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Phosphoinositides as regulators of membrane trafficking in health and disease

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Abstract. Membrane trafficking is crucial in the homeostasis of the highly compartmentalized eukaryotic cells. This compartmentalization occurs both at the organelle level, with distinct organelles maintaining their identities while also intensely interchanging components, and at a sub-organelle level, with adjacent subdomains of the same organelle containing different sets of lipids and proteins. A central question in the field is thus how this compartmentalization is established and maintained despite the intense exchange of components and even physical continuities within the same organelle. The phosphorylated derivatives of phosphatidylinositol, known as the phosphoinositides, have emerged as key components in this context, both as regulators of membrane trafficking and as finely tuned spatial and temporal landmarks for organelle and sub-organelle domains. The central role of the phosphoinositides in cell homeostasis is highlighted by the severe consequences of the derangement of their metabolism caused by genetic deficiencies of the enzymes involved, and from the systematic hijacking of phosphoinositide metabolism that pathogens operate to promote their entry and/or survival in host cells. (Part of a Multi-author Review)

Keywords. Phosphoinositides, phosphoinositide kinases and phosphatases, membrane trafficking, genetic diseases.

Introduction

The phosphoinositides (PIs) were originally described as precursors of second messengers, and they are now known to have important functions as 'constitutive' signals that influence the composition of different cell organelles. This is due to their differential intracellular distribution and their recognition by distinct sets of PI-binding proteins. As a result, the PIs are involved in and control a variety of fundamental cell processes, including membrane trafficking, cell migration and polarization, actin cytoskeleton remodelling, and, as recently shown, sphingolipid metabolism [1–6].

Phosphatidylinositol (PtdIns) is the basic building block for the PIs. The headgroup of PtdIns is subjected to reversible phosphorylation in three of the five free hydroxyl groups on the inositol ring (D3, D4 and D5), and this generates seven PI species (Fig. 1). PI metabolism is spatially and temporally regulated in the cell through controlled recruitment and activation of the different PI kinases and phosphatases. Through their distinct substrate specificities and differential intracellular localizations, these enzymes can generate a heterogeneous distribution of PI species in the cell, such that distinct PI species are apparently enriched in specific membrane compartments: PtdIns 4,5-bisphosphate (PtdIns4,5P_2) at the plasma membrane; PtdIns 3-phosphate (PtdIns3P) and PtdIns 3,5-bisphosphate (PtdIns3,5P_2) on early and late endosomes, respectively; and PtdIns 4-phosphate (PtdIns4P) at the Golgi complex [7] (Fig. 2). A distinctive property of the PIs is their fast rates of appearance/disappearance in the membrane, as the PI-metabolizing enzymes can rapidly synthesize them where and when they are required, and then rapidly

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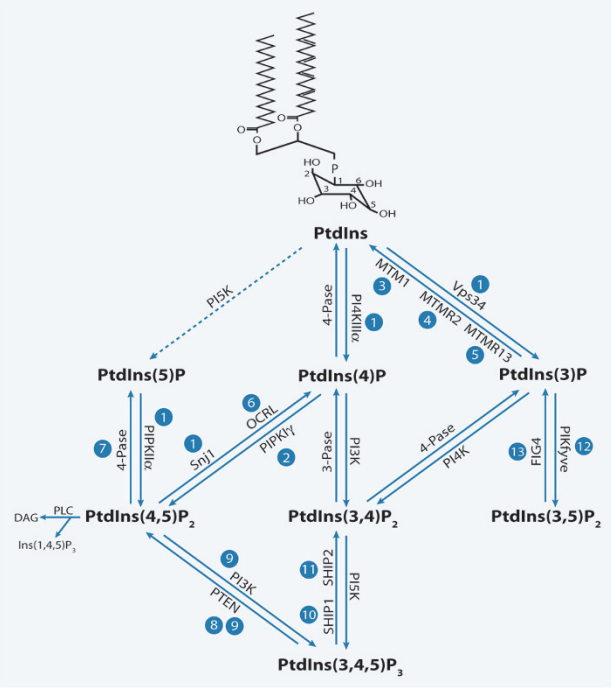

LEGEND

1. Association with Bipolar Disorder, *(PIK3C3, PIK4CA, PIP4K2A, SYNJ1) [1];*
2. Lethal Contractural Syndrome type 3 *(LCCS3), (PIP5K1C) [86];*
3. Miotubular Myopathy, *(MTM1) [87];*
4. Charcot-Marie-Tooth 4B1, *(MTMR2) [88];*
5. Charcot-Marie-Tooth 4B2, *(SBF2) [88];*
6. Lowe Syndrome, *(OCRL) [71];*
7. Bacterial Invasion *Shigella flexneri, (IpgD) [89];*
8. Association with Cell transformation, *(PTEN) [90];*
9. Association with Cancer, *(PTEN, PIK3CA) [91-92];*
10. Association with Primary myeloid Leukemia, *(INPP5D) [93];*
11. Association with Metabolic Syndrome, *(INPPL1) [94];*
12. Association with Francoise-neetens fleck cornea distrophy, *(PIP5K3) [95];*
13. Charcot-Marie-Tooth 4J, *(FIG4) [96].*

Figure 1. PI metabolism in health and disease. The inositol ring of PtdIns can be phosphorylated in the 3, 4 and/or 5 positions, giving rise to seven different PIs. The main pathways of PI synthesis and degradation in mammalian cells are indicated. Most of the PI-metabolizing pathways have been clearly associated with diseases, with the corresponding diseases indicated in blue circles (mutated genes are in italics).

consume them. This makes them ideal determinants for dynamic and vectorial processes, such as membrane trafficking.

The PIs are located at the cytosolic leaflet of cell membranes, with their headgroups accessible for the PI kinases and phosphatases, and for interactions with a wide range of cytosolic proteins that have specific PI-binding domains that can thus be recruited to the membranes [8]. The PIs can also bind integral membrane proteins, which can thus be regulated allosterically via conformational changes. These PI-binding proteins belong to many different categories, including enzymes (protein kinases, phospholipases), ion channels, scaffold proteins and trafficking regulators, with this last including membrane coats, microtubule and actin motors, accessory proteins for GTPases (such as GTP-exchange factors [GEFs] and GTPase-activating proteins [GAPs]), and tethering factors [9].

Since PI-protein binding generally occurs with low affinities, the stabilization of these membrane-protein interactions usually requires the involvement of additional binding sites of membrane-resident proteins that act as co-receptors; these can be integral membrane proteins or membrane-associated small GTPases. This combinatorial recognition mechanism, i.e. 'coincidence detection', increases the uniqueness of the 'identity codes' for each organelle and membrane domain [10].

If the highly compartmentalized and regulated metabolism of the PIs is fundamental to the function and identity of the internal organelles of eukaryotic cells, it also represents at the same time the Achilles' heel of the cell. Indeed, this system can be electively and systematically hijacked by many pathogens for their penetration into the host cells and/or for their survival inside the cell. This they achieve through 'stealing' the identity of an organelle and thus escaping the cell defence mechanisms [11]. In addition, mutations in the PI-metabolizing enzymes (and in particular of the PI phosphatases) are now the recognized causes of many degenerative and proliferative diseases (Fig. 1). Here, we will overview and update the known roles of the PIs in membrane trafficking and will report on one of the examples of genetic dysfunction of PI metabolism (Fig. 1), Lowe syndrome.

Phosphoinositides in the biosynthetic pathway

The first evidence that the PIs might have important roles in membrane trafficking came from the seminal work of the Holz [12] and Martin groups [13], who showed a requirement for the PIs in regulated secretion in neuroendocrine cells. Later, proteins involved in vesicle priming [14] and in the regulation of fusion (such as synaptotagmin, [15]) were identified as targeting to PtdIns4,5P_2, with this interaction with PtdIns4,5P_2 being confined to the pre-fusion stage; the enzymes responsible for the generation of the PtdIns4,5P_2 pool required for secretion were then identified [16–19].

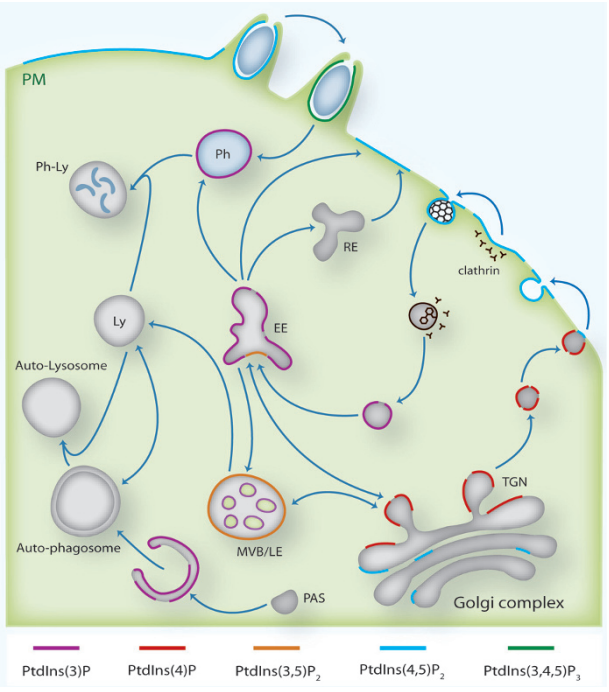

Figure 2. Schematic representation of the different trafficking pathways regulated by the PIs. PtdIns4,5P_2 is required for clathrin-mediated endocytosis, for macropinocytosis, and for fusion of secretory vesicles and granules. PtdIns3*P* is present on early endosomes (EE) and internal vesicles of the MVBs, and is required for endosomal trafficking. At the boundary of the endosomal membranes, PtdIns3*P* is converted into PtdIns3,5P_2. PtdIns4*P* localizes to the Golgi complex and regulates cargo exit from the TGN. PtdIns3,4,5P_3 is generated at the plasma membrane in response to extracellular stimuli, and is involved in signal transduction and phagocytosis. Ph, phagosome; Ph-Ly, phago-lysosome; Ly, lysosome; RE, recycling endosomes; LE, late endosomes; PAS, pre-autophagosomal structure.

While regulated secretion relies on PtdIns4,5P_2, constitutive secretion appears to be mostly under the control of PtdIns4*P*. PtdIns4*P* is produced by the phosphorylation of PtdIns by the PtdIns 4-kinases (PI4Ks). Four different PI4K isoforms have been identified so far in mammals, and two of these, PI4KIIα and PI4KIIIβ, are localized to the Golgi complex, which appears to be the organelle where PtdIns4*P* has a prominent and direct role [20, 21]. Indeed, many PtdIns4*P*-binding proteins have been identified at the Golgi complex, such as clathrin adaptors (AP1, GGAs, and epsin R) and lipid-transfer proteins (the four-phosphate-adaptor proteins, FAPPs; the ceramide transport protein, CERT; and the oxysterol-binding protein, OSBP). AP1, the GGAs, FAPP1 and FAPP2 bind not only PtdIns4*P* but also the small GTPase Arf1, and this dual recognition ensures the correct recruitment of these PtdIns4*P*-binding proteins to the *trans* compartments of the Golgi complex [21–26]. Knocking down the Golgi-localized PI4Ks results in the release of AP1, the GGAs and the FAPP proteins from the Golgi complex. This knock-down also inhibits the trafficking of the mannose-6-phosphate receptor (M6PR), due to the impaired function of AP1 and the TGN-to-plasma-membrane transport of secretory proteins [22, 23, 25, 27] that arises as a consequence of the impaired function of FAPP2. Recently, it was shown that FAPP2 is a glucosylceramide (GlcCer)-transfer protein that controls glycolipid synthesis at the Golgi complex and that its two activities, in membrane trafficking and lipid transfer, are interconnected [5]. Interestingly, CERT, which is required for sphingomyelin synthesis and for membrane trafficking, is also recruited to the Golgi complex via PtdIns4*P* [28,29]. As a consequence, interfering with PtdIns4*P* at the Golgi complex affects not only TGN-to-plasma membrane trafficking but also the synthesis of the major sphingolipids [5,6].

Phosphoinositides in the endocytic pathway

The PIs also have pivotal roles in the endocytic process, where PtdIns4,5P_2 controls the early phase of ligand internalization and PtdIn3*P* the subsequent phases of endosome dynamics, fusion and sorting.

The PtdIns4,5P_2 that is synthesized at the plasma membrane by PtdIns4*P* 5-kinases (PIP5Ks) fosters three driving forces in the membrane budding that initiates the endocytic process: it recruits the coat adaptors (e.g., AP2, AP180 and epsin), it recruits the fissioning components (e.g. dynamin), and it activates the actin-based machineries and motors (including the one based on N-WASP and Myo VI) [30,31]. After promoting these early endocytic steps, the PtdIns4,5P_2 needs to be removed to allow the subsequent membrane fission and clathrin uncoating (for clathrin-dependent endocytosis) steps that release endocytic vesicles.

Thus, a cycle of PtdIns4,5P_2 generation/removal is intimately and constitutively involved in the formation of endocytic vesicles [32–34]. The PtdIns4,5P_2 is mainly removed via its dephosphorylation, via different mechanisms: directly to PtdIns via the synaptojanins (with both 5- and 4-phosphatase activities) or to PtdIns4*P* by the inositol 5-phosphatases OCRL1 and Inpp5b [35,36]. This production/consumption of plasma membrane PtdIns4,5P_2 is therefore under strict control by the PIP5Ks and the PI 5-phosphatases, respectively, allowing temporal and spatial control of both the recruitment and the release of PtdIns4,5P_2-binding proteins that mediate the membrane-budding process (i.e., adaptors and actin-related proteins). These proteins will thus eventually be replaced by the proteins that bind mono-phosphorylated PIs (such as

GAK [37,38]) and that are required for subsequent steps of endocytosis (e.g., uncoating) and for promoting the 'maturation' of the plasma-membrane-derived endocytic membranes into early endosomes.

This maturation process is also marked by the acquisition of the different PI species, PtdIns3*P*. Among the PIs, PtdIns3*P* is highly enriched in limiting membranes of the early endosomes and in those of the intralumenal vesicles of multivesicular bodies (MVBs). PtdIns3*P* is produced by PtdIns 3-kinase (PI3K) action on PtdIns (which could derive from the complete dephosphorylation of the original PtdIns4,5P_2). In resting cells, PtdIns3*P* is mainly produced by type III PI3Ks (e.g., Vps34 in yeast), a class of kinases that is structurally and functionally conserved from lower eukaryotes to plants and mammals [39]. PtdIns3*P* thus has a central role in maintaining endosomal membrane identity, since inhibiting PtdIns3*P* production affects the endocytic routes, resulting in the accumulation of swollen endosomes with few intraluminal vesicles [40,41]; PtdIns3*P* is also involved in the coordination of the trafficking waves that flow in all directions through the endosomal membranes.

PtdIns3*P* appears to act as a membrane organizer for target proteins that have the PtdIns3*P*-binding domains, such as the FYVE and the PX domains [42]. These proteins are involved in the control of a) endosome fusion (e.g., EEA1, Rabenosyn-5, Rabankyrin-5 [43–46]); b) endosomal sorting, including Hrs and components of the heteromeric protein complex ESCRT (which are involved in the degradative sorting of ubiquitinated endosomal cargoes [47–49]), SARA (which is involved in TGFβ signalling [50]) and SNX1/SNX2 (which control the degradation of EGFR and the retrograde trafficking of the M6PR to the TGN [51–53]) and, finally, c) endosome dynamics (e.g., KIF-16B, which mediates plus-end-directed motility of early endosomes [54,55]).

Another PI with an established role in endocytic compartments is PtdIns3,5P_2. This PI is derived from the phosphorylation of PtdIns3*P* by PI3P5K, which comprises a catalaytic (PIKfyve and *Fab1*, in mammals and yeast, respectively) and a regulatory (Ar-PIKfyve/Fig4 and Vac14/Fig4, in mammals and yeast, respectively) subunit [56]. Examination of defects associated with reduced PtdIns3,5P_2 synthesis in lower and higher eukaryotes suggests a conserved role in membrane and protein retrieval via retrograde trafficking along the endocytic/lysosomal system, and in stress signalling [57]. Indeed, most of these observations stem from the original studies in yeast cells that were subjected to hyperosmotic shock, where PtdIns3,5P_2 accumulated at levels up to 30-fold higher than in control cells [58]. Later, it was shown that deletion of the *Fab1, vac14* and *fig4* genes resulted in lower levels of PtdIns3,5P_2 in the vacuole and in defects in retrograde transport, vacuole acidification and ubiquitin-dependent protein sorting into the internal vesicles of MVBs [59,60]. Along the same lines, the overexpression of a kinase-dead version of PIKfyve (K1831E) and the suppression of PIKfyve in mammals leads to the appearance of swollen endosomes that remain functional for internalization, recycling and degradative sorting of both the EGF and transferrin receptors, but are defective in endosome-to-TGN transport and in fluid-phase uptake [61,62].

Consistent with a prominent role for PtdIns3,5P_2 in the late endosomes/MVBs, several proteins associated with these compartments have been shown to bind PtdIns3,5P_2. These include a family of novel β-propeller proteins, known as the PROPPINs (e.g., WIPI49 and Atg21p [63]), proteins of the epsin family (e.g., Ent3p and Ent5p, which contribute to sorting cargoes into MVBs [64]), and components of the ESCRT-III protein complex (CHMP, Vps24p, which are involved in concentrating MVB cargoes and in the formation of MVB vesicles [65]).

Phosphoinositides and autophagy

The autophagic process shuttles cytoplasmic content (e.g., long-lived proteins and damaged organelles) to the lysosomes for degradation [66], and it is also under the control of the PIs, with a particular sensitivity to PtdIns3*P*. Three independent lines of evidence support the requirement for PtdIns3*P* in autophagy. First, promoting an increase in intracellular PtdIns3*P* levels by force-feeding with a synthetic PtdIns3*P* or by overexpression of the p150 PI3K regulatory subunit stimulates cells to undergo macroautophagy. Conversely, treatments with PI3K inhibitors block the cleavage of microtubule-associated protein light chain 3 (LC3), one of the earliest steps required for autophagosome biogenesis [67]. Second, one of the major binding partners of the PI3K subunit Vps34 is the tumour suppressor Beclin1, the depletion of which specifically interferes with autophagy (and not with endocytic trafficking). This suggests that Vps34 is selectively engaged by Beclin1 in the autophagic pathway [68]. Third, another Beclin1 interactor and putative tumour suppressor, UV irradiation resistance-associated gene (UVRAG), is involved in promoting autophagosome formation and Vps34 lipid-kinase activity [69]. Finally, PtdIns3*P* may regulate the formation of the autophagic isolation membrane via recruitment of many effectors, such as the autophagy-linked FYVE protein Alfy [70].

Despite these promising studies, the ultimate roles of PtdIns3*P* in cell autophagy remain to be clarified, along with the possibility that other PIs are involved. This issue is particularly important since by clearing the potentially cytotoxic protein aggregates, autophagy has a protective role and promotes cell survival under conditions of metabolic stress, thus representing a potential pro-tumorigenic process.

Phosphatidylinositol metabolism and disease: Lowe syndrome

The importance of the fine regulation of the levels of the PIs for cell homeostasis is highlighted by the several human diseases that are associated with mutations in the enzymes that sustain the metabolic cycling of the PIs (Fig. 1).

Oculocerebrorenal (OCRL) syndrome of Lowe (Lowe syndrome) is a rare genetic disease that arises as a result of mutations in the ocrl1 gene that lies across 24 exons on the X chromosome. This syndrome is characterized by congenital cataracts, renal Fanconi's syndrome (low molecular weight [LMW] proteinuria, tubular acidosis) and mental retardation [71]. Most recently, ocrl1 mutations have also been identified in a subset of patients affected by proximal tubulopathy, including LMW proteinuria, hypercalciuria, aminoaciduria and phosphaturia. This is a condition that has been defined as Dent disease 2 [72–74], as opposed to the classical Dent disease (Dent disease 1), which is an X-linked syndrome that is caused by mutations in the CLCN5 gene that codes for an endosomal chloride channel [75].

OCRL-1 is a type II polyphosphate 5-phosphatase, and is a ubiquitous cytosolic protein that is expressed in two splice variants: the a isoform (901 amino acids) is enriched in the brain; and the b isoform (893 amino acids) is the more abundant of these isoforms. OCRL-1 contains three major domains: a central inositol polyphosphate 5-phosphatase domain (the preferred substrates of which are PtdIns3,4,5P_3 and PtdIns4,5P_2); an ASH (ASPM, SPD2, Hydin) domain; and a C-terminal, catalytically inactive, Rho-GAP domain. OCRL-1 localizes to the TGN and endosomes, and it can translocate to plasma-membrane ruffles in response to growth-factor stimulation [76,77]. Its main interactors include small GTPases of the Rab family, and specifically Golgi-associated Rab1 and Rab6, and endosomal Rab5, and these interactions are involved in OCRL-1 membrane targeting and activation [78]. Other OCRL-1 interactors include clathrin heavy chain and the adaptors AP1 and AP2 (and indeed OCRL-1 can be found on clathrin-positive structures) and Rac1 (which mediates the localization of OCRL-1 to ruffles) [76,79]. Based on overexpression data, OCRL-1 has been implicated in retrograde transport from the endosomes to the Golgi complex [77,80].

Although much progress has been made over the last few years towards the defining of the role of OCRL-1 in the cell, there is still no real clue as to how mutations in OCRL-1 can lead to the severe pathological consequences seen in Lowe syndrome. Indeed, some of these deficits can be viewed as membrane-trafficking defects, such as Fanconi's renotubular syndrome, which is caused by the inability of proximal tubular cells (PTCs) to reabsorb salts and LMW proteins that escape into the glomerular filtrate. These LMW proteins are normally reabsorbed by clathrin-mediated endocytosis via two multiligand tandem receptors, megalin and cubilin, which are abundantly expressed at the brush border of PTCs. Megalin and cubilin are recycled between the apical plasma membrane and the early/recycling endosomes, with delivery of luminal ligands to the lysosomal compartments escorted by adaptor proteins like Disabled-2 (Dab2) and autosomal recessive hypercholesterolemia (ARH) [81].

The involvement of OCRL-1 in megalin and cubilin trafficking has so far been only hypothesized, on the basis of clinical analyses of Lowe and Dent patients, who excrete little megalin and cubulin in the urine compared to healthy subjects. Since the presence of megalin and cubilin in the urine is due to the shedding of the receptors by proteolytic cleavage at the apical surface, the absence/low amount of these receptors in the urine of Lowe and Dent syndrome patients would indicate that the apical membranes of their PTCs have lower amounts of these multiligand receptors. Reasonably, this defect may be viewed as a consequence of the mis-trafficking of megalin from the TGN to the apical endosomes and/or of a reduced rate of recycling of megalin from apical endosomes to the cell surface. This hypothesis has been tested and proven in a mouse model for classical Dent disease, in which a defective CLC-5 channel alters the endosomal pH, preventing the recycling of megalin and cubilin [82]. Unfortunately, a similar study cannot be carried out for OCRL-1, since ocrl1 knockout mice are asymptomatic [83]. A possible explanation for this lack of phenotype in these ocrl1$^{-/-}$ mice is that another enzyme can compensate for the absence of the Ocrl1 activity in these mice (but not in humans). The phosphatase enzyme that is most related to OCRL1 is Inpp5b, which has been shown to be expressed in mouse brain, kidney and eye (the tissues affected in Lowe syndrome) at higher levels than in humans. Interestingly, recent studies have revealed not only similar intracellular local-

izations for OCRL1 and Inpp5b, but also similar enzymatic properties and interactors [84].

While it remains unclear why Inpp5b does not overcome the loss of OCRL-1 in humans as it does in mice, a variability in the expression of a compensating enzyme (possibly Inpp5b) among tissues and individuals has been invoked to explain the phenotypic variability in Lowe syndrome patients with similar OCRL-1 mutations. So although the functional involvement of OCRL-1 in megalin and cubilin trafficking remains to be proven, recent findings have positioned OCRL-1 in a protein network that is relevant to kidney and brain physiology. De Camilli and colleagues (2007) have shown that the C-termini of OCRL-1 and Inpp5b, which stretch from their ASH domain to their Rho-GAP domain, binds APPL-1, an adaptor protein that acts as a Rab-5 effector [84] and is localized on the subpopulation of peripheral early endosomes that have just been formed from clathrin-coated pits. Interestingly, APPL-1 also binds to GIPC (GAIP [Gα interacting protein]-interacting protein C-terminus), an oligomeric endocytic adaptor that directly interacts with and regulates the endocytic trafficking of megalin [85]. The APPL1-OCRL-1 connection is also of particular interest as a possible mechanism for OCRL-1 recruitment and function in the early endocytic compartment, since overexpression of APPL1 increases the OCRL-1 localization on Rab5-positive structures. In this way, by acting on the membranes of early endosomes, OCRL-1 might couple the signalling and sorting of cell-surface receptors to PtdIns3,4,5P_3 and PtdIns4,5P_2 dephosphorylation.

Concluding remarks

The last two decades have been marked by a tremendous advance in our understanding of the regulation of the metabolism and of the roles of the PIs in membrane trafficking in health and in disease. We have now reached a point where the PI-metabolizing enzymes are being considered as attractive drug targets. To be successful, however, this approach has to overcome the difficulties that stem from the highly integrated, but still specialized and compartmentalized, PI metabolism in the cell. It is also important to consider that the synthesis and degradation of all seven of the PIs are interconnected, such that the modulation of the enzyme activities and/or of the PI levels can cause unwanted side effects. Thus, to be more selective in drug development for clinical intervention, the future challenges are to understand the mechanisms by which each enzyme contributes to the PI turnover within each specific subcellular compartment, and to obtain comprehensive knowledge of the targets and cell processes that are regulated by each of the individual PI species.

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