SnapShot: Class I PI3K Isoform Signaling

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LEGEND

Activation
Inhibition
Activating
Phosphorylation
Nucleotide exchange
Proposed activation

<table>
<thead>
<tr>
<th>Isoform</th>
<th>p110α</th>
<th>p110β</th>
<th>p110δ</th>
<th>p110γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue distribution</td>
<td>Ubiquitous</td>
<td>Ubiquitous</td>
<td>Hematopoietic system, endothelium, heart</td>
<td>Hematopoietic system</td>
</tr>
<tr>
<td>Upstream activators</td>
<td>RTKs (direct or via adaptors), RAS</td>
<td>GPCRs (GEP1), RTKs, FcγR, GPVIR, integrin αllβ3, RAC/Gei42</td>
<td>GPCRs (GEP1), RAS, TLR/IL1R and RTKs via RAS, FcγR via PKCβ</td>
<td>BCR/ITAM (indirect), CD28, CD19, BCAP, TRIM, FcγR, RTKs, TLRs, RAS/TC21</td>
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<tr>
<td>Physiological role</td>
<td>Insulin signaling, metabolism, angiogenesis, survival and proliferation, chemotaxis, B cell development</td>
<td>Metabolism, survival and proliferation, chemotaxis, endocytosis, autophagy, male fertility, ROS production, platelet adhesion</td>
<td>Neutrophil and macrophage chemotaxis, ROS production, T and NK cell development and function, heart contractility</td>
<td>B, T and NK cell development and function; Treg function; neutrophil; and mast cell function</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Frequently mutated oncogene, critical for RAS-driven tumors, tumor angiogenesis, cardiovascular disease</td>
<td>PTEN-negative cancer, lung fibrosis, inflammatory disease, cardiovascular disease, thrombosis</td>
<td>Tumor microenvironment, inflammation, autoimmune disease, atherosclerosis, heart disease</td>
<td>Hematological malignancies, tumor immunity, allergies, chronic inflammation, autoimmune disease</td>
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<tr>
<td>Isoform-specific inhibitors</td>
<td>A66, BYL719, MLN1117</td>
<td>TGX-221, GSK2636771, AZD6482, AZD8186</td>
<td>AS605240, IPI-145(γ, δ), CZC 24832, AS252424</td>
<td>CAL-101/GS-1101, AMG 319, IPI-145(γ, δ), CAL-263, IC87114</td>
</tr>
</tbody>
</table>

See online version for legend and references.
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Class I phosphoinositide 3-kinases (PI3Ks) phosphorylate the 3-hydroxyl group of the inositol ring of phosphoinositide (4,5) bisphosphate (PtdIns(4,5)2) to generate the lipid second-messenger phosphoinositide (3,4,5) trisphosphate (PtdIns(3,4,5)3), which binds to pleckstrin homology (PH) domains of effector proteins, inducing their plasma membrane translocation and activation. Effectors include serine/threonine and tyrosine protein kinases, adaptor proteins, guanine nucleotide exchange factors (GEFs), and GTPase-activating proteins (GAPs), altogether orchestrating a large set of cellular signaling pathways that regulate survival, growth, proliferation, motility, and metabolism. PI3K activity is tightly controlled, and deregulation leads to a wide range of pathophysiological conditions, including diabetes, inflammation, and cancer.

There exist four class I PI3K isoforms in mammals, named after their respective p110 catalytic subunits. p110α (PIK3CA) and p110β (PIK3CB) are ubiquitously expressed, whereas significant expression levels of p110γ (PIK3CG) and p110δ (PIK3CD) are restricted to hematopoietic cells and a few other tissues. Class I isoforms are heterodimers composed of a p110 catalytic subunit and a regulatory subunit. p110α, δ, and γ (class IA) engage p85-type regulatory subunits encoded by PIK3R1 (p85α, p55γ, p50δ), PIK3R2 (p85β), or PIK3R3 (p55γ). All p85 proteins contain two Src homology 2 (SH2) domains and a coiled-coil inter-SH2 (iSH2) domain, which together form the p85 core that binds, stabilizes, and inhibits the associated catalytic subunits. The precise mode of interaction between p85 and p110 varies between class IA isoforms, which may lead to distinct intrinsic biochemical properties. Upon receptor stimulation, the SH2 domains of p85 bind to phosphorytosine-containing consensus sequences on receptor tyrosine kinases (RTKs) or adaptor proteins. Recruitment of p85 to receptor tyrosine kinases can either be direct through binding of SH2 domains to YXXM motifs on the intracellular domain of the respective RTK (e.g., PDGFR) or can occur indirectly via adaptor proteins (GRB2/GAB for EGFR, IRS1/IRS2 for insulin receptor). This results in membrane recruitment of the heterodimer and deprivation of lipid kinase activity. The single class IB isoform, p110γ, engages p101 or p84 regulatory subunits with incompletely understood structural and functional consequences. Both p110γ/p101 and p110δ/p84 heterodimers are activated by Gβγ subunits from heterotrimeric G proteins, albeit to a different extent. Upon G-protein-coupled receptor (GPCR) activation, Gβγ dissociates from Gα and recruits and activates p110γ heterodimers, possibly through binding to both regulatory and catalytic subunits. Gβγ also directly binds and activates the ubiquitous class IA p110α isoform through direct interaction with its helical domain, making p110α the only PI3K isofom that is directly activated by both tyrosine-phosphorylated proteins and GPCRs. p110δ also functions in receptor-mediated endocytosis and autophagy, possibly through kinase-independent interaction with RAB5, which stabilizes the latter in its active, GTP-bound confirmation.

Another route to class I PI3K activation is through direct binding of active RAS superfamily GTPases to p110 RAS-binding domains (RBDs). p110α, γ, and δ isoforms interact with prototypical RAS proteins and a subset of closely related RAS subfamily GTPases (mainly RRAS proteins), whereas p110β is directly regulated by the RHO subfamily GTPases RAC and CDC42. How RAS superfamily GTPases are activated upstream of specific PI3K isoforms and precisely which RAS protein is involved in a given pathway may be cell type and context specific. For RAS, both SOS and RASGRF family RAS-GEFs have been implicated through indirect activation by tyrosine-phosphorylated proteins and phospholipase C (PLC)-dependent generation of diacylglycerol (DAG), respectively, whereas RAC was found to be activated downstream of GPCRs and upstream of p110β by the bipartite Dock180/Elmo1 RAC-GEF in fibroblasts, possibly through direct binding of Gβγ to Elmo1. The predominant model of class I PI3K isoform activation is based on the recruitment of the kinase complex via the regulatory subunit (or through direct Gβγ binding to p110δ), coinciding with binding of concomitantly activated RAS superfamily GTPases to p110 RBDs. GTase binding serves to fully recruit, activate, and possibly fine-tune lipid kinase activity, and the in vivo importance of the RBD route has been confirmed in mouse models for the α-, δ-, and γ-isoforms. It remains, however, unclear whether the transient and low-affinity interaction with RBD interactors alone can be sufficient to activate class I PI3K in mammalian cells under normal physiological conditions or whether this always requires coordinated input from tyrosine phosphorylated proteins or Gβγ.

REFERENCES


