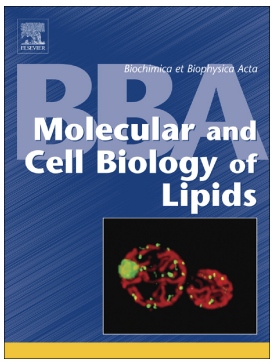

The expanding roles of PI4P and PI(4,5)P2 at the plasma membrane: Role of phosphatidylinositol transfer proteins

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PII: S1388-1981(23)00118-X

DOI: https://doi.org/10.1016/j.bbalip.2023.159394

Reference: BBAMCB 159394

To appear in: *BBA - Molecular and Cell Biology of Lipids*

Received date: 19 July 2023

Revised date: 31 August 2023

Accepted date: 5 September 2023

Please cite this article as: S. Cockcroft, The expanding roles of PI4P and PI(4,5)P2 at the plasma membrane: Role of phosphatidylinositol transfer proteins, *BBA - Molecular and Cell Biology of Lipids* (2023), https://doi.org/10.1016/j.bbalip.2023.159394

The expanding roles of PI4P and PI(4,5)P_2 at the plasma membrane: Role of phosphatidylinositol transfer proteins.

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Abstract

Phosphoinositides are phosphorylated derivatives of phosphatidylinositol, a phospholipid that is synthesised at the endoplasmic reticulum. The plasma membrane contains the enzymes to phosphorylate phosphatidylinositol and is therefore rich in the phosphorylated derivatives, PI4P and PI(4,5)P_2. PI(4,5)P_2 is a substrate for phospholipase C and during cell signalling, PI(4,5)P_2 levels are reduced. Here I discuss a family of proteins, phosphatidylinositol transfer proteins (PITPs) that can restore PI(4,5)P_2 levels.

Introduction

Of the many phospholipids of mammalian cells, phosphatidylinositol (PI) is the only lipid that can be phosphorylated; positions 3, 4, and 5 of the inositol ring are accessible for phosphorylation by lipid kinases. Cells can phosphorylate PI either singly or at multiple positions in every possible combination giving rise to seven different derivatives. Of these, PI4P and PI(4,5)P_2 are the major phosphorylated forms whilst the 3'-phosphorylated derivatives and PI5P are present at considerably lower levels. PI(4,5)P_2 is highly enriched at the plasma membrane whilst PI4P is enriched at both the plasma membrane and the Golgi. Both lipids participate in a multitude of functions, including as substrates for lipid kinases, phosphatases and phospholipases C. PI(4,5)P_2, a negatively-charged lipid, can bind and recruit hundreds of proteins either through specific domains (e.g. pleckstrin homology (PH) domains) or it can bind to unstructured clusters of positively-charged lysine and arginine residues in proteins due to electrostatic interactions. Thus, endocytosis, exocytosis, phagocytosis, ion channel function, actin dynamics are all processes that depend on PI(4,5)P_2 [1]. In addition, PI4P and PI(4,5)P_2 at the plasma membrane are utilised by lipid transfer proteins to move cholesterol and also phosphatidylserine from the endoplasmic reticulum by lipid exchange [2, 3]. New PI(4,5)P_2 functions are being constantly discovered and Table 1 provides a few recent examples.

Some recent examples of plasma membrane (PI(4,5)P_2 functions		
Hippo signaling pathway	PI(4,5)P_2 binds and recruits NF2 (neurofibromin 2) to the plasma membrane to activate the Hippo pathway.	[4]
Exocytosis	Synaptotagmin via its C2 domain docks at PI(4,5)P_2-rich clusters that define the active zones of exocytotic release.	[5]
Immunity and inflammation	PI(4,5)P_2 enrichment marks the locations where Gasdermin (GSDMD) preferentially inserts and causes calcium flares for release of proinflammatory cytokines IL-1β and IL-18 and for pyroptic cell death.	[6]
Immune Signalling	Activated Toll Receptors recruit the adaptor protein, TIRAP (Toll/IL-1R domain–containing adaptor protein) to the plasma membranes via PI(4,5)P_2.	[7]

Epithelial cell characteristics	Epithelial cells have a higher level of $PI(4,5)P_2$ than non-epithelial cells and regulates epithelial cell characteristics by recruiting PARD3 to the plasma membrane.	[8]
β-arrestin recruitment to G-protein coupled receptors	$PI(4,5,)P_2$ acts as allosteric regulators of β-arrestin conformation, and can potentiate an active conformation of β-arrestin and stabilize GPCR-β-arrestin complexes.	[9]

Table 1.

Phospholipase C signaling by G-protein-couple receptors, receptor tyrosine kinases or by cytosol Ca^{2+} in the micromolar range is a universal signaling system present in almost all mammalian cells. There are thirteen classical phospholipases C and three atypical phospholipases C [10]. $PI(4,5)P_2$ is hydrolysed by phospholipase C to the second messengers, $I(1,4,5)P_3$ and diacylglycerol, destroying the lipid,-which can only be replaced by resynthesis. The challenge for the cells is the rapid replacement of $PI(4,5)P_2$ following phospholipase C activation as this will have an impact on other cellular events. Taking endocytosis as an example, recruitment of the adaptor protein, AP2, which depends on $PI(4,5)P_2$, would be stalled; therefore a decrease in $PI(4,5)P_2$ during phospholipase C activation would result in slowing down clathrin-mediated endocytosis-[11, 12].

Mechanisms for restoring PI(4,5)P2 levels during phospholipase C signaling

During phospholipase C signaling, $PI(4,5)P_2$ levels are rapidly depleted. $PI(4,5)P_2$ is produced by phosphorylation of PI by PI 4-kinase and a PI4P-5-kinase operating sequentially at the plasma membrane. Thus, it is PI that needs to be replenished as PI levels at the plasma membrane are limited [13, 14]. The synthesis of PI is confined to the endoplasmic reticulum (Figure 1) and therefore must be transferred to the plasma membrane. In principle, lipids from the endoplasmic reticulum in the form of vesicles can be transferred to the plasma membrane through the secretory pathway. However, traffic through the secretory pathway is slow compared to transfer by lipid transfer proteins. In addition, vesicular traffic will move a mixture of lipids, rather than specific lipids [15].

A class of proteins that can facilitate PI transfer is the phosphatidylinositol transfer proteins (PITPs). PI transfer between two membrane compartments was first detected in beef brain cytosol in 1973 and subsequently characterized as a 32kDa soluble protein with the ability to bind one lipid molecule in its hydrophobic cavity; it could bind either PI or phosphatidylcholine (PC) [16]. The protein became known as PITP – phosphatidylinositol transfer protein. Since this discovery the PITP family has grown to 5 members in mammals; three soluble proteins (PITPα, PITPβ and PITPNC1) and two membrane-associated proteins containing multiple domains (PITPNM1/Nir2 and PITPNM2/Nir3) (Figure 2). Using *in vitro* assays, PI and PC lipid exchange between two membrane compartments occurs with no requirement of ATP [16]. PITPα and PITPβ are by far the best studied PITPs and are found in all cell-types examined [17-20]. PITPNC1 is the least studied PITP but it is emerging as an important contributor to cancer. PITPNC1 together with the lipid kinase, PI-4-kinase-IIIβ and GOLPH3 are highly expressed in cancer cells where they promote release of pro-tumorigenic proteins to maintain cancer cell survival and influence the pro-metastatic process in the tumor micro-environment [21]. The best studied membrane-associated PITPNM proteins is RdgB, the *Drosophila* PITP (see below) and the mammalian orthologues, Nir2 and Nir3 [22-24].

The requirement for PITP in phospholipase C signaling was first demonstrated using cytosol-depleted cells. It was observed that G-protein-stimulated phospholipase C signaling (as measured by inositol phosphate production) was greatly diminished but could be restored with bovine brain cytosol. The component in the brain cytosol responsible for restoring function was identified as PITPα [25]. Subsequent work identified a second soluble PITP, PITPβ which is highly enriched in liver and lung

tissue [26]. PITPα and PITPβ are 77% identical (94% homologous) at the primary sequence level and are differentially localised. PITPα is mainly cytosolic whilst PITPβ also localizes at the Golgi [26-28]. Both PITPs can reconstitute phospholipase C activity in permeabilized cell systems [26, 29]. A requirement for PITP has been demonstrated for different phospholipase C sub-types, G-protein-coupled phospholipase Cβ, receptor-tyrosine kinase stimulated phospholipase Cγ or Ca^{2+}-stimulated phospholipase Cδ [25, 30, 31].

Parallel studies in *Drosophila* identified RdgB (retinal degeneration Mutant B) as a PITP belonging to the PITPNM family (Figure 2) [32]. RdgB is highly expressed in photoreceptor cells required for maintaining $PI(4,5)P_2$ levels during phototransduction. Sensing of light in *Drosophila* is dependent on the activation of the Gq-phospholipase Cβ pathway and in the absence of RdgB, phototransduction is inhibited [33, 34]. The *Drosophila* system where the studies have been conducted in a living fly has provided the best evidence for the requirement of a PITP protein during phospholipase C signaling [34, 35].

RdgB is a multi-domain protein comprising of a N-terminal PITP domain followed by a long unstructured sequence, a DDHD and LNS2 domain (Figure 2). In addition, the protein contains a FFAT motif for binding to VAP, an ER protein. Thus, RdgB is localized at a special region of the ER sufficiently close to the plasma membrane, that the PITP domain could facilitate lipid transfer between the two membranes. However, the PITP domain is sufficient for restoring phototransduction although it is less efficient [36]. PI binding and transfer by the PITP domain of RdgB is essential as mutations that disrupt PI binding or transfer are unable to restore phototransduction as well as phospholipase C signalling [34]. Studies in mammalian cell-lines have also found that PITPNM proteins can participate in phospholipase C signaling [23, 24, 34]. Although PITPs were initially identified for phospholipase C signaling, its underlying function is to maintain PI4P and $PI(4,5)P_2$ levels potentially. Thus, PITPs have been shown to participate in many other signaling pathways where phosphoinositides are required. Examples include exocytosis [37], secretory vesicle formation [38], viral replication [39], membrane traffic [40] and phagocytosis [41].

Participation of PITPs in new signaling pathways where phosphoinositides are required are being discovered. PITPα/β participate in the non-canonical planar cell polarity pathway by promoting the trafficking of the planar cell polarity receptor, VANGL, from the Golgi to the plasma membrane [42]. Similarly, PITPα is required at the trans-Golgi to produce PI4P to promote insulin granule maturation [43]. In contrast, PITPα/β play a critical role in the regulation of LATS and YAP in the Hippo pathway by regulating PI4P levels at the plasma membrane [4].

Although it has been known that PITPα localizes to the nucleus, its requirement in nuclear phosphoinositide signaling had not been identified till recently [44]. PITPα/β form a complex with p53 participating in supplying PI to p53; phosphorylation of the PI by lipid kinases form a p53-$PI(3,4,5)P_3$ complex that activates nuclear Akt in response to genotoxic stress [44, 45]. PITPα/β levels increase in the nucleus following genotoxic stress.

Phagocytosis is another example where phosphoinositides play an important role. During phagocytosis, there is an increase in $PI(4,5)P_2$ at the phagocytic cup leading to actin accumulation. Nir3 is also recruited to phagocytic cups and depletion of Nir2/3 decreases peri-phagosomal PI4P and $PI(4,5)P_2$ and F-actin accumulation around the forming phagosome [41]. Thus, Class IIB PITPs appear to provide PI specifically to the forming phagosome to generate $PI(4,5)P_2$ [41].

How do PITPs maintain PI4P and $PI(4,5)P_2$ levels ?

The simplest and most parsimonious mechanism of action is that the PITP domain can transfer PI from the ER to the plasma membrane and the Golgi to maintain PI4P and/or $PI(4,5)P_2$ levels. Indeed, in flies devoid of RdgB, $PI(4,5)P_2$ levels are diminished even under basal conditions [34]. Knockdown of PITPβ reduced PI4P levels in HeLa cells [40], whilst knockout of both PITPβ and PITPα was required

for a reduction in PI4P levels in platelets [46]. Both PITPNM1 (Nir2) and PITPNM2 (Nir3) have been shown to maintain $PI(4,5)P_2$ homeostasis in angiotensin II and histamine stimulated cells [23, 24]. Like *Drosophila* photoreceptors, lipid transfer occurs at ER-plasma membrane contact sites. In neurons, Nir2 is concentrated at ER-PM contacts sites formed by ER-localised VAP and the voltage-gated potassium (Kv2.1) channels. During muscarinic signaling, the kinetics of $PI(4,5)P_2$ replenishment is slow when the Kv2.1 is deleted [47]. Whilst transfer of lipids by soluble PITPs is possible as they are single domain proteins, for the multi-domain proteins, the PITP domain would have to be sufficiently mobile to swing from one membrane to another. Molecular modelling suggests the 10nm length of the predicted RDGB-VAP complex can span the distance between the plasma membrane and the endoplasmic reticulum. Moreover, the PITP domain localizes between the two regions that interact with PM and ER and is connected to the rest of the protein by an unstructured region at one end and FFAT motif at the other [48]. Thus, in principle, the PITP domain could undergo rapid movements between the two membranes.

Concluding Remarks

In conclusion, mammalian PITPs are increasingly identified in cellular processes where phosphoinositides are required. Early studies on PITP function in the 1990's had identified roles in exocytosis [37], vesicle formation at the Golgi [38] and in phospholipase C signalling [25]. Although much progress has been made in the intervening years, our understanding of how these PITPs regulate phosphoinositide levels remains enigmatic. Nonetheless, PI binding, exchange and transfer remain properties that are essential for their function.

Acknowledgements: Thanks to Dr Paras Anand for his comments.

Figure Legends

Figure 1

$PI(4,5)P_2$ cycle during phospholipase C signalling.

Hydrolysis of $PI(4,5)P_2$ at the plasma membrane by phospholipase C results in the two second messengers, diacylglycerol (DAG) and inositol trisphosphate (IP_3). DAG is converted into phosphatidic acid (PA) by DAG kinase (DAGK) and transferred to the endoplasmic reticulum by Class II PITPs (See Figure 2). At the endoplasmic reticulum, PA is converted into the intermediate CDP-DAG by one of two CDS enzymes, CDS1 and CDS2. The final step in PI resynthesis is catalysed by PI synthase (PIS) where CDP-DAG and inositol are combined. PI is then available for transfer to the plasma membrane by the PITP family of proteins where it can be phosphorylated sequentially by the lipid kinases, PI4K and PI4P5K.

Figure 2

PITP proteins found in mammals and in *Drosophila*

PITP proteins are classified as Class I and Class II based on their binding properties. Class I PITPs bind and transfer PI and PC whilst Class II PITPs bind and transfer PI and PA. Splice variants of PITPβ and PITPNC1 are indicated. PITPNM proteins are also known as Nir proteins. PITPNM1 (Nir2) and PITPNM2 (Nir3). In *Drosophila*, the single PITPNM protein is known as RdgBα (Retinal degeneration Class B).

References

[1] M. Katan, S. Cockcroft, Phosphatidylinositol(4,5)bisphosphate: diverse functions at the plasma membrane, Essays Biochem 64 (2020) 513-531.
[2] M. Sohn, M. Korzeniowski, J.P. Zewe, R.C. Wills, G.R.V. Hammond, J. Humpolickova, L. Vrzal, D. Chalupska, V. Veverka, G.D. Fairn, E. Boura, T. Balla, PI(4,5)P2 controls plasma membrane PI4P and PS levels via ORP5/8 recruitment to ER-PM contact sites, J Cell Biol 217(5) (2018) 1797-1813.
[3] B. Mesmin, J. Bigay, J. Polidori, D. Jamecna, S. Lacas-Gervais, B. Antonny, Sterol transfer, PI4P consumption, and control of membrane lipid order by endogenous OSBP, The EMBO Journal 36(21) (2017) 3156-3174.
[4] F.L. Li, V. Fu, G. Liu, T. Tang, A.W. Konradi, X. Peng, E. Kemper, B.F. Cravatt, J.M. Franklin, Z. Wu, J. Mayfield, J.E. Dixon, W.H. Gerwick, K.L. Guan, Hippo pathway regulation by phosphatidylinositol transfer protein and phosphoinositides, Nature chemical biology 18(10) (2022) 1076-1086.
[5] J. Zhu, Z.A. McDargh, F. Li, S.S. Krishnakumar, J.E. Rothman, B. O'Shaughnessy, Synaptotagmin rings as high-sensitivity regulators of synaptic vesicle docking and fusion, Proc Natl Acad Sci U S A 119(38) (2022) e2208337119.
[6] A.B. Santa Cruz Garcia, K.P. Schnur, A.B. Malik, G.C.H. Mo, Gasdermin D pores are dynamically regulated by local phosphoinositide circuitry, Nat Commun 13(1) (2022) 52.
[7] J.C. Kagan, R. Medzhitov, Phosphoinositide-mediated adaptor recruitment controls Toll-like receptor signaling, Cell 125(5) (2006) 943-55.
[8] K. Kanemaru, M. Shimozawa, M. Kitamata, R. Fukuoka, H. Kayano, Y. Sukawa, Y. Chiba, T. Fukuyama, J. Hasegawa, H. Nakanishi, T. Kishimoto, K. Tsujita, K. Tanaka, T. Itoh, J. Sasaki, T. Sasaki, K. Fukami, Y. Nakamura, Plasma membrane phosphatidylinositol (4,5)-bisphosphate is critical for determination of epithelial characteristics, Nat Commun 13(1) (2022) 2347.
[9] J. Janetzko, R. Kise, B. Barsi-Rhyne, D.H. Siepe, F.M. Heydenreich, K. Kawakami, M. Masureel, S. Maeda, K.C. Garcia, M. von Zastrow, A. Inoue, B.K. Kobilka, Membrane phosphoinositides regulate GPCR-β-arrestin complex assembly and dynamics, Cell 185(24) (2022) 4560-4573.e19.
[10] M. Katan, S. Cockcroft, Phospholipase C families: Common themes and versatility in physiology and pathology, Prog Lipid Res 80 (2020) 101065.
[11] R. Zoncu, R.M. Perera, R. Sebastian, F. Nakatsu, H. Chen, T. Balla, G. Ayala, D. Toomre, P.V. De Camilli, Loss of endocytic clathrin-coated pits upon acute depletion of phosphatidylinositol 4,5-bisphosphate, Proc Natl Acad Sci U S A 104(10) (2007) 3793-8.
[12] N. Carvou, A.G.W. Norden, R.J. Unwin, S. Cockcroft, Signalling through phospholipase C interferes with clathrin-mediated endocytosis, Cellular Signalling 19 (2007) 42-51.
[13] J.P. Zewe, A.M. Miller, V. Sangappa, R.C. Wills, B.D. Goulden, G.R.V. Hammond, Probing the subcellular distribution of phosphatidylinositol reveals a surprising lack at the plasma membrane, J Cell Biol 219(3) (2020) e201906127.
[14] J.G. Pemberton, Y.J. Kim, J. Humpolickova, A. Eisenreichova, N. Sengupta, D.J. Toth, E. Boura, T. Balla, Defining the subcellular distribution and metabolic channeling of phosphatidylinositol, J Cell Biol 219(3) (2020) e201906130.
[15] J.C. Holthuis, A.K. Menon, Lipid landscapes and pipelines in membrane homeostasis, Nature 510 (2014).
[16] G.M. Helmkamp, Jr., M.S. Harvey, K.W.A. Wirtz, L.L.M. van Deenen, Phospholipid exchange between membranes. Purification of bovine brain proteins that preferentially catalyze the transfer of phosphatidylinositol, J. Biol. Chem 249 (1974) 6382-6389.
[17] C.P. Morgan, V. Allen-Baume, M. Radulovic, M. Li, A.J. Skippen, S. Cockcroft, Differential expression of a C-terminal splice variant of PITPβ lacking the constitutive-phosphorylated Ser262 that localises to the Golgi Compartment, Biochem. J 398 (2006) 411-421.
[18] S. Shadan, R. Holic, N. Carvou, P. Ee, M. Li, J. Murray-Rust, S. Cockcroft, Dynamics of lipid transfer by phosphatidylinositol transfer proteins in cells, Traffic 9 (2008) 1743-1756.

[19] S. Cockcroft, N. Carvou, Biochemical and biological functions of class I phosphatidylinositol transfer proteins, Biochim. Biophys Acta 1771 (2007) 677-691.
[20] S.E. Venuti, G.M. Helmkamp, Jr., Tissue distribution, purification, and characterization of rat phosphatidylinositol transfer protein, Biochim. Biophys. Acta 946 (1988) 119-128.
[21] T.G. Ashlin, N.J. Blunsom, S. Cockcroft, Courier service for phosphatidylinositol: PITPs deliver on demand, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids 1866(9) (2021) 158985.
[22] Y.J. Kim, M.L. Guzman-Hernandez, E. Wisniewski, N. Echeverria, T. Balla, Phosphatidylinositol and phosphatidic acid transport between the ER and plasma membrane during PLC activation requires the Nir2 protein, Biochem. Soc. Trans 44(1) (2016) 197-201.
[23] Y.J. Kim, M.L. Guzman-Hernandez, E. Wisniewski, T. Balla, Phosphatidylinositol-Phosphatidic Acid Exchange by Nir2 at ER-PM Contact Sites Maintains Phosphoinositide Signaling Competence, Dev. Cell 33 (2015) 549-561.
[24] C.L. Chang, J. Liou, Phosphatidylinositol 4,5-bisphosphate Homeostasis Regulated by Nir2 and Nir3 at Endoplasmic Reticulum-Plasma Membrane Junctions, J Biol. Chem 290 (2015) 14289-14301.
[25] G.M.H. Thomas, E. Cunningham, A. Fensome, A. Ball, N.F. Totty, C. Troung, J.J. Hsuan, S. Cockcroft, An essential role for phosphatidylinositol transfer protein in phospholipase C-mediated inositol lipid signalling, Cell 74 (1993) 919-928.
[26] K.J. De Vries, A.A.J. Heinrichs, E. Cunningham, F. Brunink, I. Westerman, P.J. Somerharju, S. Cockcroft, K.W.A. Wirtz, G.T. Snoek, An isoform of the phosphatidylinositol transfer protein transfers sphingomyelin and is associated with the golgi system, Biochem. J 310 (1995) 643-649.
[27] K.J. De Vries, A. Momchilova-Pankova, G.T. Snoek, K.W.A. Wirtz, A novel acidic form of the phosphatidylinositol transfer protein is preferentially retained in permeabilized Swiss Mouse 3T3 fibroblasts, Exp. Cell Res 215 (1995) 109-113.
[28] K.J. De Vries, J. Westerman, P.I.H. Bastiaens, T.M. Jovin, K.W.A. Wirtz, G.T. Snoek, Fluorescently labeled phosphatidylinositol transfer protein isoforms (α and β) microinjected into fetal bovine heart endothelial cells, are targeted to distinct intracellular sites, Exp. Cell Res 227 (1996) 33-39.
[29] E. Cunningham, S.W. Tan, P. Swigart, J. Hsuan, V. Bankaitis, S. Cockcroft, The yeast and mammalian isoforms of phosphatidylinositol transfer protein can all restore phospholipase C-mediated inositol lipid signalling in cytosol-depleted RBL-2H3 and HL60 cells, Proc. Natl. Acad. Sci. U. S. A 93 (1996) 6589-6593.
[30] A. Kauffmann-Zeh, G.M.H. Thomas, A. Ball, S. Prosser, E. Cunningham, S. Cockcroft, J.J. Hsuan, Requirement for phosphatidylinositol transfer protein in Epidermal Growth Factor signalling, Science 268 (1995) 1188-1190.
[31] V. Allen, P. Swigart, R. Cheung, S. Cockcroft, M. Katan, Regulation of inositol lipid-specific phospholipase Cδ by changes in Ca^{2+} ion concentrations, Biochem. J 327 (1997) 545-552.
[32] T.S. Vihtelic, M. Goebl, S. Milligan, S.E. O'Tousa, D.R. Hyde, Localization of Drosophila retinal degeneration B, a membrane- associated phosphatidylinositol transfer protein, J. Cell Biol 122 (1993) 1013-1022.
[33] P. Raghu, S. Yadav, N.B. Mallampati, Lipid signaling in Drosophila photoreceptors, Biochim. Biophys. Acta 1821(8) (2012) 1154-1165.
[34] S. Yadav, K. Garner, P. Georgiev, M. Li, E. Gomez-Espinosa, A. Panda, S. Mathre, H. Okkenhaug, S. Cockcroft, P. Raghu, RDGBalpha, a PtdIns-PtdOH transfer protein, regulates G-protein-coupled PtdIns(4,5)P2 signalling during Drosophila phototransduction, J Cell Sci 128(17) (2015) 3330-44.
[35] S. Cockcroft, K. Garner, S. Yadav, E. Gomez-Espinoza, P. Raghu, RdgBalpha reciprocally transfers PA and PI at ER-PM contact sites to maintain PI(4,5)P2 homoeostasis during phospholipase C signalling in Drosophila photoreceptors, Biochem. Soc. Trans 44(1) (2016) 286-292.
[36] S. Yadav, R. Thakur, P. Georgiev, S. Deivasigamani, H. Krishnan, G. Ratnaparkhi, P. Raghu, RDGBalpha localization and function at membrane contact sites is regulated by FFAT-VAP interactions, J Cell Sci 131(1) (2018).

[37] J.C. Hay, T.F.J. Martin, Phosphatidylinositol transfer protein required for ATP-dependent priming of Ca^{2+}-activated secretion, Nature 366 (1993) 572-575.
[38] M. Ohashi, K. Jan de Vries, R. Frank, G. Snoek, V. Bankaitis, K. Wirtz, W.B. Huttner, A role for phosphatidylinositol transfer protein in secretory vesicle formation, Nature 377 (1995) 544-547.
[39] H. Wang, A.W. Tai, Nir2 Is an Effector of VAPs Necessary for Efficient Hepatitis C Virus Replication and Phosphatidylinositol 4-Phosphate Enrichment at the Viral Replication Organelle, J Virol 93(22) (2019) e00742-19.
[40] N. Carvou, R. Holic, M. Li, C. Futter, A. Skippen, S. Cockcroft, Phosphatidylinositol- and phosphatidylcholine-transfer activity of PITPbeta is essential for COPI-mediated retrograde transport from the Golgi to the endoplasmic reticulum, J Cell Sci 123(Pt 8) (2010) 1262-73.
[41] M. Kaba, A. Carreras-Sureda, P. Nunes-Hasler, N. Demaurex, The lipid transfer proteins Nir2 and Nir3 sustain phosphoinositide signaling and actin dynamics during phagocytosis, J Cell Sci (2023).
[42] Z. Xie, V.A. Bankaitis, Phosphatidylinositol transfer protein/planar cell polarity axis regulates neocortical morphogenesis by supporting interkinetic nuclear migration, Cell Rep 39(9) (2022) 110869.
[43] Y.T. Yeh, C. Sona, X. Yan, Y. Li, A. Pathak, M.I. McDermott, Z. Xie, L. Liu, A. Arunagiri, Y. Wang, A. Cazenave-Gassiot, A. Ghosh, F. von Meyenn, S. Kumarasamy, S.M. Najjar, S. Jia, M.R. Wenk, A. Traynor-Kaplan, P. Arvan, S. Barg, V.A. Bankaitis, M.N. Poy, Restoration of PITPNA in Type 2 diabetic human islets reverses pancreatic beta-cell dysfunction, Nat Commun 14(1) (2023) 4250.
[44] N.D. Carrillo, M. Chen, V.L. Cryns, R.A. Anderson, Lipid transfer proteins initiate nuclear phosphoinositide signaling, bioRxiv (2023).
[45] M. Chen, S. Choi, T. Wen, C. Chen, N. Thapa, J.H. Lee, V.L. Cryns, R.A. Anderson, A p53-phosphoinositide signalosome regulates nuclear AKT activation, Nat Cell Biol 24(7) (2022) 1099-1113.
[46] L. Zhao, C.L. Thorsheim, A. Suzuki, T.J. Stalker, S.H. Min, S. Krishnaswamy, S. Cockcroft, K.E. Anderson, B. Weiderhold, C.S. Abrams, Individual phosphatidylinositol transfer proteins have distinct functions that do not involve lipid transfer activity, Blood Adv 7(16) (2023) 4233-4246.
[47] M. Kirmiz, T.E. Gillies, E.J. Dickson, J.S. Trimmer, Neuronal ER-plasma membrane junctions organized by Kv2-VAP pairing recruit Nir proteins and affect phosphoinositide homeostasis, J Biol Chem 294(47) (2019) 17735-17757.
[48] H. Krishnan, B. Basak, V.R. Nath, S. Mishra, P. Raghu, Structural organization of RDGB (retinal degeneration B), a multi-domain lipid transfer protein: a molecular modelling and simulation based approach, J Biomol Struct Dyn (2023) 1-15.

Highlights

Not relevant

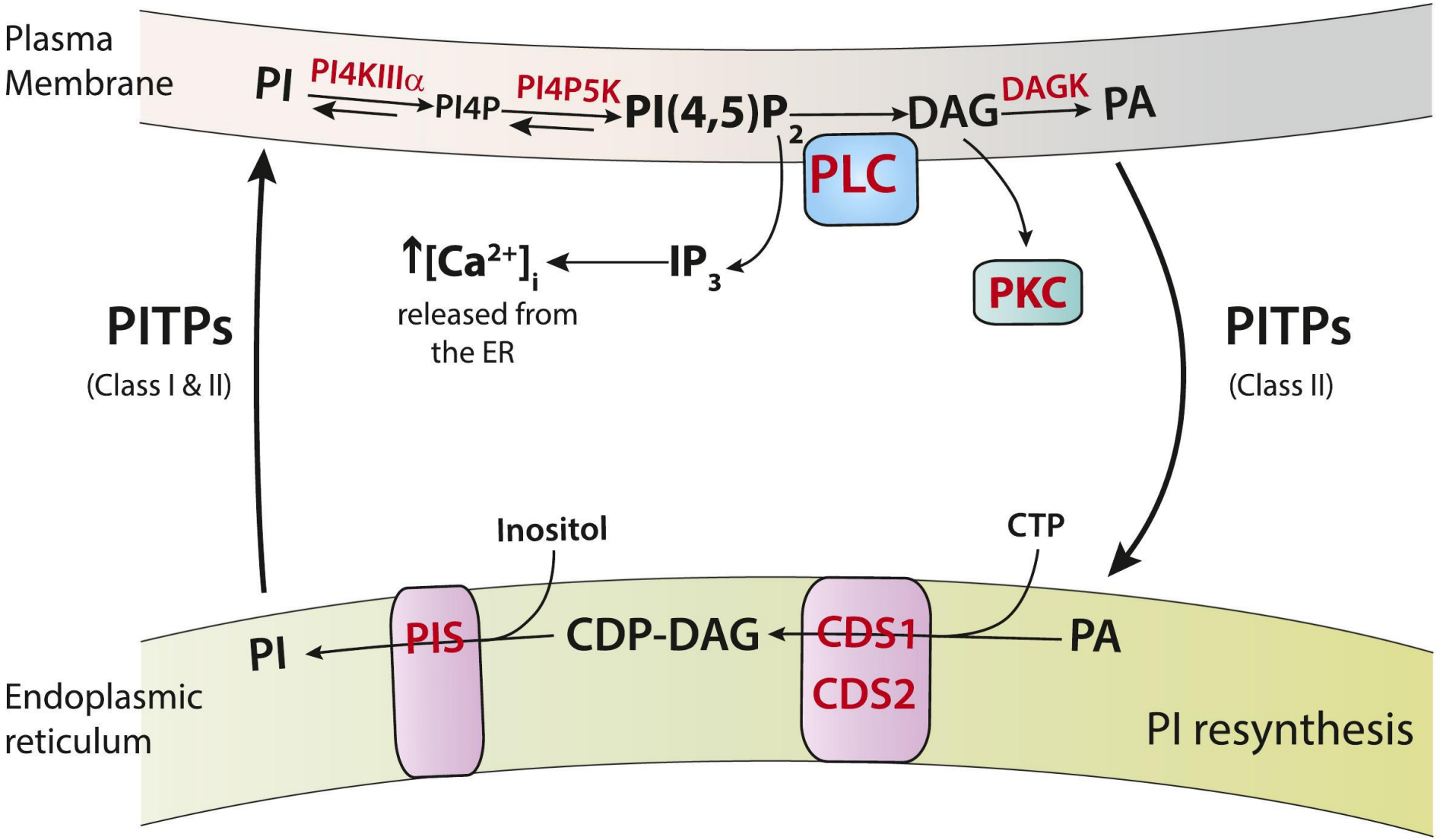
Plasma Membrane
PI
PI4KIIIα
PI4P
PI4P5K
PI(4,5)P2
DAG
DAGK
PA
PLC
↑[Ca2+]i
released from the ER
IP3
PKC
PITPs
(Class I & II)
PITPs
(Class II)
Inositol
CTP
PI
PIS
CDP-DAG
CDS1
CDS2
PA
Endoplasmic reticulum
PI resynthesis

Figure 1

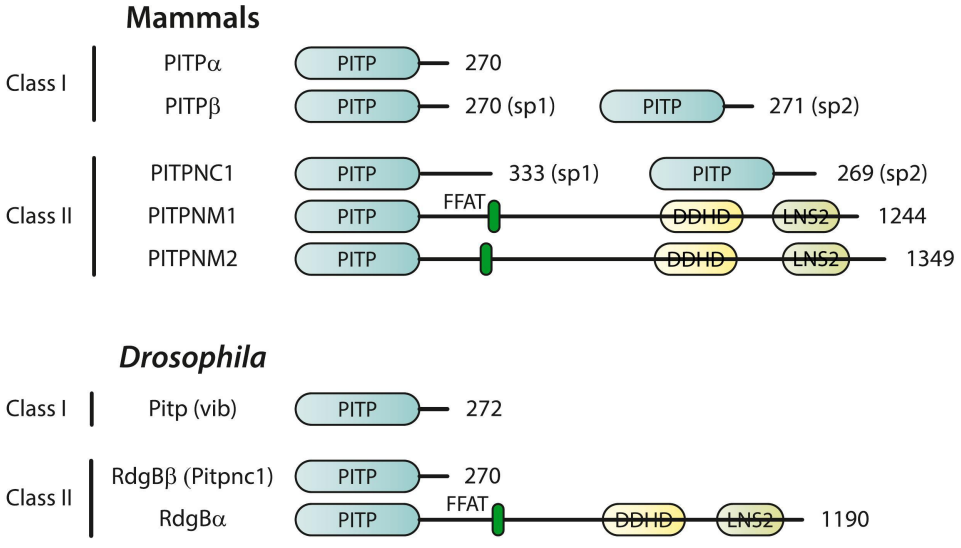
Mammals
Class I
PITPα
PITP
270
PITPβ
PITP
270 (sp1)
PITP
271 (sp2)
Class II
PITPNC1
PITP
333 (sp1)
PITP
269 (sp2)
FFAT
PITPNM1
PITP
DDHD
LNS2
1244
PITPNM2
PITP
DDHD
LNS2
1349
Drosophila
Class I
Pitp (vib)
PITP
272
Class II
RdgBβ (Pitpnc1)
PITP
270
FFAT
RdgBα
PITP
DDHD
LNS2
1190

Figure 2