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PI3K signalling in immune cells

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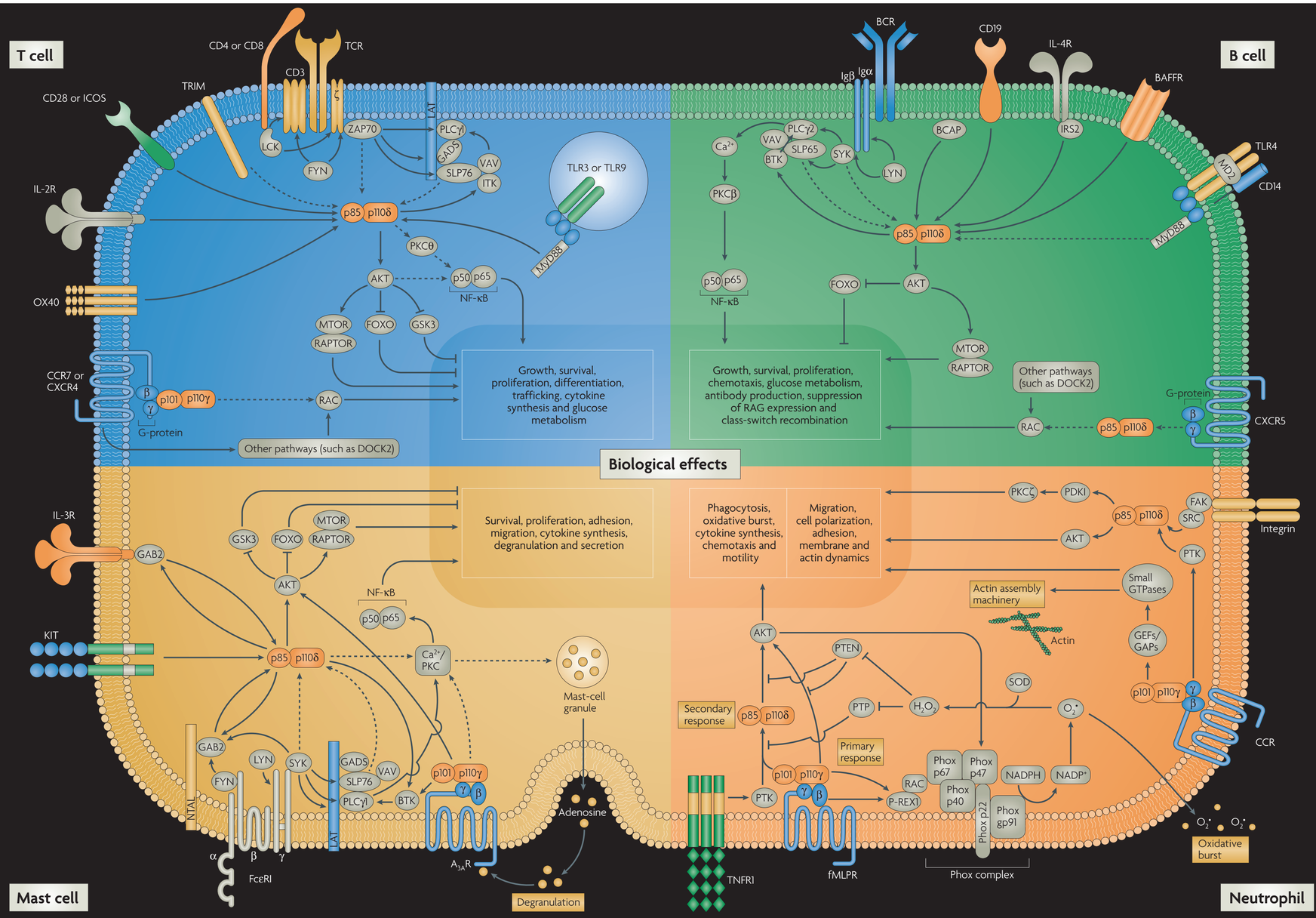
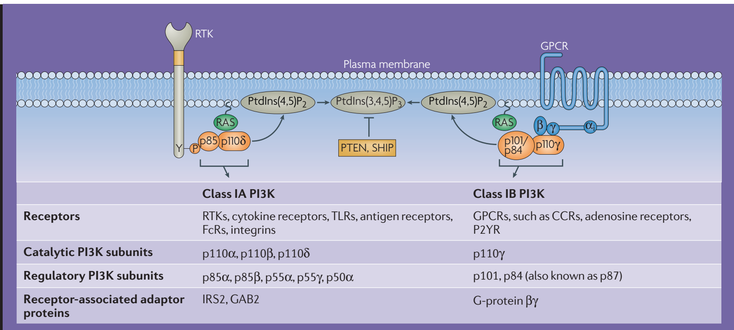
Many classes of immune-cell receptors relay intracellular signals through phosphoinositide 3-kinases (PI3Ks), which culminates in a broad variety of cell biological effects. Of the eight catalytic isoforms of PI3K that exist in mammals, p110δ and p110γ are highly expressed in all leukocyte subtypes. Pharmacological and mouse gene-targeting studies have identified these PI3K isoforms as key enzymes in immune signalling, and p110δ and p110γ are considered to be attractive pharmacological targets in inflammatory and allergic diseases, and transplantation. Other PI3K isoforms are also expressed by leukocytes, but their roles in immune signalling are largely unexplored. This Poster displays the four immune-cell types — T cells, B cells, mast cells and neutrophils — in which p110δ and p110γ signalling and their biological consequences are best characterized.





	Class IA PI3K	Class IB PI3K
Receptors	RTKs, cytokine receptors, TLRs, antigen receptors, FcRs, integrins	GPCRs, such as CCRs, adenosine receptors, P2YR
Catalytic PI3K subunits	p110α, p110β, p110δ	p110γ
Regulatory PI3K subunits	p85α, p85β, p55α, p55γ, p50α	p101, p84 (also known as p87)
Receptor-associated adaptor proteins	IRS2, GAB2	G-protein βγ

Class I PI3Ks: linking cell-surface receptors to the production of a lipid second messenger

Class IA PI3Ks are heterodimeric proteins that bind, through their regulatory subunits (known as p85 subunits), to tyrosine-phosphorylated recognition motifs in the cytoplasmic domains of RTKs or receptor-associated adaptor proteins. After cell stimulation, class I PI3Ks are recruited to the plasma membrane, where they phosphorylate PtdIns(4,5)P_2 to generate the lipid second messenger PtdIns(3,4,5)P_3.

The class IA isoforms of PI3K (p110α, p110β and p110δ) signal downstream of tyrosine kinases and RAS. The only class IB PI3K isoform, p110γ, is recruited to cytoplasmic protein complexes of GPCRs by interacting directly with G-protein βγ subunits. This binding is facilitated by the class IB PI3K regulatory subunit (p101 or p84 (also known as p87)). RAS can also activate p110γ.

Although the topic is not addressed in this Poster, distinct functions mediated by the different p85 isoforms (p85α and p85β) have been revealed by knocking out the genes encoding these regulatory subunits in mice. For example, p85α is the main regulatory isoform for many B-cell responses, but its role is more limited or redundant in T cells and mast cells.

PI3K effectors

The activation of all class I PI3Ks leads to increased levels of the lipid second messenger PtdIns(3,4,5)P_3 at the cell membrane, which serves as a docking platform for pleckstrin-homology-domain-containing proteins, which then become activated. This leads to a cascade of phosphorylation events and protein–protein interactions between downstream targets to control multiple biological processes.

The serine/threonine kinase AKT is only one of several sensors of PtdIns(3,4,5)P_3 in a cell. In leukocytes in particular, tyrosine kinases, such as members of the BTK family, are other key targets of PtdIns(3,4,5)P_3. Other effectors include adaptor proteins, such as GAB1 and GAB2, and the GEFs and GAPs for small GTPases, such as RAC and the ARF-family members. These regulators of small GTPases include the P-REX family of RAC-GEFs, the cytohesin family of ARF-GEFs and the centaurin family of ARF-GAPs. ARAP3 has recently been identified as a PtdIns(3,4,5)P_3- and RAP-dependent GAP for RHOA. The roles of these small GTPase regulators in the immune system are largely unknown.

p110δ versus p110γ

Studies involving the blockade of p110δ or p110γ function, either by gene targeting or by pharmacological inhibition, have confirmed important roles for both these PI3Ks in regulating the immune system and in immune responses *in vivo*. However, it is not clear if immune cells can sense whether PtdIns(3,4,5)P_3 is produced by p110δ or by p110γ, or whether PtdIns(3,4,5)P_3 produced by both PI3K isoforms has the same signalling output.

Some pathways, such as signalling downstream of the antigen receptors in lymphocytes and mast cells, are highly sensitive to inhibition of p110δ but not p110γ. By contrast, chemokine-receptor signalling in most cells (such as neutrophils, monocytes and macrophages) is mainly regulated by p110γ rather than by p110δ, although B-cell chemotaxis in response to CXCL13 is more dependent on p110δ than on p110γ.

Although they often operate in apparently parallel pathways, p110δ and p110γ can also operate in the same pathway, as exemplified by fMLP-stimulated PI3K activity in human neutrophils primed with TNF. Stimulation of TNF-primed neutrophils with fMLP results in the biphasic activation of PI3K, with the first phase being mainly p110γ dependent and the second phase being mainly p110δ dependent. The second phase of PI3K activation is triggered by the first phase.

Recent work has identified the p110δ and p110γ isoforms of PI3K as promising targets for immune-mediated disorders, and several drug-discovery programmes have been initiated to develop small molecule inhibitors of these isoforms as potential therapeutics for a wide range of human diseases.

$A_{3A}R$, adenosine receptor 3A; ARAP3, ARF–GAP, RHO–GAP, ankyrin repeat and pleckstrin-homology-domains-containing protein 3; ARF, ADP-ribosylation factor; BAFFR, B-cell-activating factor receptor; BCAP, B-cell PI3K adaptor; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CCR, CC-chemokine receptor; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; DOCK2, dedicator of cytokinesis 2; FAK, focal adhesion kinase; FcεRI, high-affinity Fc receptor for IgE; fMLPR, *N*-formyl-methionyl-leucyl-phenylalanine receptor; FOXO, forkhead box O; GAB, GRB2-associated binding protein; GADS, GRB2-related adaptor protein; GAP, GTPase-activating protein; GEF, guanine-nucleotide-exchange factor; GPCR, G-protein-coupled receptor; GRB2, growth-factor-receptor-bound protein 2; GSK3, glycogen-synthase kinase 3; H_2O_2, hydrogen peroxide; ICOS, inducible T-cell co-stimulator; IL, interleukin; ITK, IL-2-inducible T-cell kinase; IRS2, insulin receptor substrate 2; LAT, linker for activation of T cells; MTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary-response gene 88; NF-κB, nuclear factor-κB; NTAL, non-T-cell activation linker; $O_2^{\bullet}$, superoxide; P2YR, purinergic receptor P2Y; PDK1, 3-phosphoinositide-dependent protein kinase 1; Phox, phagocyte oxidase; PKC, protein kinase C; PLC, phospholipase C; P-REX, PtdIns(3,4,5)P_3-dependent RAC exchanger; PtdIns(4,5)P_2, phosphatidylinositol-4,5-bisphosphate; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homologue; PTK, protein tyrosine kinase; PTP, protein tyrosine phosphatase; R, receptor; RAG, recombination-activating gene; RAPTOR, regulatory associated protein of MTOR; RHOA, RAS homologue gene-family member A; RTK, receptor tyrosine kinase; SHIP, SRC-homology-2-domain-containing inositol-5-phosphatase; SLP, SRC-homology-2-domain-containing leukocyte protein; SOD, superoxide dismutase; SYK, spleen tyrosine kinase; TCR, T-cell receptor; TLR, Toll-like receptor; TNFR1, tumour-necrosis factor receptor 1; TRIM, TCR-interacting molecule; ZAP70, ζ-chain-associated protein kinase of 70 kDa.

Further reading
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