PtdIns5P: a little phosphoinositide with big functions?

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Abstract

Phosphoinositides are minor constituents of cell membranes playing a critical role in the regulation of many cellular functions. Recent discoveries indicate that mutations in several phosphoinositide kinases and phosphatases generate imbalances in the levels of phosphoinositides, thereby leading to the development of human diseases. Although the roles of phosphoinositide 3-kinase products and PtdIns(4,5)P2 were largely studied these last years, the potential role of phosphatidylinositol monophosphates as direct signaling molecules is just emerging. PtdIns5P, the least characterized phosphoinositide, appears to be a new player in cell regulation. This review will summarize the current knowledge on the mechanisms of synthesis and degradation of PtdIns5P as well as its potential roles.

Introduction

Phosphoinositides are relatively low-abundant lipids (approx. 10% of total phospholipids), their myo-inositol moiety contains five free hydroxy groups and three of them (positions D-3, D-4 and D-5) can be phosphorylated by specific kinases. Thus PtdIns, the most abundant member of the family, can be sequentially phosphorylated to generate the seven polyphosphoinositides. These bioactive lipids exert their role either as precursors of second messengers (such as Ins(1,4,5)P3 and diacylglycerol) or directly by interacting with proteins through a set of well-defined phosphoinositide binding domains [including PH (pleckstrin homology), FYVE, PX (phox homology) or FERM] and modulating their localization, conformation or activity [1].

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Phosphoinositides can be rapidly synthesized and degraded via different metabolic pathways involving specific lipid kinases, phosphatases and phospholipases in discrete membrane domains, in organelles or in subnuclear areas. These phosphoinositide kinases and phosphatases regulate very dynamically the interconversions between the different polyphosphoinositides [2]. The turnover rate of the monoester phosphates of polyphosphoinositides is rapid and a change in kinase or phosphatase activity can result in quick, and often local, modification of the concentration of these versatile lipids. Based on the use of phosphoinositide binding domains as reporters for a given phosphoinositide [3], recent data suggest that some phosphoinositides are specifically enriched in different organelles. For instance PtdIns(4,5)P$_2$ appears to be mainly present in the inner leaflet of the plasma membrane, PtdIns3P in the early endosomes and PtdIns4P in the Golgi. However, these phosphoinositide binding domains often have other determinants for their localization and it might be that these probes preferentially report peculiar pools of a phosphoinositide and do not reflect the whole picture of its localization [4]. Biochemical evidence indeed suggests that PtdIns(4,5)P$_2$ is also present in the Golgi and in the nucleus, whereas PtdIns3P and mainly PtdIns4P are also present in the plasma membrane.

The critical role of phosphoinositides is emphasized by recent discoveries indicating that mutations in several phosphoinositide kinases and phosphatases take part in the development of human diseases including cancer, X-linked myotubular myopathy, fleck corneal dystrophy or Lowe syndrome [5].

Until recently, phosphatidylinositol monophosphates (PtdIns3P, PtdIns4P and PtdIns5P) were considered as intermediate metabolites of the synthesis pathways of polyphosphoinositides. Among the phosphatidylinositol monophosphates, PtdIns4P is by far the most abundant isomer (approx. 70%). It has long been considered only as a precursor for PtdIns(4,5)P$_2$, however recent data suggest that it can contribute to the recruitment of certain proteins such as FAPPs (four-phosphate adaptor proteins) [6] or the clathrin adaptor AP1 (activator protein 1) to the trans-Golgi network [7]. PtdIns3P, which represents about 15–20% of total phosphatidylinositol monophosphates, is implicated in the regulation of vesicular trafficking by interacting with a set of FYVE domain-containing proteins involved in vacuolar sorting in yeast [8] and in intracellular trafficking in mammals [9]. PtdIns5P, the least characterized phosphoinositide [10], is just now emerging as a potentially important signalling molecule. This lipid was discovered in 1997 [10,11]. It is present in mammalian cells as well as in plant cells where it represents a small proportion of total phosphatidylinositol monophosphates, commonly less than 10% in resting cells. The fact that it is difficult to biochemically separate PtdIns5P from PtdIns4P explains why it has long been ignored. Using an appropriate HPLC technique [10] and a mass assay [12] it is now possible to monitor the level of this phosphoinositide. Interestingly, the amount of PtdIns5P, classically very low in resting cells, rises upon stimulation of blood platelets [12] or during osmotic stress in mammalian and plant cells [13–15]. Moreover, a pool of PtdIns5P has been detected in the nucleus [16] and the first PtdIns5P interacting domain, called PHD (plant homeodomain) was recently discovered in ING2, a protein involved in chromatin remodelling [17]. Moreover, some bacterial pathogens can also manipulate the level of PtdIns5P.
Functions of PtdIns5P

in the host cell [18] as part of the strategy developed to increase their virulence.
Finally, myotubularin, a mammalian phosphatase mutated in X-linked myotubular myopathy, can transform PtdIns(3,5)P2 into PtdIns5P suggesting a potential role of these lipids in the aetiology of the disease. Thus evidence is accumulating to suggest that PtdIns5P plays an important role in the regulation of different cell functions (Figure 1).

PtdIns5P synthesis and degradation

Bacterial enzymes

IpgD

*Shigella flexneri* is a facultative intracellular pathogen responsible for bacillary dysentery. This bacterial pathogen uses a type III secretion system to inject virulence factors into the host cell to promote its uptake by a mechanism related to macropinocytosis [19]. Among injected proteins, the virulence factor IpgD (invasion plasmid gene D) has two motifs related to the mammalian inositol 4-phosphatase active site. In *vitro* as well as *in vivo*, IpgD has a preference for PtdIns(4,5)P2 and transforms this lipid into PtdIns5P [18]. During infection with *S. flexneri*, we observed a massive hydrolysis of PtdIns(4,5)P2 (approx. 35% of its amount) and an accumulation of PtdIns5P reaching up to 280 pmol/mg of proteins in HeLa cells [18].

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SigD/SopB

Two homologues of IpgD, SopB in *Salmonella dublin* and SigD in *Salmonella typhimurium* (responsible for gastroenteritis) also have two motifs related to the mammalian inositol 4-phosphatase active site [20]. SopB was first demonstrated to induce the depletion of Ins6P and Ins5P and the accumulation of Ins4P, a metabolite involved in chloride ion and water secretion during infection [21]. *In vitro*, recombinant SopB can hydrolyse PtdIns3P, PtdIns(3,4)P2 and PtdIns(3,4,5)P3 [21]. Previously, it was shown that upon infection with *S. dublin*, SopB induces a rapid disappearance of host cell PtdIns(4,5)P2 at the bottom of the invagination which will become the bacteria-containing vacuole [22].

Whether SopB/SigD are capable of transforming PtdIns(4,5)P2 into PtdIns5P is unknown but our recent data suggest that *Salmonella* induces PtdIns5P production during invasion in a SigD-dependent manner (Masson, D., Mallo, G.V., Terebiznik, M.R., Payrastre, B., Finlay, B.B., Brumell, J.H. and Grinstein, S., unpublished work).

Thus IpgD, SopB and SigD are able to hydrolyse PtdIns(4,5)P2 which may explain the fact that they all contribute to actin cytoskeleton and membrane rearrangement during bacterial entry. Whether SopB and SigD, like IpgD, control the PtdIns(4,5)P2/PtdIns5P ratio remains to be firmly established. However, some of these phosphatases may also have other phosphoinositides and inositol phosphates as substrate, a diversity that could contribute to the different cellular responses against *S. flexneri* and *Salmonella* which have different intracellular lifestyles.

Eukaryotic enzymes

**Type I and II PtdIns(4,5)P2, 4-phosphatases**

Recently, a database search based on the conserved CX_R phosphatase motif led to the discovery of two mammalian orthologues of IpgD [23]. Actually, apart from the phosphatase active site, there is no marked homology with IpgD, but the characterization of these two novel human phosphatases has revealed that they are PtdIns(4,5)P2, 4-phosphatases (type I and II). They are able to convert PtdIns(4,5)P2 into PtdIns5P *in vitro*. Accordingly, the level of PtdIns(4,5)P2 was reduced by approx. 20% in an inducible stable cell line expressing the type I enzyme. However, it remains to be established whether these phosphatases transform PtdIns(4,5)P2 into PtdIns5P in physiological or pathological *in vivo* situations. Both enzymes are ubiquitously expressed and colocalize with LAMP1 and EEA1, two endosomal/lysosomal specific markers.

**Myotubularins**

MTM1 (myotubularin 1) is the prototype of the large myotubularin family of 3-phosphatases, with a substrate specificity for PtdIns3P and PtdIns(3,5)P2 [15,24]. MTM1 is mutated in the myotubular myopathy, a severe genetic disease linked to chromosome X, leading to a defect in myotube maturation [25]. MTMR2 and MTMR13 are mutated in two forms of Charcot-Marie-Tooth Disease (CMT4B1 and CMT4B2), a neuropathy with defective myelination and myelin outfolding [26,27]. MTM1 knockout mice reproduce the human...
phenotype and show a default in maintaining the mature myotubes [28]. In MTMR2 knockout mice, the myelin defect phenotype was also associated with impaired spermatogenesis and azoospermia [29]. About half of the members of the myotubularin family present a mutation in the consensus CX\_R phosphatase site and are catalytically inactive phosphatases. Several studies have now described the heterodimerization of active and inactive members of the myotubularin family. The interaction involves the coiled-coil domains of the partners and enhances the enzymatic activity of the phosphatase active myotubularin and/or changes its subcellular localization [30–33]. Since myotubularins substrates are PtdIns3\_P and PtdIns(3,5)\_P\_2, it was envisioned that these phosphatases could regulate the endocytic pathway. Several studies in mammalian cells or with the yeast and Caenorhabditis elegans myotubularin orthologues propose a role for myotubularins as negative regulators of the endocytic trafficking [34–37]. It is now clear that myotubularins can transform PtdIns(3,5)\_P\_2 into PtdIns5\_P [15,24,38]. Interestingly, PtdIns5\_P was found to be an allosteric activator of MTM1 and MTMR3 lipid phosphatase activity and a component of a positive feedback loop for myotubularin activity [38]. In the same study, it was described that MTM1 assembles into heptameric ring structures. The PH-GRAM domain of myotubularins binds phosphoinositides [35,38] but there are still discussions about its specificity for PtdIns(3,5)\_P\_2 and/or PtdIns5\_P. Convincing recent work by Lorenzo et al. [39], describes PtdIns5\_P as the prefered binder of the PH-GRAM domain that could be the allosteric binding site for this lipid. A recent large scale RNAi (RNA interference) screen to identify kinases and phosphatases regulating apoptosis has pointed out five members of the myotubularin family (MTMR1, MTMR6–8 and MTMR5/SBF1) as phosphatases regulating cell survival [40]. It is interesting to note that MTMR5 was originally found to interact with SET proteins and induce oncogenic transformation and growth stimulation of B cell precursors [41]. Thus myotubularin could control several intracellular functions like endocytosis or cell survival either by controlling the level of PtdIns3\_P and PtdIns(3,5)\_P\_2 or by generating PtdIns5\_P.

**PIKfyve**

PIKfyve is the mammalian type III PtdIns 5-kinase orthologue of the yeast Fab1p, first described to produce PtdIns(3,5)\_P\_2 in vitro and in vivo [42]. It is a dual-specificity enzyme with a lipid and protein kinase activity [43]. The structure of PIKfyve is highly conserved from prokaryotes to eukaryotes. PIKfyve is ubiquitously expressed and harbours different conserved domains including a Zn\^2+/PtdIns3\_P binding FYVE domain and a catalytic ‘phosphoinositide phosphate kinase’ domain [44]. The endogenous protein localizes on intracellular membrane structures of the late endocytic pathway via its FYVE domain interacting with PtdIns3\_P [14]. Because of its localization and its ability to produce PtdIns(3,5)\_P\_2, several studies involve PIKfyve in vesicular transport (for an excellent review on PIKfyve and PtdIns(3,5)\_P\_2, see [45]). Recently, the human PIKfyve orthologue was cloned and shown to localize in microdomains in early endosomes containing EEA1 and Hrs markers [46]. Mutations in human PIKfyve appear to be responsible for a rare
autosomal dominant corneal dystrophy, the François-Neetens Mouchetée Fleck Corneal Dystrophy [47]. It has been shown that in vitro the mouse PIKfyve can phosphorylate PtdIns to produce PtdIns5P [48] and that expression of PIKfyve in mammalian cells increases the level of PtdIns5P. There is still some controversy as to whether PIKfyve is able to directly produce PtdIns5P in vitro and in vivo [45]. In vivo, the effect of this kinase may be indirect since one cannot exclude that the PtdIns(3,5)P2 produced by PIKfyve could be transformed into PtdIns5P by myotubularins. For a better understanding of the role of PIKfyve, it will be important to determine whether or not this kinase is able to directly produce PtdIns5P in vivo.

**Type II PtdInsP kinases**

In 1997, Cantley’s laboratory demonstrated that the type II PtdInsP kinase is a 4-kinase synthesizing PtdIns(4,5)P2 from PtdIns5P [10]. This study provided the first evidence of the existence of PtdIns5P in vivo. Three isoforms of type II PtdInsP kinase (α, β, and γ) exist in mammalian cells (Table 1). The recombinant type II PtdInsP kinase α is now used to monitor the amount of PtdIns5P in cell extracts by a sensitive mass assay [12]. Although a recent study suggests that the type II PtdInsP kinase β is not very efficient in transforming basal PtdIns5P into PtdIns(4,5)P2 [49], it seems to perform the conversion when the level of PtdIns5P has increased. In normal cells, the amount of PtdIns(4,5)P2 synthesized from PtdIns5P is probably minor compared to the amount formed by other pathways (i.e. via PtdIns4P 5-kinase). As discussed below, these kinases appear to have an important function in cell regulation [10].

**PLIP**

PLIP, or PTEN (phosphatase and tensin homologue deleted on chromosome 10)-like phosphatase, is so far the only mammalian lipid phosphatase described to specifically hydrolyze PtdIns5P. The enzyme was originally found in a Dictyostelium database genomic search for additional PTEN homologues [50] and it defines a new family with orthologues in eukaryotes and prokaryotes [51]. Apart from the phosphatase signature, PLIP has only a weak overall similarity to PTEN and harbours a transmembrane domain in its N-terminus. Interestingly, in contrast to the 3-phosphatase activity of PTEN on PtdIns(3,4)P2 and PtdIns(3,4,5)P3, PLIP exhibits a highly specific 5-phosphatase activity against PtdIns5P in vitro [50]. The murine orthologue of PLIP shows the same high specificity towards PtdIns5P, however its capacity to modulate PtdIns5P in vivo is still not proven [51]. In Dictyostelium, overexpressed PLIP localizes in the Golgi, suggesting the presence of a co-localized PtdIns5P pool. The knockout of PLIP in Dictyostelium indicates that this phosphatase is required for cell aggregation, however the link between a defect in the Golgi system and the aggregation phenotype was not established [50]. Thus whether this PTEN-related phosphatase is regulating specific mechanisms via PtdIns5P degradation remains to be demonstrated.
Table 1 Enzymes involved in PtdIns5P metabolism.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Activity</th>
<th>Substrate</th>
<th>Organism</th>
<th>Knockout phenotype</th>
<th>Associated diseases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II PtdInsP kinases 4-Kinase</td>
<td>PtdIns5P</td>
<td>C. elegans, D. melanogaster, mammals</td>
<td>Mice: increased insulin sensitivity, reduced growth rates and lower fat</td>
<td>Not described</td>
<td>[56,57]</td>
<td></td>
</tr>
<tr>
<td>PIKfyve(PIPKIII) 5-Kinase</td>
<td>PtdIns</td>
<td>Conserved from yeast to mammals</td>
<td>Not described</td>
<td>François-Neetens Mouchetée Fleck Corneal Dystrophy</td>
<td>[44,47]</td>
<td></td>
</tr>
<tr>
<td>MTM1 3-Phosphatase</td>
<td>PtdIns(3,5)P_2</td>
<td>Conserved from yeast to mammals</td>
<td>Mice: generalized and progressive myopathy starting around 4 weeks of age, with atrophy and accumulation of central nuclei in skeletal muscle fibres, leading to death after 6–14 weeks</td>
<td>X-linked myotubular myopathy</td>
<td>[24,28]</td>
<td></td>
</tr>
<tr>
<td>SigD/SopB 4-Phosphatase</td>
<td>PtdIns(4,5)P_2</td>
<td>Human</td>
<td>Not described</td>
<td>Not described</td>
<td>[23]</td>
<td></td>
</tr>
<tr>
<td>IpgD</td>
<td>PtdIns(4,5)P_2</td>
<td>Salmonella dublin &amp; typhimurium, S. flexneri</td>
<td>Gastroenteritis</td>
<td>Bacillary dysentery</td>
<td>[20–22]</td>
<td></td>
</tr>
<tr>
<td>PLIP</td>
<td>PtdIns5P</td>
<td>Highly conserved from Protista to mammals</td>
<td>Dictyostelium: defect in aggregation of cells</td>
<td>Not described</td>
<td>[18,53,50,51]</td>
<td></td>
</tr>
</tbody>
</table>
Functions of PtdIns5P

Role in bacterial invasion

Interestingly, several microbial pathogens exploit the phosphoinositide metabolism of host cells to promote their entry and develop their virulence [52]. The formation of *Salmonella* or *S. flexneri* entry structures results from the concerted action of injected bacterial proteins and components of the host cell. The virulence factor IpgD, delivered into nonphagocytic cells by the type III secretion system of the pathogen *S. flexneri* is a phosphoinositide 4-phosphatase transforming a significant part of PtdIns(4,5)P$_2$ into PtdIns5P [18]. This transformation is rapid and occurs primarily at the entry foci of bacteria [53]. While this local breakdown of PtdIns(4,5)P$_2$, a lipid known to regulate actin cytoskeleton dynamics [2], results in dramatic plasma membrane and cytoskeleton rearrangements [18], PtdIns5P production activates specific host cell signalling pathways. Indeed, we recently showed that PtdIns5P plays a key role in class IA PI3K (phosphoinositide 3-kinase)/Akt (protein kinase B) activation in the host cell, a mechanism particularly important in regulating the survival of infected cells in order to maintain efficient bacterial replication and colonization [53]. Ectopic expression of IpgD in various cell types, but not of its inactive mutant, or addition of short-chain penetrating PtdIns5P are sufficient to induce Akt phosphorylation. Conversely, sequestration of PtdIns5P or reduction of its level strongly decreases Akt phosphorylation in infected cells or in IpgD expressing cells. Thus, *S. flexneri* parasitism is shedding light on a new mechanism of PI3K/Akt activation via PtdIns5P production that plays an important role in host cell responses such as survival. The molecular mechanism responsible for PtdIns5P-induced class IA PI3K activation involves a tyrosine phosphorylation process and is currently under characterization.

Two homologues of IpgD, SopB in *S. dublin* and SigD in *Salmonella typhimurium* are also inositol polyphosphate-phosphatases [20]. Recent data suggest that *Salmonella* induces PtdIns5P production during invasion in a SigD-dependent manner (Masson, D., Mallo, G.V., Terebiznik, M.R., Payrastre, B., Finlay, B.B., Brumell, J.H. and Grinstein, S., unpublished work) and is required for Akt activation in Hela cells infected with *Salmonella* [54,55]. Thus it is tempting to propose that, as in the case of *S. flexneri* infection, *Salmonella* induces the PI3K/Akt survival pathway via PtdIns5P production.

In agreement with the results obtained in the *S. flexneri* infection model, overexpression of the type II PtdInsP kinase β [which transforms PtdIns5P into PtdIns(4,5)P$_2$] reduces the level of PtdIns(3,4,5)P$_3$ and, in turn, decreases Akt activation under insulin stimulation [56]. Accordingly, type II PtdInsP kinase β knockout mice show a hypersensitivity to insulin; Akt activation induced by insulin was greatly increased in skeletal muscle and liver from the knockout mice [57]. These results suggest a general regulatory role of PtdIns5P upstream of Akt. In this context, type II PtdInsP kinase β may be a sensor modulating the level of PtdIns5P and in turn the PI3K/Akt signalling pathway.

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Nuclear functions

The first biochemical evidence for a potential role of PtdIns5P in the nucleus came from the observation that the amount of this phosphoinositide (as well as others) increased by 20-fold in the nucleus of murine erythroleukaemia cells during the G1-phase of the cell cycle [16]. Moreover, the type II PtdInsP kinase β has also been found in the nucleus [58]. More recently, the nuclear tumor suppressor ING2 (inhibitor of growth 2) has been shown to be a PtdIns5P receptor via its PHD domain [17]. PtdIns5P binding to the PHD of ING2 regulates the ability of ING2 to induce p53-dependent apoptotic pathways as part of the nuclear response to DNA damage [17]. The PHD domain is organized in a zinc finger structure and is related to the FYVE and RING domains. It is mainly found in nuclear proteins, including chromatin regulators such as ACF, acetyltransferase-like CBP/300 and RAG2 [59], suggesting a role for PtdIns5P in chromatin remodelling and transcription regulation. The potential role of PtdIns5P in transcription is also suggested by its interaction with the PH domain of a general transcription factor, TFIIH, a RNA polymerase II component. PtdIns5P may compete with the transactivator VP16 binding site, also located on the PH domain of TFIIH [60]. Finally, by imaging PtdIns5P with a recombinant biotinylated PHD probe we observed that, after 1 h of infection by S. flexneri, a significant pool of PtdIns5P is present in the nucleus of infected cells [53]. Altogether these results suggest a role for PtdIns5P in the nucleus, however its exact function in this cell compartment remains to be established and the next few years should bring very exciting information in this area.

Vesicular transport

Although a direct role of PtdIns5P in vesicular trafficking has not been clearly demonstrated so far, several studies suggest the involvement of this lipid.

In CHO (Chinese-hamster ovary) cells stably expressing the insulin receptor and in 3T3-L1 adipocytes, PtdIns5P production under insulin stimulation results in GLUT4 (glucose transporter 4) vesicle translocation to the cell surface. Interestingly, the same effect was observed when PtdIns5P was microinjected or when PIKfyve was overexpressed. Conversely, sequestration of intracellular PtdIns5P by expression of the ING2 PHD domain abrogates GLUT4 vesicle translocation [61]. This effect seems to be independent of PI3K but remains ill-defined.

As mentioned above, the 5-phosphatase PLIP, known to hydrolyse PtdIns5P, localizes at the Golgi membrane [50] suggesting that a pool of PtdIns5P could exist in this organelle. However, in Dictyostelium, the knockout of PLIP does not lead to an evident implication of Golgi membrane trafficking [50]. Interestingly, overexpression of MTMR2, leads to an inhibition of the EGF (epidermal growth factor) receptor trafficking from late endosomes to lysosomes under EGF stimulation and induces a large endosomal vacuolization. It has been suggested that this effect implicates an interaction between the GRAM domain of MTMR2 and PtdIns(3,5)P2 [35]. However, the GRAM domain has recently been shown to bind PtdIns5P which could play a role in this process.
Overexpression of the recently cloned human PtdIns(4,5)P_2 4-phosphatases in HeLa cells enhanced the degradation rate of EGF receptor [23]. In cells infected with S. dublin, Dukes et al. [62] describe that SopB/SigD, the orthologue of IpgD, can inhibit EGF receptor degradation, but it is not clear which lipid is involved in this effect. Finally, a recent study shows that an important regulator of the trafficking of the EGF receptor, SNX5, whose overexpression leads to EGF receptor degradation, specifically binds PtdIns5P via its PX domain [63]. The identification of PtdIns5P interacting proteins may help to clarify its role in vesicular trafficking.

**Cytoskeleton organization**

A recent study [61] suggests that PtdIns5P is involved in insulin-induced actin stress fibre disassembly. Microinjection of PtdIns5P mimics the disassembly of actin stress fibres evoked by insulin in cells, whereas sequestration of PtdIns5P, by overexpression of a tandem of PHD domain, blocked this actin disassembly. This effect of PtdIns5P appears independent of PI3K [61]. Accordingly, we also observed that ectopic expression of IpgD or micro-injection of this phosphatase has a dramatic effect on actin cytoskeleton organization with loss of actin fibres. In this case, in addition to PtdIns5P production, the decrease in PtdIns(4,5)P_2 level may strongly cooperate to efficiently reorganize the actin filament system [18]. The role of PtdIns5P in actin cytoskeleton organization is still unclear and additional investigation of the molecular mechanisms is required before this lipid may be added to the list of cytoskeleton regulators.

**Conclusion**

Evidence reviewed in the present chapter strongly suggests that PtdIns5P is a new important player in cell regulation. The strategy developed by a microbial pathogen to precisely manipulate the level of this lipid has provided interesting insights into the role of PtdIns5P. Moreover, several exiting ongoing studies concerning the nuclear pool of PtdIns5P and its receptors, as well as the potential roles for this phosphoinositide in vesicular trafficking and cytoskeleton organization, should provide new lipid-mediated mechanisms of cell regulation.

The authors thank Dr M. Plantavid, Dr C. Racaud-Sultan, Dr M.P. Gratacap and Dr S. Manenti for critical reading of the manuscript. This work was supported by grants from Inserm, Association pour la Recherche contre le Cancer, la Ligue Nationale Contre le Cancer and Association Française contre les Myopathies.

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