as membrane targeting [37, 110]. With respect to PI3K isoform-specific inhibitors in use, apart from a p110δ-specific inhibitor, known as GS-1101 or CAL-101, which is beneficial in certain B-cell malignancies [111-113], they are in various stages of clinical trials, but redundancy of expression and functions between the different isoforms decreases their significance. The redundancy in signaling, seen at least in part due to the ubiquitous expression of p110α and p110β, suggests that dual inhibition of these isoforms may be beneficial to prevent compensation, and may even allow the use of lower doses of the individual isoform-specific inhibitors in combinations to decrease negative side effects and increase efficacy in targeting the tumor [104]. The most clinically significant inhibitors are pan-PI3K inhibitors or those targeting multiple class I isoforms, or even dual PI3K/mTOR inhibitors [104, 114, 115]. Ongoing clinical trials focusing on isoform-specific as well as multi-isoform and pan-PI3K inhibitors will provide insight into the benefits of targeting each isoform or a combinatorial approach, and should yield benefits for therapeutics as well as understanding the interplay between the different isoforms.

The surge of data on p110β has provided intriguing insights into a unique class I PI3K isoform that is distinct in its regulation and interactions from the other catalytic isoforms. These interactions are essential for understanding the function of p110β in various physiological and cellular processes, as well as in tumors and other diseases. The careful characterization of p110β interaction interfaces and identification of unique point mutations that block one function but not another will allow careful studies into p110β functions and dissection of its role in different processes. Seeing as this isoform is ubiquitous and knockout shows such an early embryonic lethality [45], the roles of this PI3K isoform as well as the

importance of different functions and interactions need to be explored in a wider range of tissues. For instance, the role of p110β and its interactions in embryonic and adult stem cells needs to be further explored [116, 117], as well as its function in energy homeostasis and nutrient signaling and responses [118], in particular seeing its impact on autophagy and vps34 activity and signaling [40, 101], and even in male fertility [61]. Furthermore, the individual and distinct interaction surfaces on p110β may be useful for drug design and targeting specific functions of p110β without altering others, thereby minimizing potential side effects. Importantly, while these interactions have been mainly described individually, there is a need to address the interplay between these p110β-interacting proteins and how they are coordinated relative to one another in order to modulate p110β functions. Deciphering the complexity of kinase-dependent and -independent functions of p110β mediated by its various interacting partners will yield valuable insight into the roles of this PI3K isoform in physiology and disease.

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