Phosphoinositide Kinases

Key References

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Overview

The membranes of mammalian cells contain substantial quantities of phosphatidylinositol (PtdIns) and small amounts of at least seven phosphorylated PtdIns derivatives (PPI). Phosphoinositide kinases synthesize PPI by adding phosphate groups to pre-existing inositol glycerophospholipids (see scheme below).

The kinase domains of the two subfamilies of PtdIns 4-kinases and all of the phosphoinositide 3-kinase (PI3K) subfamilies are closely related to each other and also to protein kinases. However, the three types of phosphatidylinositol phosphate (PIP) kinases (PIPkin), kinases which donate a phosphate to one of the three isomeric PtdIns*P*s, constitute a kinase family that shares some kinase domain motifs with other kinases, but are otherwise unique.

Four of the kinases are responsible for biosynthesis of PtdIns(4,5)P_2, the key phosphoinositide that is the shared substrate of two widespread receptor-activated signaling pathways: the phospholipase C-catalyzed formation of Ins(1,4,5)P_3 and 1,2-diacylglycerol (DAG); and synthesis by Type I PI3Ks of the membrane-associated messenger molecule PtdIns(3,4,5)P_3. PtdIns(4,5)P_2 is also essential for a substantial number of other cell functions, including actin-based motility, secretory vesicle trafficking, exocytosis and phospholipase D activation.

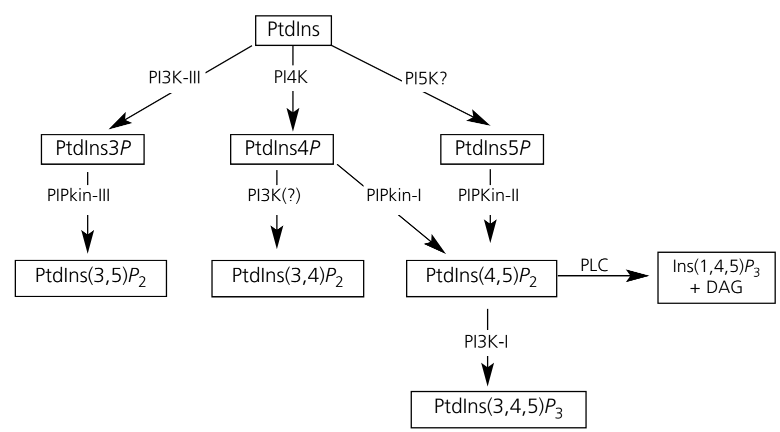
PtdIns(4,5)P_2 is synthesized, via PtdIns4*P*, in the plasma membrane, secretory vesicles, Golgi and nuclei, and probably elsewhere. Why cells use an uncharacterized PtdIns 5-kinase and a PIPkin-II to make a small proportion of cellular PtdIns(4,5)P_2 by an alternative pathway, via PtdIns5*P*, is not known. Some PtdIns(4,5)P_2 is made and undoubtedly functions in the nucleus, but in what manner is not known. There is evidence for partial nuclear localization of PIPkin-I and of PIPkin-II.

The individual PI3K subfamilies phosphorylate different phosphoinositides. Type I enzymes phosphorylate PtdIns(4,5)P_2 to PtdIns(3,4,5)P_3 and thereby transmit signals from numerous receptor tyrosine kinases (PI3K-IA: activated by the insulin receptor and many growth factor receptors) and from some G protein-coupled receptors (PI3K-IB: particularly in hemopoietic cells, by receptors that influence motility and the bactericidal oxidative burst of neutrophils).

PtdIns(3,4,5)P_3 is a remarkable membrane-associated second messenger molecule. It appears to have many direct target proteins, each of which it interacts with through highly PtdIns(3,4,5)P_3-selective pleckstrin homology (PH) domains. Some of these are protein kinases (e.g. PDK1, PKB, Btk, Itk), while others include regulators of small GTPases (GTP/GDP exchange factors and GTPase-activating factors). The PtdIns(3,4,5)P_3-activated protein kinases have numerous substrates, and sometimes initiate downstream protein kinase cascades.

Type III PI3Ks convert PtdIns to PtdIns3*P*. This lipid is essential for vesicle trafficking from the trans-Golgi to vacuole/lysosome compartments. It appears to exert its effects through interactions with target proteins that include PtdIns3*P*-specific FYVE domains.

The functions of Type II PI3Ks remain uncertain. In addition, there is a diverse group of 'Type IV PI3K-related kinases' – comprising Tor (target of rapamycin) proteins, DNA-dependent protein kinase (DNA-PK) and ATM (Ataxia Telangiectasia Mutated). These have kinase domains that are related to those of *bona fide* PI3Ks, but are probably protein kinases rather than phosphoinositide kinases.



Phosphoinositide Kinases

Kinase	PtdIns 4-kinase (PI4K)	PtdIns4*P* 5-kinase (PIPkin-I)	PtdIns5*P* 4-kinase (PIPkin-II)	PtdIns3*P* 5-kinase (PIPkin-III)
Reaction *In Vivo*	PtdIns (P 8443, P 2517) > PtdIns4*P* (P 9638)	PtdIns4*P* (P 9638) > PtdIns(4,5)P_2 (P 9763)	PtdIns5*P* > PtdIns(4,5)P_2 (P 9763)	PtdIns3*P* > PtdIns(4,5)P_2 (P 9763)
Structure	Two subfamilies: I: ~100 kDa – prototype is yeast Pik1p II: ~200 kDa (some have SH3 and PH domains) – prototype is yeast Stt2p	~60-90 kDa: multiple forms - prototype is yeast Mss4p	~45 kDa: multiple forms	~200-250 kDa: includes FYVE, CCP1-chaperone-like domains -prototype is yeast Fab1p
Localization/Control/Comments	Some types may be regulated by phosphorylation	Major route for PtdIns(4,5)P_2 synthesis	Minor route for PtdIns(4,5)P_2 synthesis. May be regulated by phosphorylation	Hyperosmotic stress in yeast, unknown in animal cells
Inhibitors	Adenosine (A 9251) Wortmannin for some forms (W 1628)	Stimulated by phosphatidate (P 9511)	Heparin (H 3393 (p), H 0777 (b))	

Phosphoinositide Kinases (continued)

Kinase	Type IA PI3K	Type IB PI3K	Type II PI3K	Type III PI3K
Reaction *In Vivo*	PtdIns(4,5)P_2 (P 9763) > PtdIns(3,4,5)P_3 (also has protein kinase activity)	PtdIns(4,5)P_2 (P 9763) > PtdIns(3,4,5)P_3	PtdIns4*P* (P 9638) > PtdIns(3,4)P_2	PtdIns (P 8443, P 2517) > PtdIns3*P*
Structure	p85(α,β) or p55γ regulatory subunit: p110 (α, β or δ) catalytic subunit	p101 regulatory subunit: p110γ catalytic subunit	>170 kDa, C-terminal C2 domain	~80-110 kDa - prototype is yeast Vps34p
Localization/Control/Comments	p85 SH2 domain interacts with P-Tyr residues. p110 activated by p85* and by activated Ras	p101 activated by $\beta\gamma$-complexes liberated from activated G_i and/or G_o	May be activated by some tyrosine kinases	Putative 150 kDa regulatory partner in mammalian cells
Inhibitors	Wortmannin (W 1628) LY-294002 (L 9908) Dominant-negative p85 constructs	Wortmannin (W 1628) LY-294002 (L 9908)		

Abbreviations
PI3K: phosphoinositide 3-kinase
PIK: PtdIns kinase
PIP: Phosphatidylinositol phosphate
PIPkin: PtdInsP kinase
PPI: Polyphosphoinositides
PtdIns: Phosphatidylinositol
PtdIns3*P*: PtdIns 3-phosphate
PtdIns4*P*: PtdIns 4-phosphate
PtdIns5*P*: PtdIns 5-phosphate
PtdIns(3,4)P_2: PtdIns 3,4-bisphosphate
PtdIns(3,5)P_2: PtdIns 3,5-bisphosphate
PtdIns(4,5)P_2: PtdIns 4,5-bisphosphate
PtdIns(3,4,5)P_3: PtdIns 3,4,5-trisphosphate
Ins(1,4,5)P_3: Inositol 1,4,5-trisphosphate

Footnotes