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Phosphoinositide Kinases as Enzymes that Produce Versatile Signaling Lipids, Phosphoinositides

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Phosphoinositide kinases comprise a unique family of enzymes that catalyze the phosphorylation of phosphatidylinositol and its phosphorylated metabolites to produce seven phosphoinositides. Recent advances have revealed that these phosphoinositides have specific physiological functions, such as actin cytoskeletal reorganization, membrane transport, cell proliferation and survival, in eukaryotic cells and that each phosphoinositide kinase is differently and precisely regulated. Here we describe the diverse regulation and physiological functions of phosphoinositide kinases involving their products.

Key words: phosphoinositide kinases, phosphoinositides, signal transduction.

Phosphatidylinositol (PI) is phosphorylated separately or at all possible combinations of the D-3, D-4, and D-5 positions of the inositol ring to produce biologically significant phosphoinositides (Fig. 1). So far, seven phosphoinositides have been identified in mammalian cells. The phosphorylation of PI and its metabolites is catalyzed by multiplex phosphoinositide kinases, each of which phosphorylates at specific positions of hydroxyl groups of the inositol ring (Fig. 1). Phosphoinositide kinases so far identified are classified into two families, PI kinases and PI phosphate (PIP) kinases, fundamentally based on their substrate specificities and the similarity in their sequences (Fig. 2). The PI kinase family comprises PI 3-kinases, which phosphorylate at the D-3 position and include three classes of isozymes with different substrate specificities, and PI 4-kinases, which phosphorylate at the D-4 position and are further classified into two types of the enzymes, types II and III. The PIP kinase family consists of PI 4-phosphate 5-kinases [PI(4)P 5-kinases], PI 5-phosphate 4-kinases [PI(5)P 4-kinases], and PI 3-phosphate [PI(3)P] 5-kinase [PI(3)P 5-kinase], which phosphorylate PI(4)P at the D-5 position, PI(5)P at the D-4 position, and PI(3)P at the D-5 position, respectively (Fig. 1). These phosphoinositide kinases are activated in response to a wide variety of agonists, such as hormones, growth factors, and neurotransmitters, to produce the signaling lipids, phosphoinositides, shown in Fig. 1, and therefore are the central players in cell signaling pathways. This review summarizes our current knowledge on the structures, characteristics, regulations, and functions of these phosphoinositide kinases, especially mammalian enzymes other than PI 3-kinase (see another section of this series of reviews).

Phosphatidylinositol 4-kinases (PI 4-kinases)

Structures, characteristics, and regulations. PI kinases were initially classified into three categories, termed types I to III, based on the results of chromatographic purification of their activities (*1, 2*). Type I was subsequently identified as PI 3-kinase (*3*), and types II and III as PI 4-kinases with different properties (Fig. 2), the exciting developments regarding PI 3-kinases are covered in a separate chapter and will not be discussed further here. The type II PI 4-kinases, which were classically characterized as membrane-associated 45–55 kDa proteins, are potently activated by nonionic detergents and inhibited by adenosine, while the type III enzymes with higher molecular weights are soluble or loosely associated with membranes, less activated by detergents, and insensitive to adenosine (*2, 4*). Three isozymes for the type II PI 4-kinases, *i.e.* PI 4-kinase α of 97 kDa (*5*), and PI 4-kinase IIα and IIβ of 52–55 kDa (*6, 7*), and two isozymes for the type III ones, *i.e.* PI 4-kinase IIIα of 210–230 kDa (*8*) and IIIβ of 92–110 kDa (*9, 10*), have so far been identified; 97 kDa PI 4-kinase α is a spliced variant of PI 4-kinase IIIα, although they have different biochemical properties (*5, 8, 11*). Interestingly, PI 4-kinase IIα and IIβ do not possess the lipid kinase unique domain of unknown function or the kinase domain that are commonly found in other PI 4-kinases (Fig. 2). In addition to these domains, 97 kDa PI 4-kinase α of type II, PI 4-kinase IIIα, and a yeast homologue of PI 4-kinase IIIα, STT4, possess a pleckstrin homology (PH) domain, while the β isozymes and a yeast homologue of PI 4-kinase IIIβ, PIK1, do not.

Thus, the identification of PI 4-kinase isozymes has rapidly progressed, whereas elucidation of the activation mechanisms of PI 4-kinases has lagged behind. Although there is indirect evidence of regulation of type II PI 4-kinase activity by serine and tyrosine residue phosphorylation (*12, 13*), receptor association (*14, 15*), and heterotrimeric G-proteins (*16*), PI 4-kinase IIIβ seems to be activated by the small G protein ADP-ribosylation factor (ARF), which is known to regulate the structure and function of the Golgi complex and membrane traffic: PI 4-kinase IIIβ,

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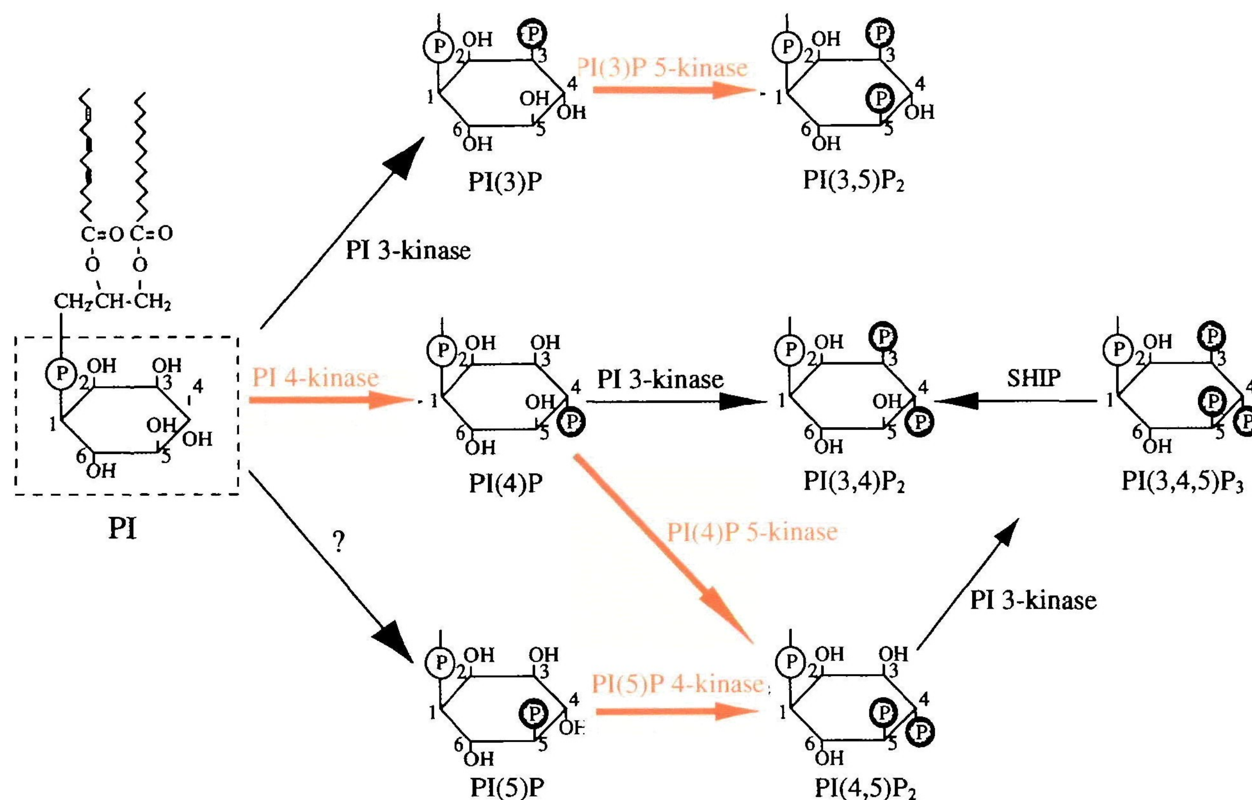

Fig 1 **Synthetic pathways for phosphoinositides with phosphoinositide kinases.** To date, seven phosphoinositides, which are indicated in blue, have been identified The phosphoinositide kinases and reactions catalyzed by them described in this review are shown in red $PI(3,4)P_2$ is predominantly produced from $PI(3,4,5)P_3$ through the action of SHIP, which dephosphorylates $PI(3,4,5)P_3$ at the D-5 position

but not PI 4-kinase IIIα, is recruited to the Golgi complex by the GTP-bound, active form of ARF, and thereby the synthesis of PI(4)P is potently stimulated (*17, 18*) In addition to ARF, neuronal calcium sensor–1 (NCS-1) and its yeast homologue, Frq1, have quite recently been identified as direct activators of PI 4-kinase IIIβ and the yeast homologue of the PI 4-kinase IIIβ, Pik1, respectively (*19, 20*). However, the relationship between ARF and NCS-1 activation of PI 4-kinase IIIβ and the activation mechanisms of other PI 4-kinase isozymes remain to be clarified.

Physiological functions. In the classically defined PI turnover pathway, the PI 4-kinase product, PI(4)P, is further phosphorylated at the D-5 position to produce phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] (for the details see below), which serves as a substrate for phospholipase C, which produces two well-known intracellular messengers, inositol 1,4,5-trisphosphate and diacylglycerol: the former is a stimulator of intracellular Ca^{2+} release and the latter an activator of certain protein kinase C isoforms (*21–23*). Therefore, PI 4-kinases were first recognized as the enzymes that provide the substrate for the synthesis of the biologically important phosphoinositide $PI(4,5)P_2$.

Interestingly, it has more recently been reported that PI 4-kinase IIIβ activity, but not PI 4-kinase IIIα, is required to create and maintain the structural integrity of the Golgi complex (*17*), consistent with the predominant localization of PI 4-kinase IIIα and IIIβ to the endoplasmic reticulum and Golgi membrane, respectively (*24*). This function of PI 4-kinase IIIβ appears to be conserved from yeast to mammals, as the *pik1* mutant of *S. cerevisiae* has a defect in the Golgi function (*25, 26*). However, it is not yet clear whether the PI 4-kinase product PI(4)P itself or its subsequent metabolite, $PI(4,5)P_2$, is essential for the function described above, inasmuch as a still unidentified PI(4)P 5-kinase is coordinately recruited with PI 4-kinase IIIβ to the Golgi complex in an ARF-regulated manner (*17*). The elucidation of the precise mechanisms through which PI 4-kinase IIIβ regulates the structural integrity of the Golgi complex and the physiological functions of other PI 4-kinase isozymes remains a challenge for future studies.

Phosphatidylinositol 4-phosphate 5-kinases [PI(4)P 5-kinases]

Structures, characteristics, and regulations. PI(4)P 5-kinases catalyze the phosphorylation of PI(4)P at the D-5 position of the inositol ring to produce the versatile phosphoinositide $PI(4,5)P_2$ (Fig. 1). Three isozymes of mammalian PI(4)P 5-kinase, α, β, and γ, have thus far been identified (Fig. 2) (*27, 28*). The nomenclature for isozymes of this enzyme is very confusing, since mouse isozymes of the enzyme, α, β, and γ, with 539–661 amino acid residues correspond to human PI(4)P 5-kinase β, α, and γ, respectively (*27, 29*); therefore, we hereinafter use the nomenclature for mouse isozymes. Sequence similarity among the three members of the PI(4)P 5-kinase family is restricted to a central "kinase core" domain separated by an insert domain, N- and C-terminal regions outside this domain with unknown functions being specific to each isozyme.

In general, PI(4)P 5-kinase isozymes are all activated by phosphatidic acid (PA) *in vitro* (*27, 28, 30*). Recently, the

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Family/Member	Type/Class	Substrate	Product	Mammalian homologue	Structure	Predicted M_r
PI kinases						
PI 3-kinase	I_A	PI(4,5)P$_2$	PI(3,4,5)P$_3$	p110 α/β/δ	p85 binding region; Ras binding domain; lipid kinase unique domain; kinase domain	119-123 kDa
	I_B	PI(4,5)P$_2$	PI(3,4,5)P$_3$	p110 γ		120 kDa
	II	PI/PI(4)P	PI3P/PI(3,4)P$_2$	PI3K-C2 α/β/γ	C2 domain	170-210 kDa
	III	PI	PI(3)P	VPS34		101 kDa
PI 4-kinase	II	PI	PI(4)P	97 kDa PI 4-kinase α	PH domain	97 kDa
				PI 4-kinase IIα	palmitoylation motif	54 kDa
				PI 4-kinase IIβ		55 kDa
	III	PI	PI(4)P	PI 4-kinase IIIα	SH3 domain	231 kDa
				PI 4-kinase IIIβ	PIK1 unique domain	92 kDa
PIP kinases						
PI(4)P 5-kinase		PI(4)P	PI(4,5)P$_2$	PI(4)P 5-kinase α	kinase core domain; insert region	61 kDa
				PI(4)P 5-kinase β		60 kDa
				PI(4)P 5-kinase γ		70-72 kDa
PI(5)P 4-kinase		PI(5)P	PI(4,5)P$_2$	PI(5)P 4-kinase α		47 kDa
				PI(5)P 4-kinase β		47 kDa
				PI(5)P 4-kinase γ		47 kDa
PI(3)P 5-kinase		PI(3)P	PI(3,5)P$_2$	PIKfyve	FYVE domain; DEP domain; chaperonin-like region	233 kDa

Fig 2 **Phosphoinositide kinases.** Phosphoinositide kinases that were cloned from mammalian cells and tissues, and their substrates, products, and structures are shown 97 kDa PI 4-kinase α is a spliced variant of PI 4-kinase IIIα

small G-proteins, RhoA and Rac1, have been demonstrated to activate PI(4)P 5-kinase in lysates of mouse fibroblasts and permeabilized human platelets, respectively (*31, 32*). Furthermore, it has also been reported that the RhoA target protein, Rho-kinase (ROCK), activates PI(4)P 5-kinase β (*33*). However, the interaction of these small G-proteins with PI(4)P 5-kinase is independent of the presence of GTP or GDP (*34*). Thus, the molecular mechanisms underlying the PI(4)P 5-kinase activation by these small G-proteins remain to be clarified. Interestingly, we and others have demonstrated that another small G-protein, ARF, activates PI(4)P 5-kinase α in the reconstituted system with the purified recombinant proteins and permeabilized HL-60 cells, respectively (*35, 36*). Under our reconstituted conditions, neither RhoA nor Rac1 activates the three isozymes of PI(4)P 5-kinases, suggesting that these small G-proteins indirectly activate the enzymes or alternatively are involved in the activation of a still unidentified PI(4)P 5-kinase, although the possibility of direct activation of the enzymes by ROCK cannot be totally ruled out. In addition, we found that the activation by ARF of PI(4)P 5-kinase α is dependent of the presence of PA under certain conditions (*35*). Although the requirement of PA for the activation of PI(4)P 5-kinase α is controversial (*18*), a recent report suggested that the phospholipase D–catalyzed PA production is, at least in part, involved in the activation mechanism for the enzymes (*37*). PI(4)P 5-kinases may also be negatively regulated through phosphorylation. PI(4)P 5-kinase α is phosphorylated by cyclic AMP-dependent protein kinase, which results in inhibition of the enzyme activity, and dephosphorylation by protein phosphatase 1 activates the enzyme (*38*). It would be of interest to determine how small G-proteins and phosphorylation/dephosphorylation coordinately regulate PI(4)P 5 kinase α.

Physiological functions. In addition to the role of the PI(4)P 5-kinase product PI(4,5)P$_2$ as a precursor of two second messengers, inositol 1,4,5-trisphosphate and diacylglycerol, this phosphoinositide can be further phosphorylated by PI 3-kinase to produce phosphatidylinositol 3,4,5-trisphosphate [PI(3,4,5)P$_3$] which plays a crucial role in cell proliferation and survival signaling pathways (*39*). PI(4,5)P$_2$ by itself also functions in the binding to and regulation of a subset of PH domain-containing proteins, and control of reorganization of the actin cytoskeleton through its direct regulation of actin-binding proteins, such as gelsolin, profilin, and α-actinin (*40–42*). Thus, the PI(4)P 5-kinase (and its product) seems to play a crucial role in cell signaling and cellular processes. First evidence of the involvement of PI(4)P 5-kinase in physiological cell functions was the identification of the enzyme as a priming exocytosis protein in the ATP-dependent step in Ca^{2+}-activated secretion from PC12 cells (*43*). In conjunction with the regulation by PI(4,5)P$_2$ of actin cytoskeletal reorganization, we recently demonstrated that the Rac1-dependent, actin-based membrane ruffle formation is attributable to an increase in the production of PI(4,5)P$_2$ through the action of the activated PI(4)P 5-kinase α (*35*). In the signaling pathway of the membrane ruffle formation, the activation of PI(4)P 5-kinase α by the active form of Rac1 seems to be mediated by ARF6, inasmuch as a dominant negative ARF6 mutant inhibits the Rac1-dependent membrane ruffle formation, consistent with the observation of PI(4)P 5-kinase α activation by ARF6 *in vitro* as described above (*35*). Furthermore, a more recent study demonstrated that

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a novel functional domain found in endocytic proteins such as epsin, AP180, and Hip 1R, termed the epsin NH2-terminal homology (ENTH) domain, interacts with $PI(4,5)P_2$, the interaction of epsin with $PI(4,5)P_2$ through its ENTH domain playing a crucial role in endocytosis mediated by clathrin-coated pits (*44*). In addition to these $PI(4,5)P_2$ functions, the enzyme appears to play critical roles in the activation of phospholipase D (*45–49*), a guanine nucleotide exchange factor for ARF named ARNO (*50, 51*), and ARF GTPase-activating protein (*52*), through its product, $PI(4,5)P_2$. Thus, PI(4)P 5-kinases play important roles in a wide variety of cellular responses.

Phosphatidylinositol 5-phosphate 4-kinases [PI(5)P 4-kinases]

Structures, characteristics, and regulations. PI(5)P 4-kinases were initially classified as type II PI(4)P 5-kinases based on their biochemical properties and sequence similarities (*53*), and quite recently found to catalyze the phosphorylation at the D-4 position of PI(5)P, which was also found to occur in mammalian fibroblasts (*54*) The earlier error in characterization of the activity of the PI(5)P 4-kinase was due to the contamination by PI(5)P of commercial preparations of PI(4)P. Thus, there are two pathways for the synthesis of $PI(4,5)P_2$ in mammalian cells. So three isozymes of mammalian PI(5)P 4-kinases, α, β, and γ, with apparent molecular weights of 53, 47, and 47 kDa, respectively, have been identified (*55–57*). All isozymes of PI(5)P 4-kinases, like PI(4)P 5-kinases, possess the conserved kinase core domain and the disordered loop composed of 20–25 amino acid residues, termed the "activation loop," in the C-terminal kinase core domain. The study with chimeric kinases containing reciprocal swaps of the activation loops of PI(5)P 4-kinase and PI(4)P 5-kinase elegantly demonstrated that the activation loops determine the substrate specificity and subcellular targeting of two closely related enzymes; while PI(4)P 5-kinase is predominantly located in the plasma membrane, PI(5)P 4-kinase is distributed in the nuclei and throughout the cytosol (*58, 59*).

The activity of PI(5)P 4-kinase is insensitive to PA and ARF (*18, 30*). It was recently reported that the activity of PI(5)P 4-kinase α is regulated through tyrosine phosphorylation in rod outer segments, although it is not clear whether the enzyme itself is phosphorylated at tyrosine residue(s) or other tyrosine-phosphorylated protein(s) in rod outer segments stimulate the enzyme activity (*60*). PI(5)P 4-kinase γ also seems to be phosphorylated at serine residues in response to mitogenic stimulation; however, it is not clear whether or not serine phosphorylation of the enzyme regulates the enzymatic activity (*57*) Thus, the regulatory mechanisms for PI(5)P 4-kinase activity remain to be further investigated.

Physiological functions. Although both PI(4)P 5-kinases and PI(5)P 4-kinases synthesize the same product, $PI(4,5)P_2$, they appear to be functionally nonredundant. Unlike PI(4)P 5-kinases, PI(5)P 4-kinases do not regulate actin cytoskeleton reorganization (*28*). How do PI(5)P 4-kinases function differently form PI(4)P 5-kinases? The cellular distribution of the substrates for these kinases may be distinct. Alternatively, the activation loops of these two enzymes may provide a clue for answering this question. As described above, the activation loops determine the subcellular targeting of PI(4)P 5-kinase and PI(5)P 4-kinase, resulting in the localization of the former to the plasma membrane, and the latter in the nuclei and throughout the cytosol, which in turn may cause different spatial regulation of $PI(4,5)P_2$ synthesis Thus, the activation loop seems to be critical as to not only the substrate specificity and subcellular targeting but also the physiological functions of PI(5)P 4-kinases, although further investigations are required to elucidate the functions of the enzymes. Although there is no evidence of distinct functions of PI(4)P 5-kinases and PI(5)P 4-kinases, PI(5)P 4-kinase α has been reported to be involved in Ca^{2+}-induced α-granule secretion from platelets (*61*).

Phosphatidylinositol 3-phosphate 5-kinases [PI(3)P 5-kinases]

Structures, regulations, and functions. PI(3)P 5-kinases, which phosphorylate PI(3)P at the D-5 position of the inositol ring, have been cloned from yeast and mouse adipocytes, and are termed Fab1p and PIKfyve (phosphoinositide kinase for five position containing a fyve finger), respectively (*62, 63*). PIKfyve with a predicted molecular weight of 233 kDa, as well as Fab1p, contains an N-terminal FYVE (Fab1, YOTB, Vac1, and EEA1) domain, which functions to bind to the substrate PI(3)P, and the C-terminal kinase core domain. Although no direct regulators of PI(3)P 5-kinase have yet been identified, PIKfyve activity may be regulated through autophosphorylation at the serine residues: PIKfyve possesses intrinsic protein kinase activity as well as lipid kinase activity, and its autophosphorylation decreases its lipid kinase activity (*64*).

In mammalian cells, PIKfyve seems to play an essential role in maintaining cell morphology and endocytic membrane homeostasis, as overexpression of the kinase-deficient mutant of PIKfyve in COS-7 and HEK293 cells causes the progressive accumulation of multiple swollen vacuoles, which originated from late endosomes/multivesicular bodies (*65*). Although the *fab1* mutant causes swollen vacuoles and a vacuolar acidification defect, the physiological functions of Fab1p have not yet been clearly elucidated; it is plausible for this lipid kinase to play an important role in retrograde transport from vacuoles. Since the *vac7* mutant shows a very similar phenotype to that of the *fab1* mutant, such as swollen vacuoles and a vacuolar acidification defect, a concomitant decrease in the $PI(3,5)P_2$ level, Vac7 is a putative activator of Fab1p (*66*). In the *Δvac7* yeast strain, the retrograde transport out of vacuoles is inhibited, which consequently yields the enlarged vacuoles (*67*). These observations, taken together, indicate the functional conservation in mammalian and yeast PI(3)P 5-kinases. This function of PI(3)P 5-kinases seems to be attributable to the $PI(3,5)P_2$ production through its lipid kinase activity, since microinjection of $PI(3,5)P_2$ into COS-7 cells abolishes the endomembrane swelling induced by the kinase-deficient PIKfyve mutant (*68*).

Perspective

Recent advances in phosphoinositide research have changed our understanding of the physiological functions of phosphoinositides Based on the results of *in vitro* analyses, in particular, $PI(4,5)P_2$ seems to play versatile roles in signal transduction and cellular regulation through its target proteins, such as proteins with PH domains, actin-binding proteins, phospholipase D (*45–49*), a guanine nucleotide ex-

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change factor for ARF1, ARNO (*50, 51*), and ARF GTPase-activating protein. These observations in *in vitro* systems, however, do not reflect the physiological functions of PI-(4,5)P_2 in the living cell. Furthermore, thorough exploration has revealed a novel phosphoinositide kinase, PI(5)P 4-kinase, demonstrating that there are two pathways for the synthesis of PI(4,5)P_2. In addition, several isozymes of each phosphoinositide kinase have been identified. These discoveries clearly suggest that the physiological functions of phosphoinositide kinases and their products, notably PI-(4,5)P_2, are more complex than previously thought. One of the approaches for clarifying the physiological functions of individual isozymes of phosphoinositide kinases may be temporal and spatial analyses of the enzymes themselves, their substrates and products in living cells. Closely related to this approach, the development of specific probes for detecting each substrate and product is required Alternatively, analysis of mice lacking the gene of each phosphoinositide kinase may be useful.

REFERENCES

1 Endemann, G, Dunn, SN, and Cantley, LC (1987) Bovine brain contains two types of phosphatidylinositol kinase. *Biochemistry* **26**, 6845–6852
2 Whitman, M, Kaplan, D, Roberts, T, and Cantley, L (1987) Evidence for two distinct phosphatidylinositol kinases in fibroblasts Implications for cellular regulation *Biochem J* **247**, 165–174
3 Whitman, M., Downes, CP, Keeler, M, Keller, T, and Cantley, L (1988) Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nature* **332**, 644–646
4 Balla, T (1998) Phosphatidylinositol 4-kinases. *Biochim Biophys. Acta* **1436**, 69–85
5 Wong, K. and Cantley, LC (1994) Cloning and characterization of a human phosphatidylinositol 4-kinase. *J Biol Chem* **269**, 28878–28884
6 Barylko, B, Gerber, SH, Binns, DD, Grichine, N, Khvotchev, M, Sudhof, TC, and Albanesi, JP (2001) A novel family of phosphatidylinositol 4-kinases conserved from yeast to humans. *J Biol Chem* **276**, 7705–7708
7 Minogue, S, Anderson, JS, Waugh, MG, dos Santos, M, Corless, S, Cramer, R, and Hsuan, JJ (2001) Cloning of a human type II phosphatidylinositol 4-kinase reveals a novel lipid kinase family *J Biol Chem.* **276**, 16635–16640
8 Nakagawa, T, Goto, K., and Kondo, H (1996) Cloning, expression, and localization of 230-kDa phosphatidylinositol 4-kinase. *J Biol Chem* **271**, 12088–12094
9 Nakagawa, T, Goto, K., and Kondo, H (1996) Cloning and characterization of a 92 kDa soluble phosphatidylinositol 4-kinase *Biochem. J* **320 (Pt 2)**, 643–649
10 Meyers, R. and Cantley, LC (1997) Cloning and characterization of a wortmannin-sensitive human phosphatidylinositol 4-kinase *J. Biol Chem* **272**, 4384–4390
11 Balla, T, Downing, GJ, Jaffe, H, Kim, S, Zolyomi, A, and Catt, KJ (1997) Isolation and molecular cloning of wortmannin-sensitive bovine type III phosphatidylinositol 4-kinases. *J Biol Chem* **272**, 18358–18366
12 Kauffmann-Zeh, A, Klinger, R, Endemann, G, Waterfield, MD, Wetzker, R, and Hsuan, JJ (1994) Regulation of human type II phosphatidylinositol kinase activity by epidermal growth factor-dependent phosphorylation and receptor association. *J. Biol Chem* **269**, 31243–31251
13 De Neef, RS, Hardy-Dessources, M.D, and Giraud, F (1996) Relationship between type II phosphatidylinositol 4-kinase activity and protein tyrosine phosphorylation in membranes from normal and sickle red cells. *Eur J Biochem.* **235**, 549–556
14 Cochet, C, Filhol, O, Payrastre, B, Hunter, T, and Gill, GN (1991) Interaction between the epidermal growth factor receptor and phosphoinositide kinases. *J Biol Chem* **266**, 637–644
15. Kauffmann-Zeh, A., Thomas, GM, Ball, A., Prosser, S, Cunningham, E., Cockcroft, S, and Hsuan, JJ (1995) Requirement for phosphatidylinositol transfer protein in epidermal growth factor signaling *Science* **268**, 1188–1190
16 Pike, LJ. and Eakes, AT (1987) Epidermal growth factor stimulates the production of phosphatidylinositol monophosphate and the breakdown of polyphosphoinositides in A431 cells. *J Biol Chem* **262**, 1644–1651
17 Godi, A., Pertile, P, Meyers, R, Marra, P, Di Tullio, G, Iurisci, C, Luini, A., Corda, D, and De Matteis, M.A. (1999) ARF mediates recruitment of PtdIns-4-OH kinase-β and stimulates synthesis of PtdIns(4,5)P_2 on the Golgi complex. *Nat Cell Biol* **1**, 280–287
18 Jones, DH, Morris, JB., Morgan, CP, Kondo, H, Irvine, RF, and Cockcroft, S (2000) Type I phosphatidylinositol 4-phosphate 5-kinase directly interacts with ADP-ribosylation factor 1 and is responsible for phosphatidylinositol 4,5-bisphosphate synthesis in the golgi compartment *J Biol Chem* **275**, 13962–13966
19 Zhao, X., Varnai, P, Tuymetova, G, Balla, A., Toth, Z, Oker-Blom, C, Roder, J, Jeromin, A., and Balla, T (2001) Interaction of neuronal calcium sensor-1 (NCS-1) with phosphatidylinositol 4-kinase beta stimulates lipid kinase activity and affects membrane trafficking in COS-7 cells. *J Biol Chem* **276**, 40183–40189
20 Hendricks, K.B, Wang, BQ, Schnieders, EA., and Thorner, J (1999) Yeast homologue of neuronal frequenin is a regulator of phosphatidylinositol-4-OH kinase. *Nat Cell Biol* **1**, 234–241
21 Berridge, MJ and Irvine, R.F (1984) Inositol trisphosphate, a novel second messenger in cellular signal transduction *Nature* **312**, 315–321
22 Nishizuka, Y (1984) The role of protein kinase C in cell surface signal transduction and tumour promotion *Nature* **308**, 693–698
23 Berridge, MJ (1987) Inositol trisphosphate and diacylglycerol two interacting second messengers. *Annu Rev Biochem* **56**, 159–193
24 Wong, K., Meyers, ddR, and Cantley, LC (1997) Subcellular locations of phosphatidylinositol 4-kinase isoforms. *J. Biol Chem* **272**, 13236–13241
25 Hama, H, Schnieders, E.A., Thorner, J, Takemoto, JY, and DeWald, DB (1999) Direct involvement of phosphatidylinositol 4-phosphate in secretion in the yeast *Saccharomyces cerevisiae*. *J Biol Chem* **274**, 34294–34300
26 Walch-Solimena, C and Novick, P (1999) The yeast phosphatidylinositol-4-OH kinase pik1 regulates secretion at the Golgi *Nat Cell Biol* **1**, 523–525
27 Ishihara, H, Shibasaki, Y, Kizuki, N, Katagiri, H, Yazaki, Y, Asano, T, and Oka, Y (1996) Cloning of cDNAs encoding two isoforms of 68-kDa type I phosphatidylinositol-4-phosphate 5-kinase *J Biol Chem* **271**, 23611–23614
28 Ishihara, H, Shibasaki, Y, Kizuki, N, Wada, T, Yazaki, Y, Asano, T, and Oka, Y (1998) Type I phosphatidylinositol-4-phosphate 5-kinases. Cloning of the third isoform and deletion/substitution analysis of members of this novel lipid kinase family *J Biol Chem* **273**, 8741–8748
29 Loijens, JC and Anderson, R.A. (1996) Type I phosphatidylinositol-4-phosphate 5-kinases are distinct members of this novel lipid kinase family *J. Biol Chem* **271**, 32937–32943
30 Jenkins, GH, Fisette, PL, and Anderson, R.A. (1994) Type I phosphatidylinositol 4-phosphate 5-kinase isoforms are specifically stimulated by phosphatidic acid. *J Biol Chem.* **269**, 11547–11554
31 Chong, LD, Traynor-Kaplan, A., Bokoch, GM, and Schwartz, M.A (1994) The small GTP-binding protein Rho regulates a phosphatidylinositol 4-phosphate 5-kinase in mammalian cells. *Cell* **79**, 507–513
32 Hartwig, JH, Bokoch, GM, Carpenter, CL., Janmey, P.A., Taylor, L.A., Toker, A, and Stossel, T.P (1995) Thrombin receptor ligation and activated Rac uncap actin filament barbed ends

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through phosphoinositide synthesis in permeabilized human platelets *Cell* **82**, 643–653
33 Oude Weernink, P.A., Schulte, P, Guo, Y, Wetzel, J, Amano, M, Kaibuchi, K., Haverland, S, Voss, M, Schmidt, M, Mayr, G W, and Jakobs, K.H. (2000) Stimulation of phosphatidylinositol-4-phosphate 5-kinase by Rho-kinase. *J. Biol Chem* **275**, 10168–10174
34. Tolias, K.F., Cantley, L C, and Carpenter, C.L (1995) Rho family GTPases bind to phosphoinositide kinases. *J Biol Chem.* **270**, 17656–17659
35 Honda, A., Nogami, M, Yokozeki, T., Yamazaki, M, Nakamura, H, Watanabe, H, Kawamoto, K., Nakayama, K., Morris, A.J, Frohman, M A., and Kanaho, Y (1999) Phosphatidylinositol 4-phosphate 5-kinase alpha is a downstream effector of the small G protein ARF6 in membrane ruffle formation *Cell* **99**, 521–532
36 Martin, A., Brown, F.D, Hodgkin, M N, Bradwell, A.J, Cook, S J, Hart, M, and Wakelam, M J (1996) Activation of phospholipase D and phosphatidylinositol 4-phosphate 5-kinase in HL60 membranes is mediated by endogenous Arf but not Rho *J Biol Chem* **271**, 17397–17403
37 Skippen, A., Jones, D., Morgan, C, Li, M, and Cockcroft, S (2002) Mechanism of ARF-stimulated phosphatidylinositol 4,5-bisphosphate synthesis in HL60 cells. *J Biol Chem* **277**, 5823–5831
38 Park, S J, Itoh, T, and Takenawa, T (2001) Phosphatidylinositol 4-phosphate 5-kinase type I is regulated through phosphorylation response by extracellular stimuli *J Biol Chem* **276**, 4781–4787
39 Katso, R, Okkenhaug, K., Ahmadi, K., White, S, Timms, J, and Waterfield, M (2001) Cellular function of phosphoinositide 3-kinases implications for development, homeostasis, and cancer *Annu Rev Cell Dev Biol* **17**, 615–675
40 Janmey, P.A. and Stossel, T P (1987) Modulation of gelsolin function by phosphatidylinositol 4,5-bisphosphate. *Nature* **325**, 362–364
41 Lassing, I and Lindberg, U (1985) Specific interaction between phosphatidylinositol 4,5-bisphosphate and profilactin *Nature* **314**, 472–474
42 Fukami, K., Furuhashi, K., Inagaki, M, Endo, T, Hatano, S, and Takenawa, T (1992) Requirement of phosphatidylinositol 4,5-bisphosphate for α-actinin function *Nature* **359**, 150–152
43 Hay, J C, Fisette, P L, Jenkins, G H, Fukami, K., Takenawa, T, Anderson, R A., and Martin, T F (1995) ATP-dependent inositide phosphorylation required for Ca^{2+}-activated secretion *Nature* **374**, 173–177
44 Itoh, T, Koshiba, S, Kigawa, T, Kikuchi, A., Yokoyama, S, and Takenawa, T (2001) Role of the ENTH domain in phosphatidylinositol-4,5-bisphosphate binding and endocytosis. *Science* **291**, 1047–1051
45 Brown, H.A, Gutowski, S, Moomaw, C R., Slaughter, C, and Sternweis, P C (1993) ADP-ribosylation factor, a small GTP-dependent regulatory protein, stimulates phospholipase D activity *Cell* **75**, 1137–1144
46 Hammond, S M, Altshuller, Y.M, Sung, T.C, Rudge, S.A., Rose, K., Engebrecht, J, Morris, A.J, and Frohman, M.A. (1995) Human ADP-ribosylation factor-activated phosphatidylcholine-specific phospholipase D defines a new and highly conserved gene family *J Biol Chem* **270**, 29640–29643
47. Hammond, S M., Jenco, J M, Nakashima, S, Cadwallader, K., Gu, Q, Cook, S, Nozawa, Y, Prestwich, G D, Frohman, M A., and Morris, A.J (1997) Characterization of two alternately spliced forms of phospholipase D1 Activation of the purified enzymes by phosphatidylinositol 4,5-bisphosphate, ADP-ribosylation factor, and Rho family monomeric GTP-binding proteins and protein kinase C-α. *J Biol Chem.* **272**, 3860–3868
48 Colley, W C, Sung, T C, Roll, R., Jenco, J, Hammond, S M, Altshuller, Y, Bar-Sagi, D, Morris, A.J, and Frohman, M.A. (1997) Phospholipase D2, a distinct phospholipase D isoform with novel regulatory properties that provokes cytoskeletal reorganization. *Curr Biol* **7**, 191–201
49 Divecha, N., Roefs, M, Halstead, J R., D'Andrea, S, Fernandez-Borga, M, Oomen, L, Saqib, K.M, Wakelam, M J, and D'Santos, C (2000) Interaction of the type Iα PIPkinase with phospholipase D a role for the local generation of phosphatidylinositol 4,5-bisphosphate in the regulation of PLD2 activity. *EMBO J* **19**, 5440–5449
50 Chardin, P, Paris, S, Antonny, B, Robineau, S, Beraud-Dufour, S, Jackson, C L, and Chabre, M (1996) A human exchange factor for ARF contains Sec7- and pleckstrin-homology domains *Nature* **384**, 481–484
51 Paris, S, Beraud-Dufour, S, Robineau, S, Bigay, J, Antonny, B, Chabre, M., and Chardin, P. (1997) Role of protein-phospholipid interactions in the activation of ARF1 by the guanine nucleotide exchange factor Arno *J Biol Chem.* **272**, 22221–22226
52 Randazzo, P.A. and Kahn, R.A. (1994) GTP hydrolysis by ADP-ribosylation factor is dependent on both an ADP-ribosylation factor GTPase-activating protein and acid phospholipids. *J Biol Chem* **269**, 10758–10763
53 Bazenet, C E, Ruano, A.R, Brockman, J L, and Anderson, R.A. (1990) The human erythrocyte contains two forms of phosphatidylinositol-4-phosphate 5-kinase which are differentially active toward membranes. *J Biol Chem.* **265**, 18012–18022
54 Rameh, L E, Tolias, K.F, Duckworth, B C., and Cantley, L C (1997) A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate *Nature* **390**, 192–196
55 Boronenkov, I V and Anderson, R.A. (1995) The sequence of phosphatidylinositol-4-phosphate 5-kinase defines a novel family of lipid kinases. *J Biol Chem* **270**, 2881–2884
56 Castellino, A.M., Parker, G.J, Boronenkov, I V, Anderson, R.A, and Chao, M V (1997) A novel interaction between the juxtamembrane region of the p55 tumor necrosis factor receptor and phosphatidylinositol-4-phosphate 5-kinase. *J Biol Chem* **272**, 5861–5870
57 Itoh, T, Ijuin, T, and Takenawa, T (1998) A novel phosphatidylinositol-5-phosphate 4-kinase (phosphatidylinositol-phosphate kinase IIγ) is phosphorylated in the endoplasmic reticulum in response to mitogenic signals. *J Biol. Chem* **273**, 20292–20299
58. Rao, V D, Misra, S, Boronenkov, I V, Anderson, R A, and Hurley, J H (1998) Structure of type IIβ phosphatidylinositol phosphate kinase a protein kinase fold flattened for interfacial phosphorylation *Cell* **94**, 829–839
59 Kunz, J, Wilson, M P, Kisseleva, M, Hurley, J H, Majerus, P W, and Anderson, R A (2000) The activation loop of phosphatidylinositol phosphate kinases determines signaling specificity *Mol Cell* **5**, 1–11
60 Huang, Z, Guo, X.X., Chen, S X., Alvarez, K.M, Bell, M W, and Anderson, R E. (2001) Regulation of type II phosphatidylinositol phosphate kinase by tyrosine phosphorylation in bovine rod outer segments. *Biochemistry* **40**, 4550–4559
61. Rozenvayn, N and Flaumenhaft, R (2001) Phosphatidylinositol 4,5-bisphosphate mediates Ca^{2+}-induced platelet alpha-granule secretion evidence for type II phosphatidylinositol 5-phosphate 4-kinase function *J Biol Chem* **276**, 22410–22419
62 Yamamoto, A., DeWald, D B, Boronenkov, I V, Anderson, R.A., Emr, S D, and Koshland, D (1995) Novel PI(4)P 5-kinase homologue, Fab1p, essential for normal vacuole function and morphology in yeast. *Mol Biol. Cell* **6**, 525–539
63 Shisheva, A., Sbrissa, D., and Ikonomov, O (1999) Cloning, characterization, and expression of a novel Zn^{2+}-binding FYVE finger-containing phosphoinositide kinase in insulin-sensitive cells *Mol Cell. Biol* **19**, 623–634
64 Sbrissa, D, Ikonomov, O C., and Shisheva, A. (2000) PIKfyve lipid kinase is a protein kinase downregulation of 5'-phosphoinositide product formation by autophosphorylation *Biochemistry* **39**, 15980–15989
65 Ikonomov, O.C, Sbrissa, D, and Shisheva, A. (2001) Mammalian cell morphology and endocytic membrane homeostasis require enzymatically active phosphoinositide 5-kinase PIKfyve. *J Biol. Chem* **276**, 26141–26147
66 Bonangelino, C J, Catlett, N L., and Weisman, L.S (1997) Vac7p, a novel vacuolar protein, is required for normal vacuole inheritance and morphology. *Mol. Cell. Biol* **17**, 6847–6858

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67 Bryant, N J , Piper, R C , Weisman, L S , and Stevens, T H (1998) Retrograde traffic out of the yeast vacuole to the TGN occurs via the prevacuolar/endosomal compartment *J Cell Biol.* **142**, 651–663
68 Ikonomov, O , Sbrissa, D , Mlak, K., Kanzaki, M , Pessin, J , and Shisheva, A. (2002) Functional dissection of lipid and protein kinase signals of PIKfyve reveals the role of PtdIns 3,5-P_2 production for endomembrane integrity *J Biol Chem* **277**, 9206–9211

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