



Lipid transfer proteins and instructive regulation of lipid kinase activities: Implications for inositol lipid signaling and disease

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ABSTRACT

Cellular membranes are critical platforms for intracellular signaling that involve complex interfaces between lipids and proteins, and a web of interactions between a multitude of lipid metabolic pathways. Membrane lipids impart structural and functional information in this regulatory circuit that encompass biophysical parameters such as membrane thickness and fluidity, as well as chaperoning the interactions of protein binding partners. Phosphatidylinositol and its phosphorylated derivatives, the phosphoinositides, play key roles in intracellular membrane signaling, and these involvements are translated into an impressively diverse set of biological outcomes. The phosphatidylinositol transfer proteins (PITPs) are key regulators of phosphoinositide signaling. Found in a diverse array of organisms from plants, yeast and apicomplexan parasites to mammals, PITPs were initially proposed to be simple transporters of lipids between intracellular membranes. It now appears increasingly unlikely that the soluble versions of these proteins perform such functions within the cell. Rather, these serve to facilitate the activity of intrinsically biologically insufficient inositol lipid kinases and, in so doing, promote diversification of the biological outcomes of phosphoinositide signaling. The central engine for execution of such functions is the lipid exchange cycle that is a fundamental property of PITPs. How PITPs execute lipid exchange remains very poorly understood. Molecular dynamics simulation approaches are now providing the first atomistic insights into how PITPs, and potentially other lipid-exchange/transfer proteins, operate.

1. Introduction

In the not-so-distant past, membranes were considered simple biochemical barriers that define the physical boundaries of the cell and of intracellular compartment, and the precursor of the modern membrane view of membrane structure and dynamics was born with the Singer and Nicolson “fluid mosaic” model (Singer and Nicolson, 1972). The recognition that the cytosolic leaflets of intracellular membranes are highly complex and integrated signaling platforms heralded another signature advance. In that regard,

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recent years have witnessed the advent of our understanding that eukaryotic cell membranes are comprised of hundreds of different lipids, representing over a thousand molecular species diversified by their various headgroup and fatty acid compositions. Membrane lipids recruit privileged protein-binding partners, are both substrates and cofactors for enzyme activities, and impart biophysical properties to membranes—such as bilayer thickness, fluidity, permeability, curvature, etc. (Holthuis and Menon, 2014). Moreover, lipids are not homogeneously distributed throughout the cell as demonstrated by the fact that intracellular membranes that confer compartmentalization of specific biochemical activities display uniquely characteristic lipid profiles (van Meer, 2005; McDermott and Mousley, 2016). Lipid compositional heterogeneity is evident even within a single membrane bilayer as both leaflets frequently exhibit different lipid compositions (Contreras et al., 2010), and lateral heterogeneities also exist as distinct membrane regions can be enriched or depleted of particular lipids such as the cholesterol and sphingolipids (Sezgin et al., 2017).

1.1. Enter inositol lipid signaling

In the 1950s, phosphatidylinositol (PtdIns) and its phosphorylated phosphoinositide (PIP) derivatives began to attract attention following demonstration of increased ^{32}P incorporation by pancreatic tissue after stimulation of the tissue with secretagogues such as acetylcholine- or carbamylcholine (Hokin and Hokin, 1953). Subsequent technological innovations such as lipid deacylation and chromatographic separation of glycero-phospholipids demonstrated that ^{32}P incorporation was primarily channeled into PtdIns synthesis and, to lesser degrees, into phosphatidylcholine (PtdCho), phosphatidylserine (PtdSer), and phosphatidic acid (PtdOH) (Hokin and Hokin, 1955; Hokin and Hokin, 1958; Michell, 2003; Kresge et al., 2005). This first demonstration of receptor-stimulated lipid turnover was termed the PIP effect/response and it stimulated interest in lipid biochemistry and PIP signaling. Subsequently, phospholipase C (PLC) was proposed to be responsible for the effect (Hokin and Hokin, 1964; Hokin-Neaverson, 1974), and a decade later PLC-catalyzed hydrolysis of PtdIns(4,5)P₂ downstream of receptor activation and subsequent resynthesis of PtdIns was shown to be the general mechanism behind the PIP effect (Michell, 1975). Questions regarding the mechanism by which hydrolyzed plasma membrane PIP pools are replenished to facilitate continued PLC activity were subsequently raised following these discoveries, and it was in this context that the concept of PtdIns-transfer proteins emerged. A ‘PtdIns-transfer’ model was postulated in which PtdIns produced at the endoplasmic reticulum (ER) would be transported to the plasma membrane by dedicated soluble carriers, thereby supplying the plasma membrane with PtdIns for replenishment of the depleted PIP pool—thus fueling continued performance of the PIP cycle (Michell, 1975). While many proteins with the capacity to transfer lipids between membrane bilayers in vitro have now been described, including PITPs, direct and convincing evidence for the *in vivo* relevance of such activities remains scarce (Wong et al., 2017). That topic will be the primary focus of this review.

1.2. Inositol lipid signaling—an overview

myo-Inositol (inositol) is the most abundant of the eight inositol isomers found in nature. This six-carbon cyclic polyol forms the molecular scaffold for generation of inositol phosphates (phosphorylated *myo*-inositols), as well as the glycerophospholipid PtdIns and its phosphorylated phosphoinositide derivatives (PIPs). These molecules participate in an impressive array of signaling processes including: membrane trafficking, control of intracellular calcium, chemotaxis, ion channel activity, and nuclear signaling (Balla, 2013). As such, the inositol and phosphoinositide pathways represent major eukaryotic intracellular signaling systems—derangements in which are the causative basis for a number of disease states (Majerus and York, 2009; McCrea and De Camilli, 2009; Liu and Bankaitis, 2010; Nicot and Laporte, 2008; Pendares et al., 2003).

The large chemical diversity that is generated from positionally-specific phosphorylation of inositol justifies its nomination for the title of ‘nature’s favorite molecule’ (Irvine, 2005). Since each position of the inositol ring harbors a hydroxyl group that can be phosphorylated (theoretically), a trinary code allowing both mono- and pyro-phosphorylation potentially yields 728 distinct inositol phosphates plus inositol. These distinct forms define unique chemical codes whose decoding contributes to the regulation of diverse biological outcomes (Grabon et al., 2015). As described below, the soluble inositol phosphates (InsPx) are predominantly derived from the hydrolysis of a specific PIP species [i.e. PtdIns(4,5)P₂] to release Ins(1,4,5)P₃ from which the other soluble InsPx are derived (Hatch and York, 2010; Otto et al., 2007). The large chemical diversity established for the soluble InsPx cohort is not reflected in the PIPs, however. Lipid kinase mediated phosphorylation of the PtdIns scaffold on the 3-, 4-, or 5-OH positions of the inositol ring results in production of PtdIns3P, PtdIns4P, PtdIns5P, PtdIns(3,5)P₂, and PtdIns(4,5)P₂ in plants and budding yeast. Mammals additionally produce PtdIns(3,4)P₂ and PtdIns(3,4,5)P₃. Despite the central involvement of PIPs in modulating the activities of a diverse array of cellular processes, PtdIns and PIPs occupy only a minor mass component of total eukaryotic lipidome. PtdIns is far more abundant than its phosphorylated derivatives as it comprises 90% of the total PtdIns/PIP population under basal conditions. Yet, PtdIns is itself a minor lipid that accounts for less than 5% of total cellular lipid. Of the singly phosphorylated PIPs PtdIns4P is the most abundant, representing 90–96% of the total PIP population in mammalian and plant cells (Balla, 2013; Vanhaesebroeck et al., 2001, 2010; Rusten and Stenmark, 2006; Sauer et al., 2009; Clark et al., 2011; Guillou et al., 2007).

Despite their low mass abundance, studies focused on the spatial- and temporal enrichment of PIPs in specific subcellular locations gave rise to the concept that distinct chemical PIP classes were localized to specific intracellular compartments. For example, PtdIns3P is highly enriched at the early endosomes and PtdIns4P was initially considered to be enriched at the Trans-Golgi Network (TGN) (McDermott and Mousley, 2016; van Meer et al., 2008). These observations prompted proposals that the molecular identities of intracellular organelles were substantially determined by their PIP content—i.e. the ‘PIP-code’ hypothesis for compartmental identity (McDermott and Mousley, 2016; Di Paolo and De Camilli, 2006; Behnia and Munro, 2005). Recent data demonstrate that notions of absolute PIP- compartmental specificity are misleading over-simplifications, however (Wang et al., 2019; Simon et al., 2016). That

realization derives from demonstrations that the 'PIP-code' is not only organism-specific, but that it is a function of the vital probe used to make localization assignments (Hammond et al., 2014). These vital probes are typically constructed as phosphoinositide binding domains fused to a fluorescent protein such as green fluorescent protein. Recent studies in this arena with high affinity and high-specificity binding modules are painting a different picture. Examples to this effect include the *L. pneumophila* SidM P4M-domain PtdIns4P probe, which reports multiple PtdIns4P pools at the mammalian plasma membrane, the Golgi system, and late endosomes/lysosomes (Hammond et al., 2014).

The cellular roles of PIPs are well documented (Balla, 2013; Di Paolo and De Camilli, 2006; Michell, 2008). PIPs act in multiple signaling capacities as: 1) metabolic precursors for production of other second messenger signaling molecules, 2) cofactors for enzymes and ion channels, 3) docking platforms for proteins containing lipid-binding domains, among other capacities. Cells modify their PIP complement via an array of kinases, phosphatases, and lipases, resulting in the production of other lipid species and in the production of powerful secondary messengers (Vanhaesebroeck et al., 2001, 2010). The classic example in this regard is the case of PLC-mediated hydrolysis of PtdIns(4,5)P₂ to produce diacylglycerol (DAG) and Ins (1,4,5)P₃ (IP₃). The DAG product regulates protein kinase C isoforms, while IP₃ regulates intracellular calcium and acts as a precursor for other lipid species (Berridge and Irvine, 1984).

Whereas initial ideas that evolved from the PLC work viewed PIPs as precursors to second messenger signaling molecules, the realization that PIPs phosphorylated on the 3-OH of the Ins-headgroup were refractory to PLC-mediated hydrolysis provided the first demonstration that PIPs themselves execute signaling functions (Whitman et al., 1987, 1988; Toker and Cantley, 1997; Auger et al., 1989). PIPs are now known to be allosteric cofactors for a number of enzymes and ion channels (Di Paolo and De Camilli, 2006; Hilgemann et al., 2001). Importantly, membrane PIP signatures also facilitate interaction with specific assemblies of lipid-binding proteins (Balla, 2013). The decoding aspect of this signaling system rests with the fact that many proteins contain PIP-binding domains such as PH- (Pleckstrin Homology), PX- (Phox), FYVE- (Fab1p, YOTB, Vac1 and EEA), and ENTH- (Epsin N-terminal Homology) domains (Balla, 2013; Stahelin et al., 2014). These modules bind PIPs with varying affinities and specificities (Lindsay et al., 2006). A full discussion of those domains is outside the scope of this article and we limit the discussion here to a brief summary.

PH-domains are perhaps the best characterized lipid binding domains, and these modules interact with a range of soluble inositol phosphates as well as PtdIns(3,4)P₂, PtdIns(4,5)P₂, and PtdIns(3,4,5)P₃ (Lemmon, 2007; Jiang et al., 2015). PX-domains are generally selective for 3-phosphoinositides and are found in proteins involved in endosomal sorting processes (Parker, 2004), although other subsets exist that include PtdIns(5)P binding modules (Chandra et al., 2019). FYVE-domains preferentially bind PtdIns3P and are found in proteins regulating membrane traffic through the endosomal system (Gaullier et al., 1998). ENTH-domains are PtdIns(4,5)P₂ and PtdIns(3,5)P₂ binding modules, and ENTH-domain proteins regulate endocytic processes and protein targeting to multi-vesicular bodies (De Camilli et al., 2002). The known functions of these modules are becoming ever more complex the more they are investigated. Some PX-domains are now recognized as participating in both protein-protein and protein-PIP interactions (Vollert and Uetz, 2004). Moreover, current estimates suggest that less than 10% of the PH-domains identified by homology criteria are high affinity lipid-binding modules (Yu et al., 2004).

Given the limited nature of the PIP code, the cohort of lipid-binding domains that have additional binding activities is postulated as the coincidence detection strategy by which the simple chemical heterogeneity of the PIP code is diversified to produce the large variety of signaling outcomes (Grabon et al., 2015, 2019). While there is no doubt that this coincidence-detection strategy contributes to the diversification of PIP signaling outcomes, new ideas are gaining traction with regard to functional compartmentalization and functional channeling of PIP pools (Grabon et al., 2015). The case of PtdIns4P signaling in the unicellular budding yeast *Saccharomyces cerevisiae* provides a system to dissect how diversification of PtdIns4P signaling is functionally channeled via a mechanism that does not solely rely on either the chemical identity of the PIP, or on the identity of the lipid kinase which produces the PIP of interest (Grabon et al., 2019; Bankaitis et al., 1990). It is upon this theme which the remainder of this article is focused.

1.3. PtdIns4P signaling

The mammalian PtdIns 4-OH kinase (PI4K) family which produces PtdIns4P is divided into two classes based on sequence and biochemical properties. These constitute the type II enzymes (PI4KIIα and PI4KIIβ in mammals and Lsb6 in yeast) and the type III enzymes (PI4KIIIα and PI4KIIIβ in mammals and Stt4 and Pik1 in yeast) enzymes (Balla and Balla, 2006; Minogue and Waugh, 2012; Clayton et al., 2013). The precise role of the type II proteins is still being elucidated and, at least in yeast, the type II Lsb6 is dispensable for viability and endosomal function (Chang et al., 2005). Type III proteins are individually essential for cell viability, execute distinct functions, and are responsible for producing in excess of 90% of the total PtdIns4P pool in yeast (Audhya et al., 2000).

At the TGN, PtdIns4P is produced by PI4KIIα and PI4KIIIβ in mammals, and Pik1 in yeast (Balla, 2013; Audhya et al., 2000; Blagoveshchenskaya et al., 2008; Graham and Burd, 2011; Flanagan et al., 1993; Strahl and Thorner, 2007). The importance of PI4K activity at this location is demonstrated by the fact that impaired yeast Pik1 results in impaired protein trafficking from late Golgi compartments (Walch-Solimena and Novick, 1999). PI4KIIα is also detected at the ER (Waugh et al., 2003), synaptic vesicles (Guo et al., 2003), and at the endosome where it recruits AP3 for the purpose of promoting protein sorting to late endosomes and lysosomes (Craige et al., 2008). PI4KIIIβ is also present on lysosomes where it plays an important role in maintaining lysosomal identity and integrity (Sridhar et al., 2013), and in a PKD-phosphorylated form in the nucleus where its role remains unclear (Szivak et al., 2006). The mammalian plasma membrane pool is maintained by PI4KIIIα which is recruited from the cytosol by the palmitoylated, membrane-resident proteins EFR3B and TTC7B (Nakatsu et al., 2012). This process is conserved in yeast where Stt4, the yeast ortholog of PI4KIIIα, is localized to Stt4-enriched plasma membrane patches on the basis of its interactions with the Ypp1 and Efr3 plasma membrane proteins.

PtdIns4P was initially believed to act as a simple intermediate in the production of PtdIns(4,5)P₂ and PtdIns(3,4,5)P₃ during

receptor activated PLC and PI-3-kinase signaling. However, studies of yeast mutants compromised for PtdIns4P production indicated defects in the early secretory pathway at the Golgi, and it is now clear that PtdIns4-OH kinases and PtdIns4P play significant roles in the biology of this organelle (Graham and Burd, 2011; Walch-Solimena and Novick, 1999; Hama et al., 1999). Many PtdIns4P effectors have now been identified that promote the execution of diverse downstream signaling events. These effectors include the PH-domain containing CERT (ceramide transfer protein) and FAPP (four phosphate adaptor protein) which integrate binding of PtdIns4P with glucosylceramide and ceramide respectively (Waugh et al., 2003; Guo et al., 2003). Moreover, these proteins regulate both lipid synthesis at the Golgi and Golgi-endosomal vesicular trafficking through recruitment of AP1 and AP3 (Craige et al., 2008; Wang et al., 2003). The activities of CERT and FAPP proteins in regulating Golgi membrane sphingolipid homeostasis, and the complex integration of PtdIns4P and sphingolipid synthesis, are beyond the scope of this article. Those subjects have recently been discussed elsewhere (Wang et al., 2019).

PtdIns4P is proposed to regulate non-vesicular lipid transport to and within the Golgi system (Toth et al., 2006; D'Angelo et al., 2007), to function in maintenance of Golgi structure (Dippold et al., 2009), and to control broader aspects of lipid distribution within the TGN/endosomal system. An example of the latter includes its regulation of the activity of the amino-phospholipid flippase Drs2, which binds PtdIns4P via a split PH-domain motif (Natarajan et al., 2009). Drs2 activity acts in concert with clathrin to stimulate vesicle budding (Costaguta et al., 2001; Gall et al., 2002; Chen et al., 1999), and it does so via a mechanism suggested to involve induction of membrane curvature (Muthusamy et al., 2009; Graham, 2004). The basic circuit is proposed to involve stimulation of Drs2 activity by PtdIns4P and ARF-GEF Gea2 binding, with the resultant translocation of phosphatidylethanolamine (PtdEtn) and PtdSer from the luminal to the cytosolic leaflets of endosomal and TGN membranes (Chen et al., 1999; Chantalat et al., 2004). PtdSer flipping is proposed to promote membrane curvature and to provide an acidic membrane platform for promoting vesicle biogenesis (Xu et al., 2013). Drs2 also links PtdIns4P to sterol homeostasis as there is evidence that lateral sterol distribution in TGN membranes is sensitive to Drs2 activity and that lateral distribution of sterol modulates cargo loading into transport vesicles (Hankins et al., 2015).

The most significant intracellular pool of PtdIns4P in mammalian cells by mass (>50% of total) resides at the plasma membrane (Nakatsu et al., 2012; Hammond et al., 2009; Sarkes and Rameh, 2010). PtdIns4-OH kinase inhibitor studies report that PtdIns4P depletion at this location results in surprisingly minor consequences on PtdIns(4,5)P₂ levels—strongly suggesting that PtdIns4P is not solely a metabolic precursor for PtdIns(4,5)P₂ (Hammond et al., 2009, 2012). Some functions for PtdIns4P at this location are its contributions to the recruitment of polybasic lipid-binding domains such as those of Merck and K-Ras (Clayton et al., 2013; Hammond et al., 2012). PtdIns4P also regulates plasma membrane ion channels such as the transient receptor potential vanilloid 1 (TRPV1) cation channel, the activity of which can be inhibited through depletion of either PtdIns4P or PtdIns(4,5)P₂ (Lukacs et al., 2007). Furthermore, both PtdIns4P and PtdIns(4,5)P₂ play important, but distinct, roles in endocytosis as evidenced from studies using temperature-sensitive yeast mutants of the Stt4 and Pik1 PtdIns4-OH kinases and the yeast PtdIns4P-5-OH kinase Ms4. PtdIns4P is required for receptor and ENTH/ANTH domain-containing clathrin-adaptor recruitment to clathrin-coated pits and PtdIns(4,5)P₂ is required for subsequent membrane internalization (Yamamoto et al., 2018). One factor which may contribute to the formation of membrane invaginations at clathrin-coated pits is significant local synthesis of PtdIns4P given that local PtdIns4P concentrations as low as 2 mol % can induce membrane curvature (Furse et al., 2012).

PtdIns4P signaling represents a balance of PtdIns4P production, turnover and availability for binding by effector proteins. In that regard, most attention is focused on regulation of the PtdIns 4-OH kinases themselves. However, PtdIns transfer proteins (PITPs) are now recognized as key regulators of PtdIns4P signaling as evidenced by the demonstration that yeast cells defective in the Sec14 PITP fail in protein trafficking through the TGN/endosomal system because of PtdIns4P deficits in those membranes (Bankaitis et al., 1989, 1990; Hama et al., 1999; Cleves et al., 1991). The proposal that PITPs facilitate PtdIns presentation to PI4Ks to solve the intrinsic biological insufficiency of these enzymes, and that they do so via heterotypic lipid exchange cycle, describes a novel mechanism for diversifying the biological outcomes of PIP signaling (Bankaitis et al., 2010). This thesis is described in greater detail below.

1.4. PITPs as regulators of PtdIns4P signaling

PITPs are highly conserved proteins found throughout the Eukaryota. Since the seminal discovery of their function in yeast, PITPs have been identified in organisms as diverse as apicomplexans, plants, flies, fish, and mammals (Nile et al., 2010; Cockcroft and Garner, 2011). These proteins are classified based on structure into two families: the Sec14-like PITPs bearing similarity to the yeast proteins, and the evolutionarily unrelated and structurally distinct START-like PITPs (StAR-related lipid transfer domain). PITPs lack enzymatic activity, and are named for their *in vitro* abilities to transfer lipids between membranes in an energy-independent manner. Arguably the best studied PITP is the *S. cerevisiae* Sec14 which executes the transfer of PtdIns and PtdCho between membrane bilayers *in vitro*. This PITP is essential for secretion from the Golgi and therefore for yeast cell viability (Bankaitis et al., 1989, 1990; Cleves et al., 1991). While the *in vitro* lipid transfer activities of PITPs in general are commonly extrapolated to *in vivo* lipid transfer functions despite the absence of direct evidence to that effect (Cockcroft and Carvou, 2007), strong evidence from multiple lines of investigation of Sec14 function provides a compelling case arguing that these proteins are actually PtdIns-presentation modules, functioning in highly local activation of PI4Ks rather than inter-organelle lipid transporters. First, yeast naturally contain large amounts of PtdIns, roughly 20–25 mol % of total glycerophospholipid (compared with about 5% in mammals) (Strahl and Thorner, 2007). Given this excess, it is not obvious why yeast should require PITP activities to mediate PtdIns supply to organelle membranes. This issue is further emphasized by demonstrations that increasing bulk PtdIns levels even further do not alleviate the essential cellular requirement for Sec14 function (Cleves et al., 1991). Moreover, Sec14 is expressed at levels in large excess of those required for cell viability—presenting a capacity paradox, as one would expect significant monomeric lipid transfer systems must have high capacity (Bankaitis et al., 2010; Schaaf et al., 2008). Perhaps the most striking evidence for Sec14 not being required for transport activity however, comes from

genetic studies demonstrating that the Sec14 requirement for yeast cell viability is obviated by inactivation of the Sac1 PtdIns4P-phosphatase, of the CDP-choline pathway for PtdCho biosynthesis, or of the PtdIns4P/ergosterol exchange protein Kes1/Osh4 (Cleves et al., 1991; Rivas et al., 1999; Xie et al., 1998). These studies all converge on the conclusion that Sec14 regulates lipid metabolism and not inter-organelle lipid transport.

The underlying mechanism is posited to rest on the fact that PI4Ks are biologically-insufficient interfacial enzymes that cannot efficiently access PtdIns monomers residing in bilayers as substrates for phosphorylation. As a result, these enzymes are incapable of producing sufficient PtdIns4P to overcome the activities of antagonists or ‘erasers’ of PtdIns4P-mediated signaling (Grabon et al., 2015, 2019; Bankaitis et al., 2010; Schaaf et al., 2008). PITPs are proposed to potentiate PI4K activity by ‘presenting’ PtdIns to the kinase—thereby making the phospholipid a more accessible substrate for the enzyme and potentiating PtdIns 4-OH kinase activity. This presentation mechanism relies on a heterotypic lipid-exchange cycle to serve as the engine for PtdIns presentation. How might this work? The PITP lipid-binding pocket can only be fully occupied by a single lipid molecule at any time. Homotypic PtdIns/PtdIns exchanges or the counter-ligand exchanges (PtdCho/PtdCho as in the case of Sec14) are ineffective in stimulating PI4K activity *in vivo* (Schaaf et al., 2008, 2011). However, a PtdIns/PtdCho heterotypic exchange cycle where Sec14-bound PtdCho is being exchanged for membrane resident PtdIns is effective. The idea is the PITP is primed for presentation by binding of the counter ligand PtdCho, and heterotypic exchange for PtdIns is accompanied by multiple abortive attempts by PtdIns to enter the PITP pocket (a ‘fast’ half-reaction) whose completion is frustrated by egress of PtdCho (a ‘slow’ half-reaction). This kinetic mismatch promotes multiple rounds of transient exposure of PtdIns to the kinase in a non-bilayer state that renders the lipid more accessible to the enzyme (Grabon et al., 2015; Bankaitis et al., 2010; Schaaf et al., 2008) (Fig. 1).

Yeast cells express five additional Sec14-like proteins termed Sfh (Sec14 homolog) proteins (Li et al., 2000a). These proteins perform diverse cellular functions that include regulation of: (i) squalene homeostasis, (ii) a specific pathway for PtdSer decarboxylation, and (iii) mobilization of fatty acids from lipid droplets (Ren et al., 2014; Tripathi et al., 2019). Since individual Sfh proteins differentially localize in cells, and each binds a different counter-ligand, this system allows for a diverse set of inputs into PI4K activation at single molecule levels—thereby translating to a diverse set of biological outcomes stemming from the same chemical code (i.e. PtdIns4P). For example, in yeast, a Sec14-dependent PtdIns4P pool determines the trafficking competence of TGN/endosomal membranes, whereas Sfh-dependent PtdIns4P pools are channeled to other biological activities in a functionally non-redundant manner (Grabon et al., 2015; Schaaf et al., 2008; Li et al., 2000a; Ren et al., 2014). We term this mode of PtdIns 4-OH kinase control as instructive regulation as it is the identity of the PITP engaged with the lipid kinase that specifies how the PtdIns4P product will be channeled to a specific biological outcome.

1.5. Mammalian Sec14-domain proteins

The Sec14-domain containing proteins form a large superfamily of more than 1500 proteins, with yeast expressing six members, and plants, flies, worms, and mammals expressing more than twenty (Bankaitis et al., 2010; Nile et al., 2010; Phillips et al., 2006). Mammals deploy the Sec14-domain in a variety of contexts. Some proteins are single Sec14-domains modules while most others incorporate Sec14-like modules into larger multi-domain configurations. The mammalian Sec14-domain containing proteins remain poorly studied, and the Sec14-domain ligands of most of these proteins still await characterization. Most Sec14 superfamily members

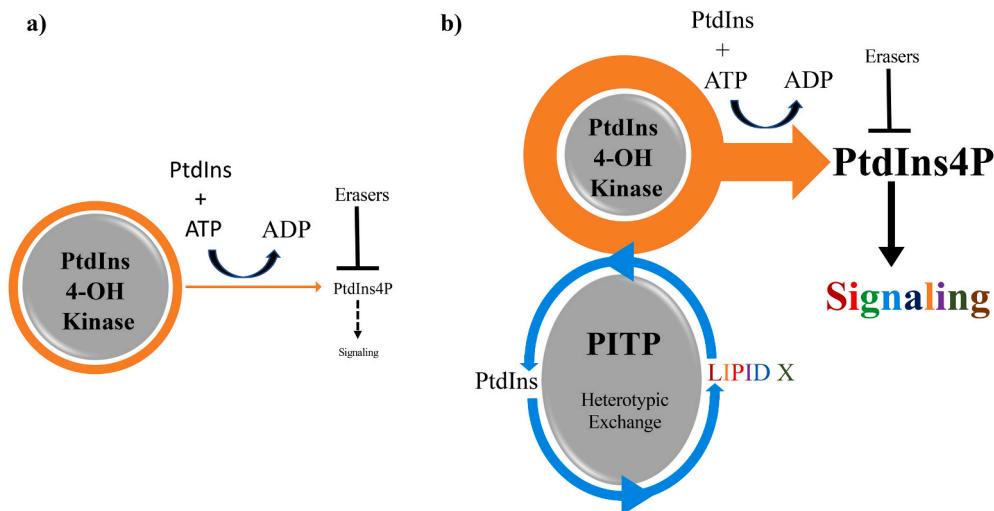


Fig. 1. PtdIns 4-OH kinases are biologically insufficient enzymes. Unassisted, they are unable to produce sufficient PtdIns4P to overcome the actions of antagonists of PtdIns4P signaling and enzymes that degrade PtdIns4P (e.g. lipid phosphatases such as Sac1) (a). PITPs present PtdIns to PtdIns 4-OH kinases through a heterotypic exchange reaction that involves exchange of a bound counter-ligand for PtdIns. This exchange cycle renders the PtdIns substrate more accessible to the kinase and thereby making the lipid a better substrate. This results in enhanced PtdIns4P production that is sufficient to support PtdIns4P signaling (b).

conserve an obvious PtdIns-binding barcode (Schaaf et al., 2008), raising the possibility that many (most? all?) of the Sec14-domains proteins exhibit inositol phospholipid binding or exchange activities. This is a matter of major interest given small GTPases, GTPase-activating-proteins (GAPs) for Rho, Ras, and Cdc42, cellular retinaldehyde binding protein (CRALBP), caytaxin, and the α -tocopherol, and retinaldehyde transfer proteins all have obvious Sec14-domains (Nile et al., 2010). The human MEG2 protein tyrosine phosphatase (also termed PTPN9) provides yet another interesting example. This protein is widely expressed and consists of an N-terminal Sec14 domain fused to a tyrosine phosphatase module that exhibits protein tyrosine phosphatase activity when expressed in isolation as a recombinant protein (Gu et al., 1992). The Sec14-domain inhibits this catalytic activity and inhibition is relieved by PIP binding—presumably to the Sec14 domain. The data suggest that the MEG2/PTPN9 Sec14-domain functions in recruitment of the catalytic domain to the phagosome in neutrophils via its PIP binding activity, resulting in a spatially localized activation of the enzyme (Kruger et al., 2002). The Sec14-domain is also proposed to be required for recruitment of MEG2/PTPN9 to transport vesicles where it dephosphorylates trafficking components such as N-ethylmaleimide sensitive factor and is required for optimal secretion of interleukin 2 by murine hematopoietic cells (Huynh et al., 2004; Saito et al., 2007; Wang et al., 2005).

Sec14 domain proteins are implicated in many cellular activities, including essential roles in housekeeping membrane trafficking pathways (Skinner et al., 1995), dimorphic transitions in fungi (Lopez et al., 1994), and in various developmental processes in higher plants that rely on highly polarized membrane trafficking (Ghosh et al., 2015; Vincent et al., 2005). Single domain Sec14-like proteins are associated with multiple human diseases ranging from neurological disorders to cancers. Comprehensive discussions of those topics are found elsewhere (Nile et al., 2010). As a general summary, several examples include: 1) Ataxia with vitamin E deficiency (AVED), an autosomal recessive, progressive neurodegenerative disorder results from deficiency of the Sec14-like α -tocopherol binding protein (Nile et al., 2010); 2) Defects in the Sec14-domain containing presynaptic protein caytaxin result in Cayman-type cerebellar ataxia, a rare autosomal recessive disorder found on the Grand Cayman island; and 3) The Sec14-like cellular retinal-binding protein 1 (CRALBP1) is associated with a number of pathologies including *retinitis pigmentosa*, *fundus albipunctatus*, Newfoundland rod/cone dystrophy and Bothnia dystrophy (Nile et al., 2010; Saari et al., 2001; Saari and Crabb, 2005; Golovleva et al., 2003, 2010).

Multidomain proteins containing Sec14-like modules are also proteins linked to human diseases. These include the Rho guanine nucleotide exchange factor (GEF) Dbl where N-terminal truncations that delete the Sec14-domain and multiple spectrin repeats result in pro-oncogenic forms of the protein (Vanni et al., 2002; Fardin et al., 2009). Kalirin/Duo is a GEF with a Sec14 domain and is a genetic risk factor for ischemic stroke (Krug et al., 2010), coronary artery disease (Wang et al., 2007), schizophrenia (Cahill et al., 2009), and Alzheimer's disease (Youn et al., 2007). The isolated Kalirin Sec14 domain binds PIPs in crude lipid blot analyses (Schiller et al., 2008). Sec14 domains are also present in GAP proteins—including the CDC42 GAP/p50 Rho GAP which is linked to human disorders such as Waldenstrom macroglobulinemia, a type of non-Hodgkin lymphoma (Hatjiharissi et al., 2007), and chronic myeloid leukemia (Jin et al., 2009).

1.6. START-like PITPs

The START-like PITPs do not share any structural homology with Sec14-like PITPs (Bankaitis et al., 1989). However, these too stimulate PtdIns4P production in vivo as evidenced by demonstrations that: (i) high level expression of mammalian START-like PITPs rescues the yeast growth and Golgi secretory defects associated with Sec14 deficiency (Skinner et al., 1993; Milligan et al., 1997a), and

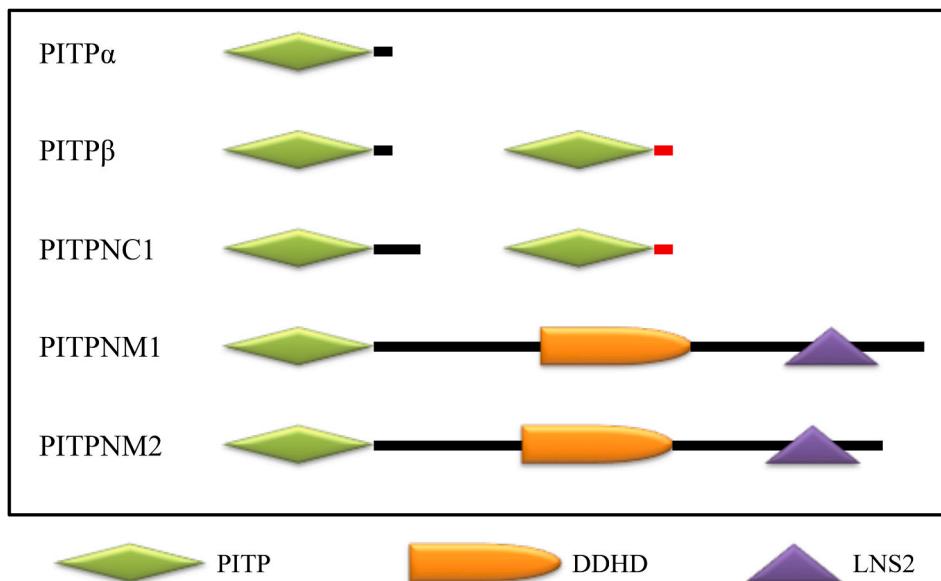


Fig. 2. Figure panel illustrates the domain architecture of START-like PITPs. Protein domains are color coded: PIP (green); DDHD (orange); LNS2 (purple). The alternative spliceforms of PIP β and PITPNC1 differ in their C-terminal regions (indicated in red).

(ii) PITP α and PITP β regulate PtdIns4P homeostasis in the TGN of embryonic neural stem cells (Xie et al., 2018). As such, these two unrelated PITP structural modules share at least some degree of functional conservation and thereby offer a remarkable example of convergent evolution.

The mammalian START-like PITP family is variously classified within the literature according to two main systems: 1) protein physical characteristics and behavior, and 2) protein homology and evolutionary descent. Type I proteins consist of a single stand-alone PITP domain. The Type II proteins are multi-domain proteins that are tightly membrane-bound. These Type II proteins exhibit N-terminal START-like PITP domains and are orthologues of the *Drosophila* RdgB α protein (Grabon et al., 2015) (Fig. 2). In both classification systems, PITP α and PITP β are classified as type I PITPs. These small soluble PITPs are highly homologous and share 77% primary structure identity and 95% primary structure similarity (Phillips et al., 2006). Moreover, PITP α and PITP β are both PtdIns/PtdCho exchange proteins with an affinity for PtdIns that is some 20-fold greater than that for PtdCho (Wirtz, 1991). The third member of this class, PITPNC1 (homolog of the *Drosophila melanogaster* retinal degeneration B protein RdgB β) is also a small soluble protein like PITP α and PITP β . It is for this reason that we refer to PTPNC1 as a type I protein in this review. However, PTPNC1 diverges from PTP α and PTP β in several important respects and it is for two primary reasons that PTPNC1 is occasionally classified as a type II PTP. First, PTPNC1 shares greater primary sequence homology with members of the type II group (Cockcroft and Carvou, 2007). Second, this relatedness extends to lipid-binding specificities that are distinct from those of PTP α and PTP β . PTPNC1 and the other type II PTPs are PtdIns/PtdOH exchange proteins that neither robustly bind, nor exchange PtdCho (Li et al., 2000b; Routt et al., 2005; Cockcroft et al., 2016; Garner et al., 2012).

2. Type 1 START-like PTPs

2.1. PTP α and PTP β

2.1.1. PTP α and PTP β expression and localization

PTP α and PTP β represent the best studied mammalian PTPs. These are ubiquitously expressed proteins with highest levels of PTP α expression recorded in the brain, while PTP β is expressed most robustly in liver and neutrophils (Cosker et al., 2008; De Vries et al., 1996; Swigart et al., 2000; Utsunomiya et al., 1997; Venuti and Helmckamp, 1988a, 1988b). Despite their structural and biochemical similarities these PTPs are differentially localized within the cell. PTP α localizes predominantly to the cytoplasm and nucleus, while PTP β localizes to the Golgi/TGN system and to the cytoplasm (Cosker et al., 2008; Swigart et al., 2000; DeVries et al., 1996). PTP β is expressed as two splice variants—PTP β sp-1 and PTP β sp-2 (Morgan et al., 2006). It was initially postulated that phosphorylation of PTP β sp-1 Ser₂₆₂ (a residue absent from PTP α) was required for Golgi localization of this spliceoform (Snoek, 2004). However, this residue is absent from PTP β sp-2 which targets efficiently to Golgi membranes (Morgan et al., 2006).

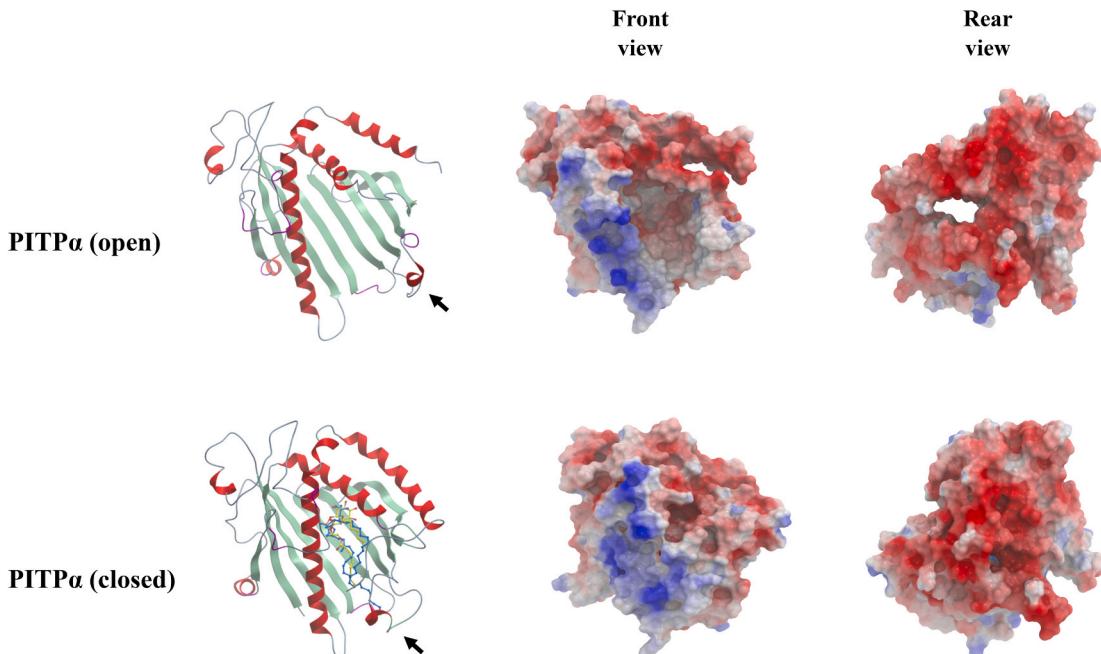


Fig. 3. Structural models for the open PTP α conformer (top left) and the closed conformer (bottom left) are shown. The positions of the lipid exchange loop/gate in the two conformers are indicated (arrow). The electrostatic potentials of the PTP α protein surface (front and rear view) are shown for each conformer as indicated. Blue areas indicate electropositive potential while red regions indicate electronegative regions.

2.1.2. PITPa and PITP β protein structure

Crystal structures of both PITPa and PITP β are available in the RSCB protein data bank (PDB <https://www.rcsb.org>) and, together with modeling data, these data provide insights into functional mechanisms. PITPa crystal structures are available both in an apo or ‘open’ conformation (PDB id 1KCM), and in ‘closed’ conformations bound to PtdIns (PDB ID 1UW5) and to PtdCho (PDB ID 1T27) (Fig. 3). A closed-conformation PITP β crystal structure in complex with PtdCho (PDB ID 2A1L) is also available. Although the Sec14-like and START-like PITPs are structurally unrelated, these PITPs all fold around a single lipid-binding pocket (Grabon et al., 2019).

Comparisons of phospholipid-bound and apo-PITP structures project that PITPs display large conformational motions associated with membrane interaction and phospholipid exchange (Grabon et al., 2017, 2019). START-like PITP domains are characterized by a large lipid binding domain (LBD) that forms a hydrophobic channel to host phospholipids. The LBD is flanked by the C-terminal helix and a lipid-exchange loop on one side, which act as a ‘lid’, and is involved in membrane association and lipid extraction. The ‘open’ and ‘closed’ conformations are distinguished primarily by large conformational transitions in the ‘lipid-exchange’ loop (Grabon et al., 2017, 2019). In an ‘open’ conformation, the lipid-exchange loop is swung open by ~90° allowing wide access to the LBD, and this conformer is also characterized by a significant unwinding of the C-terminal G-helix. Upon PtdIns or PtdCho binding, the lipid-exchange loop swings closed—thereby restricting access to the LBD. Closure of the LBD is further consolidated by the C-terminal G-helix whose reformation also helps occlude LBD access (Fig. 3) (Grabon et al., 2017, 2019).

The PITP crystal structures are also revealing the importance of molecular surface electrostatics in governing membrane recognition and phospholipid extraction. Surface charge distributions orient PITP molecules in such a way that PITP electropositive regions are directed towards electronegative membrane surfaces (Fig. 3). As is evident from the available PITPa crystal structures, the α helix region (Helix F) around the lipid-exchange loop, and proximal to the LBD entrance, is distinctly more electropositive than other regions of the protein, suggesting a critical role in phospholipid extraction and exchange on the membrane surface. A similar pattern of surface charge distribution is also observed in PITP β , where the electropositive charge is localized at the LBD entrance. However, unlike PITPa, the electropositive region is localized at the surface of the β sheet, near the binding-pocket entrance instead of on the F-Helix. The functional significance of these distinct surface charge distributions between PITPa and PITP β remains to be determined.

Even though yeast Sec14 and mammalian PITPa/PITP β are all PtdIns/PtdCho exchange proteins, and PITPa and PITP β are like Sec14 in that both proteins bind PtdIns with higher affinities than PtdCho (Vordriede et al., 2005), they accommodate these phospholipids in their respective lipid binding pockets via remarkably distinct mechanisms. Sec14 incorporates PtdIns and PtdCho into its lipid-binding cavity via surprisingly distinct mechanisms from the spatial point of view, whereas the poses of phospholipids in PITPa/PITP β are essentially superimposable (Grabon et al., 2019; Tripathi et al., 2019). This difference is largely accounted for by the way the headgroups of these two phospholipids are coordinated. Even though the PtdIns and PtdCho binding space is largely superimposable, these two binding activities could be uncoupled—as demonstrated by an unbiased genetic screen that identified PITPa missense substitutions for Thr₅₉ and Glu₂₄₈ that specifically inactivated PtdIns-binding/exchange with no deleterious effect on PtdCho-binding/exchange (Alb et al., 1995). Structural studies precisely assigned interactions between these START-like PITPs and bound lipid headgroups, and these can be grouped into two distinct categories: i) residues that coordinate the PtdIns headgroup (Thr₅₈, Lys₆₀, Glu₈₅, Gln₈₉), and ii) residues involved in coordination of both PtdIns and PtdCho (Glu₈₆, Thr₉₇, Lys₁₉₅) (Grabon et al., 2017; Alb et al., 1995; Tilley et al., 2004) (Fig. 4). In addition to these sets of residues, conserved interactions with water molecules within the binding pocket also play important roles in mediating PITP-lipid interactions (Thr₅₈, Lys₆₀, Glu₈₅, Ala₈₇, Asn₈₉, Thr₉₆).

Recently, the first mechanistic description of dynamic aspects of the PITPa PtdIns/PtdCho exchange cycle was reported (Grabon

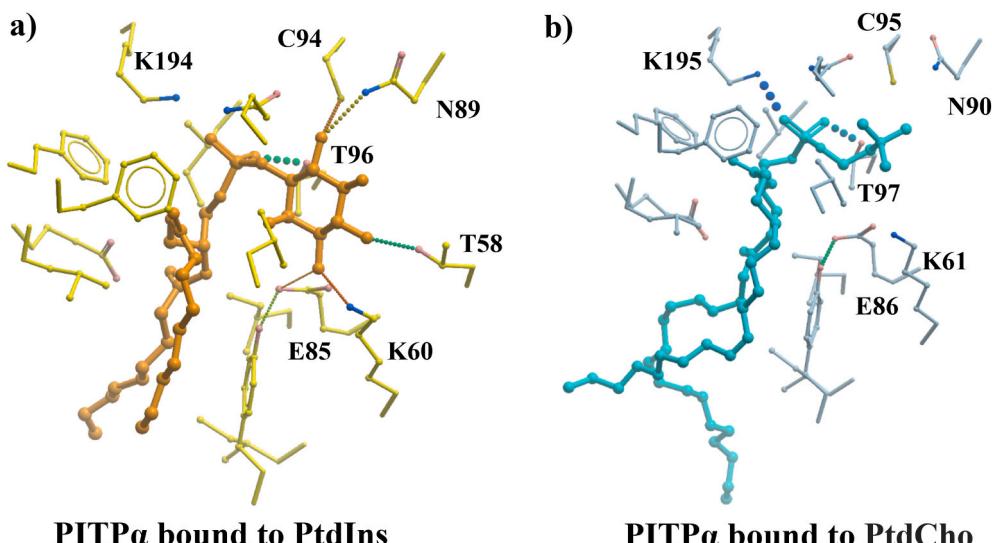


Fig. 4. Coordination strategy for PtdIns (a) and PtdCho (b) binding by PITPa. Panel (a) illustrates PtdIns binding (orange, ball and stick rendering) by human PITPa (Pdb i.d.1UW5). Panel (b) shows binding of PtdCho (cyan, ball and stick rendering) by rat PITPa (Pdb i.d. 1T27).

et al., 2017). That study describes the initial steps in a pathway of conformational transition from an apo-PITP α conformer to a phospholipid-bound holo-PITP α conformer, and described conformational transitions in the C-terminal G-helix that exhibited surprisingly long range headgroup-specific involvements during the phospholipid exchange cycle. The study further demonstrated that sets of residues conserved throughout the START-like PITP family are engaged in the trajectory of PtdIns or/and PtdCho into the LBD. These findings were of interest not only because these distinguished structural elements that influence PtdIns-exchange from those that affect PtdCho-exchange, but these identified small nucleotide polymorphisms (SNPs) circulating in the human population that may perturb key elements of the PITP α lipid exchange cycle. These SNPs may therefore be relevant from the human health perspective (Grabon et al., 2017).

2.1.3. Implications for PITP α and PITP β in physiology and disease

Studies from multiple animal models indicate PITP α and PITP β execute important in vivo activities. In zebrafish, PITP α is essential for embryogenesis, with PITP α morpholinos inducing an early failure in development at 80% epiboly (8–10 h post-fertilization). Expression of morpholino resistant mammalian (rat) PITP α efficiently rescued progression into later developmental stages, but neither expression of PITP β nor of a mammalian PtdIns binding/transfer mutant (PITP α^{T59D}) was able to do so. These data emphasize both the functional conservation between mammalian and zebrafish PITP α proteins and demonstrate that PtdIns-binding is essential to the in vivo function of these proteins (Ile et al., 2010a). In contrast to PITP α , knockdown of zebrafish PITP β compromised the development and maintenance of retinal double cone photoreceptor cell outer segments, and it is in double cone cells where zebrafish PITP β is most highly expressed (Ile et al., 2010b).

In mice, the naturally occurring murine vibrator (*vb*) mutation is a hypomorphic allele of PITP α , resulting from insertion of an endogenous transposable element (intracisternal A particle [IAP]) into the fourth intron, resulting in 80% knockdown of PITP α gene expression (Floyd et al., 2003; Weimar et al., 1982). The *vb* allele results in a neurodegenerative disease described by a progressive whole-body tremor, and spinocerebellar neurodegeneration in the face of unimpaired PITP β expression (Floyd et al., 2003; Weimar et al., 1982; Hamilton et al., 1997; Alb et al., 2003, 2007a; Concepcion et al., 2011). *vb* mice in the C57/B6 (Black 6) genetic background die within 42 days, but lifespan is extended in other genetic backgrounds for as long as one year. These data reveal the existence of genetic modifiers (Weimar et al., 1982; Concepcion et al., 2011). One such modifier is the *Modifier-of-vibrator-1* locus (nuclear export factor-1 [Nxf1/TAP]) which improves the splicing efficiency of the IAP-containing intron, thereby elevating levels of PITP α expression (Floyd et al., 2003).

Ablation of the mouse PITP α gene results in mice that are born at normal Mendelian ratios but which die as neonates. Mortality results from a complex phenotype including spinocerebellar neurodegeneration, hypoglycemia, and intestinal and hepatic steatosis (Alb et al., 2003). The neurodegenerative disease presents with a very rapid onset and is characterized by wholesale reactive gliosis of the brain and brain stem, and rampant demyelination of motor neurons in the spinal cord (Hamilton et al., 1997; Alb et al., 2003, 2007b). Recent studies link PITP α with Duchenne muscular dystrophy (DMD)—a genetic disorder characterized by progressive muscular degeneration and weakness (Vieira et al., 2017a). Decreased expression of PITP α ameliorated the pathological consequences of the disease in a Duchenne muscular dystrophy dog model (Vieira et al., 2017b). Decreased PITP α expression was associated with decreased levels of the phosphatase and tensin homolog (PTEN) and with increased AKT-phosphorylation. These effects promote muscle growth and metabolism to counteract the pathologies associated with muscular dystrophy (Vieira et al., 2017a). Similar changes in PTEN and Akt regulation were also observed following shRNA-mediated knockdown of PITP α in human DMD myoblasts and upon PITP α knockdown in a dystrophin-deficient *sapje* mutant zebrafish DMD model (Vieira et al., 2017a).

Consistent with a conserved function between mammalian and yeast PITPs, PITP α is implicated in TGN secretory vesicle biogenesis (Ohashi et al., 1995; Jones et al., 1998; Hay and Martin, 1993), and high-level expression of PITP α , or PITP β expression rescues Sec14 deficiencies in yeast (Skinner et al., 1993; Tanaka and Hosaka, 1994). Other reports implicate PITP α as an obligate regulator of plasma membrane receptor signaling circuits, notably those of the Epidermal growth factor receptor (EGFR) and the netrin receptor ‘deleted in colorectal cancer’ (DCC) (Cunningham et al., 1996; Kauffmann-Zeh et al., 1995; Xie et al., 2005). In the case of netrin signaling, a system for processing and responding to secreted guidance cues for axon elongation and pathfinding, required for major commissure formation in the brain and spinal cord (Fazeli et al., 1997; Serafini et al., 1996), PITP α is reported to interact with the cytoplasmic C-terminal domain of the activated DCC while PITP β does not. In both EGFR and DCC contexts, PITP α -receptor engagement is postulated to be required for localized generation of phosphoinositide pools facilitated by PITP α -mediated lipid transport from the ER. These reports promulgated the idea that PITP α plays an essential role in growth factor signaling (Kauffmann-Zeh et al., 1995).

However, those conclusions regarding growth factor receptor and morphogen signaling were based largely on the results of cell-free or permeabilized cell reconstitution studies. Physiologically relevant in vivo studies indicate these conclusions are likely incorrect. For example, PITP α null murine embryonic stem cells do not betray growth factor signaling defects, these cells are neither compromised for growth or bulk phospholipid metabolism, and appear to have normal PtdIns4P and PtdIns(4,5)P₂ homeostasis (Alb et al., 2002). Moreover, murine embryonic stem cells ablated for PITP α exhibit: 1) normal bulk protein trafficking through the constitutive secretory pathway, 2) uncompromised endocytic trafficking and recycling of transferrin receptor—a constitutively recycled cargo, 3) uncompromised regulatory secretory pathway activity as judged by normal biogenesis of mast cell dense core secretory granules, and 4) robust agonist-induced fusion of dense core granules with the mast cell plasma membrane. These PITP α null stem cells also retain their pluripotency and are proficient at forming large teratomas in nude mice (Alb et al., 2002). PITP $\alpha^{-/-}$ knockout mice similarly fail to display any of the many phenotypes associated with EGFR or netrin signaling deficits. For example, PITP $\alpha^{-/-}$ knockout mice form a seemingly normal corpus callosum (our unpublished observations), a structure which joins the two hemispheres of the brain. Notably, the corpus callosum is absent from the brains of *kanga* mice (DCC^{Kanga}) that express mutated DCC receptors deleted for the PITP α interaction domain (Finger et al., 2002; Xie et al., 2005). The mouse data consistently argue that PITP α does not play a major role in

promoting EGFR or netrin signaling in vivo.

Early attempts to knock out PITP β in embryonic stem cells or mice failed—initially leading to suggestion that it may represent a mammalian counterpart to Sec14 that executes an essential housekeeping function at the level of the Golgi system (Alb et al., 2002). While the influence of genetic background on phenotype is yet to be explored, PITPNB null mice produced in the C57B6 background are born at Mendelian frequencies, are fertile and appear overtly normal past one year of age (Xie et al., 2018). This finding suggests a degree of redundancy exists between PITP α and PITP β —a finding confirmed by recent studies in murine embryonic neural stem cells addressing the role of PITP α and PITP β in mouse brain development (Xie et al., 2018).

Neural stem cell (NSC) expansion and differentiation drives development of the mammalian neocortex, and both PITP α and PITP β act in a redundant fashion to potentiate synthesis and/or maintenance of a TGN/endosomal PtdIns4P pool that subsequently recruits phosphoinositide effectors such as GOLPH3 and CERT (ceramide transfer protein) to those membranes. GOLPH3 in turn initiates MYO18A and F-actin mediated loading of the Golgi system into the apical processes of the NSCs—thereby generating a critical polarity signal in the highly polarized neuroepithelial cells (Xie et al., 2018). Interestingly, expression of the yeast Sec14 PITP fails to substitute for mammalian PITP α during mouse brain development (Xie et al., 2018), despite the fact that the biochemical properties and lipid-binding affinities and specificities of these proteins are very similar. These data argue strongly against models where PITPs function in lipid-supply capacities as lipid-transporters between intracellular compartments—the directionality of which is regulated by differential lipid gradients between donor and acceptor compartments. This particular role of vertebrate PITPs in CNS development appears to be conserved since deficiencies in the single *Drosophila* PITP α/β ortholog (Vib) perturb homeostatic regulation of neuroblasts—the fly equivalents of mammalian NSCs. In that case, the fly Vib PITP regulates a plasma membrane PtdIns4P pool, likely produced by PI4KIII α , that facilitates myosin and actin-dependent asymmetric partitioning of cell fate determination factors into mother and daughter cells during cytokinesis (Koe et al., 2018).

2.1.4. PTPNC1

PTPNC1 (Phosphatidylinositol Transfer Protein, Cytoplasmic 1 or RdgB β) is the least characterized soluble START-like PITP. This cytoplasmic protein is diverged from PITP α and PITP β in that it shares only 39% identity with the PITP domains of these Class I PITPs (Garner et al., 2012). Unlike PITP α and PITP β , PTPNC1 binds/exchanges PtdIns and PtdOH in vitro, but does not efficiently exchange PtdCho (Garner et al., 2012). PTPNC1 also binds PtdIns4P in crude lipid overlay and vesicle binding experiments (Halberg et al., 2016). No PTPNC1 crystal structures are available but, as expected, molecular modeling analyses indicate this protein assumes a typical START-like PITP fold (our unpublished data). PTPNC1 is encoded by a single gene on chromosome 17 and two splice variants have been described. Splice variant 1 (PTPNC-sp1) is the larger of the two (332 amino acids, 38 kDa) and contains a longer C-terminus (80 versus 16 amino acids) than splice variant 2 (PTPNC-sp2) the shorter variant (268 amino acids, 32 kDa) (Garner et al., 2011). Mammalian PTPNC1 mRNA is expressed in heart muscle kidney liver, brain, testes and peripheral blood leukocytes (Takano et al., 2003; Fullwood et al., 1999). The two splice variants display distinct expression patterns in the developing mouse brain, suggestive of differing functions (Takano et al., 2003). PTPNC1-sp1 is expressed in mouse heart and brain—especially in the dentate gyrus, thalamus and cerebellar Purkinje cells (Garner et al., 2011; Takano et al., 2003). Moreover, PTPNC-sp1 binds 14-3-3 proteins following phosphorylation of Ser²⁷⁴ and Ser²⁹⁹ in its C-terminus with the result that the protein is spared from degradation (Garner et al., 2011). By contrast, the shorter PTPNC-sp2 does not interact with 14-3-3 proteins.

The PTPNC1 PTP-domain is also reported to have a protein-binding activity as it interacts with ATRAP (angiotensin II type I receptor-associated protein), and this interaction promotes PTPNC1 membrane recruitment (Garner et al., 2011). Moreover, PTPNC1 is described as a pro-angiogenic gene (Png et al., 2011), is amplified in approximately 46% of breast cancers, and is highly expressed in metastases of breast, melanoma, and colon tumors (Halberg et al., 2016). In that regard, PTPNC1 is a major target of the miR-126 microRNA which downregulates PTPNC1-expression and inhibits breast cancer cell angiogenesis and lung metastasis (Png et al., 2011; Zhang et al., 2013). PTPNC1 is suggested to promote enhanced secretion of tumorigenic/metastatic proteins via enhanced membrane recruitment of GOLPH3 and the Rab1B GTPase to TGN membranes (Halberg et al., 2016). Given ample precedent, it is an attractive possibility that PTPNC1 does so by expanding the TGN PtdIns4P pool. The observation that PTPNC1 itself binds PtdIns4P suggests the possibility of a positive feedback loop where PTPNC1 regulation of PtdIns4P levels promotes its own recruitment to TGN membranes (Halberg et al., 2016).

Recent studies in zebrafish link PTPNC1 to regulation of circadian rhythm (Ashlin et al., 2018). Zebrafish express two PTPNC1 isoforms. PTPNC1a (331 amino acids, 81% identity and 90% similarity to human PTPNC-sp1) is expressed from a structural gene that resides on chromosome 3, whereas PTPNC1b (305 amino acids; 81% primary structure identity and 90% similarity to human PTPNC-sp1) is expressed from a structural gene that resides on chromosome 16. Only the longer zebrafish PTPNC1a variant possesses the conserved 14-3-3 protein interaction motif found in mammalian PTPNC-sp1, but both isoforms contain the conserved residues T₅₉, K₆₁, E₈₆ and N₉₀, which coordinate interaction with the PtdIns headgroup (Tilley et al., 2004). PTPNC1a and -PTPNC1b display distinct tissue and subcellular distributions in vivo. PTPNC1a expressed in larval and adult brain but not in heart, liver, eye, skin or muscle (Ashlin et al., 2018). By contrast, PTPNC1b is not widely expressed in the CNS. It is transiently expressed in developing brain ventricles at 48 h post fertilization, in the pronephric duct, in pharyngeal arches, and in olfactory vesicles (Ashlin et al., 2018). PTPNC1a null zebrafish appear overtly normal but display aberrantly elevated neuronal activity in arousal related circuits and increased wakefulness across the day/night cycle. The PTPNC1 deficit was associated with elevated insulin-like growth factor (IGF) signaling in the brain (Ashlin et al., 2018).

Increases in IGF brain signaling are linked to increased brain growth (Duan et al., 1999) and PTPNC1a null fish also displayed significant increases in brain width and a trend towards increased length (Ashlin et al., 2018). Inhibition of IGF pathways in the PTPNC1a null zebrafish was sufficient to rescue neuronal and behavioral hyperactivity (Ashlin et al., 2018). The link between

PITPNC1 and IGF-signaling may also apply to mammalian systems since PITPNC1 acts upstream of secretion of insulin growth factor binding protein 2 (IGFB2) in miR-126 regulated metastasis (Halberg et al., 2016; Png et al., 2011). Also consistent with a role in insulin signaling, polymorphisms in the PITPNC1 gene are associated with type 2 diabetes mellitus (Greenawalt et al., 2012; Liu et al., 2017).

3. Type 2 START-like PITPs

3.1. *PITPnm1*, *PITPnm2* and *PITPnm3*

Mammalian PITPnm1 (also termed Nir2, m-rdgB1, PITPnm α , and mrdgB α), PITPnm2 (Nir3 or m-rdgB2, PITPnm β) and PITPnm3 (Nir1) are homologs of the PITP-domain-containing *Drosophila* retinal degeneration B (rdgB) protein. Multiple naming systems are used for these proteins. Herein we adhere to the ‘nm’ acronym, which refers to the presence of six short hydrophobic sequences in these proteins. These hydrophobic regions were initially believed to constitute a multiple pass trans-membrane module, although PITPnms are now established to be tightly-associated peripheral membrane proteins (Takano et al., 2003; Lu et al., 1999; Litvak et al., 2002). The other commonly used ‘Nir’ acronym acknowledges the interaction of mammalian paralogs of the *Drosophila* RdgB α with the Pyk2 tyrosine kinase—leading to the designation ‘Pyk2 N-terminal domain-interacting receptor’ (Lev et al., 1999). As expression of the full-length mammalian PITPnm1 ortholog is able to functionally substitute for RdgB in flies (Chang et al., 1997) (Lu et al., 1999; Lev et al., 1999; Chang et al., 1997; Allen-Baume et al., 2002), the fly RdgB α and mammalian PITPnm1 and PITPnm2 likely operate via similar functional mechanisms.

Mammalian PITPnm1 and PITPnm2 exhibit N-terminal PITP domains, which display ~40% sequence identity at the amino acid level with mammalian PITP α and PITP β (Fullwood et al., 1999; Lu et al., 1999). PITPnm3 lacks a PITP-domain and will only be briefly mentioned here. Unlike type I START-like PITPs, class II PITPs are multi-domain proteins. PITPnm1 is arguably the best studied of the mammalian PITPnm proteins. Its subcellular localization is variously assigned to the cytoplasm (Kim et al., 2016), the Golgi system (Peretti et al., 2008; Litvak et al., 2004, 2005; Kim et al., 2013), ER membranes (Peretti et al., 2008; Amarilio et al., 2005) lipid droplets (Litvak et al., 2002) and the cleavage furrow during cytokinesis (Litvak et al., 2004). PITPnm1 is also reported to translocate to the plasma membrane (PM) (Peretti et al., 2008; Kim et al., 2013; Amarilio et al., 2005) or to ER-PM membrane contact sites (MCS) following agonist-mediated stimulation of cells (Kim et al., 2015, 2016). One study reports PITPnm1 primarily localizes to the Golgi system in interphase cells (Litvak et al., 2004, 2005), and that the N-terminal PITP-domain is required for this localization (Kim et al., 2013). PITPnm proteins possess FFAT (two phenylalanines in an acidic tract, EFFDAxE) motifs which play important roles in localization and function and will be further discussed below (Amarilio et al., 2005; Loewen et al., 2003). PITPnm1 interaction with the ER is attributed to interaction of the FFAT-domain with the ER resident protein VAP (VAMP-associated protein) (Peretti et al., 2008; Amarilio et al., 2005).

The highly conserved PITPnm C-termini contain 130aa long LNS2 (Lipin/Nde1/Smp2) domains which are also critical for localization. These haloacid dehalogenase (HAD)-like domains were first described in lipins as Mg²⁺-dependent PtdOH phosphatase (PAP) modules that convert PtdOH to DAG (Han et al., 2006; Donkor et al., 2007). The PITPnm LNS2 domains exhibit substitutions for a critical catalytic aspartate residue and therefore lack PAP-activity. Instead, LSN2 domains are hypothesized to serve as PtdOH-binding modules, and the PITPnm1 LNS2-module binds PtdOH in liposome-sedimentation assays (Kim et al., 2013). The LNS2-domain is implicated in targeting of PITPnm1 to the PM upon stimulation of cells with EGF or upon addition of exogenous PtdOH to cells (Kim et al., 2013).

PITPnm proteins also contain conserved, yet poorly characterized, 180aa long DDHD-domains that too show lipid-binding activities. These domains are identified by signature DDHD residues which form a putative metal-coordination motif found in phosphoesterases. Such domains are essential for the catalytic activities of mammalian phospholipase A₁ isoforms—specifically PtdOH-preferring phospholipase A₁ (PA-PLA₁) and KIAA0275p (DDHD2). Mutational analyses of KIAA0275p indicate the DDHD-domain cooperates with the adjacent sterile alpha domain motif (SAM) to bind PtdIns4P in vitro, and to target the proteins to Golgi membranes in vivo (Inoue et al., 2012; Klinkenberg et al., 2014). The isolated DDHD domain associates with PtdIns4P-rich Golgi membranes—in particular the ER-Golgi intermediate compartment (ERGIC), cis-Golgi and TGN (Klinkenberg et al., 2014). In crude lipid overlay assays, GST-DDHD fusion proteins display promiscuous binding to acidic phospholipids such as PtdIns4P and PtdOH. Specificity of binding to these phospholipids is enhanced in the presence of the SAM sequence (Klinkenberg et al., 2014).

3.2. Cellular functions of PITPnm1

With regard to cellular functions for PITPnm proteins, PITPnm1 is linked to membrane fission and vesicle biogenesis at the TGN (Litvak et al., 2005). PITPnm1 depletion in cells was observed to result in swelling and dispersal of Golgi cisternae accompanied by the inability of cargo to exit the Golgi complex. Rather, cargo was retained in Golgi tubules as a result of decreased Golgi DAG—likely as a result of elevated consumption by the CDP-choline pathway for PtdCho biosynthesis (Litvak et al., 2005). This interface with the CDP-choline pathway essentially recapitulates the metabolic cross-talk described for the yeast Sec14 PITP and the CDP-choline pathway (Cleves et al., 1991; Bankaitis et al., 2010; Ile et al., 2006; Kearns et al., 1997).

While the role of PtdIns4P signaling in the PITPnm1-mediated Golgi trafficking scheme is suggested to be secondary, and perhaps nonessential, this conclusion was based on the lack of significant effect of PITPnm1 knockdown on targeting of a single PtdIns4P probe (PH-OSBP) to the TGN (Litvak et al., 2005). Given the caveats associated with use of such probes as indirect reporters of phosphoinositide mass, this conclusion should be considered tentative. However, the involvements of PITPnm1 and PITPnm2 at inter-organelle membrane contact sites, and their roles at such sites in cell physiology and signaling define active topics of discussion in contemporary

cell biology.

3.3. PITPnm proteins and membrane contact sites

Membrane contact sites (MCSs) are defined as regions within the cell where two membranes are in close (10–20 nm) apposition to each other (Friedman and Voeltz, 2011; Levine, 2004; Helle et al., 2013). There are numerous examples of these including MCSs between the ER and PM (Manford et al., 2012; West et al., 2011), and the ER and TGN (Ladinsky et al., 1999). Typically, MCS assemblies harbor at least one protein proposed to possess lipid-transfer ability (Levine, 2004; Helle et al., 2013; Lev, 2010). At the ER-Golgi MCSs these include: PITPnm1 (Litvak et al., 2005), the ceramide transfer protein (CERT) (Hanada et al., 2003); the glucosylceramide transporter four phosphate adaptor protein 2 (FAPP2) (D'Angelo et al., 2007), and oxysterol binding protein (OSBP) and its related paralogs (ORPS) that are proposed to sense or transfer sterol (Mousley et al., 2012; Raychaudhuri et al., 2006; Beh and Rine, 2004; Perry and Ridgway, 2006; Wang et al., 2008). A number of proteins at ER-Golgi membrane contact sites (including CERT and specific ORPs) contain both PH-domains that bind PtdIns4P, and FFAT-motifs thought to promote ER-Golgi tethering by bridging interactions with Golgi phosphoinositides and ER-localized FFAT receptors (VAPs), respectively.

There are various proposals that PITPnm proteins function at ER-TGN contact sites and at ER-PM contact sites. In both cases, the PITPnm proteins are conceptualized as functioning in PtdIns supply from ER membranes to the partner membrane that consumes its PtdIns resources in driving phosphoinositide signaling. For example, PITPnm1 is proposed to function at ER-TGN MCSs to establish/maintain TGN PtdIns4P pools to facilitate docking of PtdIns4P binding effector proteins such as oxysterol binding protein and ceramide transfer protein (Peretti et al., 2008). This hypothesis is based on demonstrations that PITPnm1 localizes to the ER-TGN MSC through interaction of its FFAT motif with ER-localized VAPs (Peretti et al., 2008). The role of the FFAT domains is evolutionarily conserved as evidenced by the fact that FFAT-domain/VAP interaction is also required for localization of *Drosophila* RdgB α (the PITPnm1 homolog) to sub-microvillar cisternae. That is, specialized ER compartments at the base of the rhabdomere plasma membrane, structures bearing similarity to ER-PM MCSs (Yadav et al., 2016).

PITPnm1 and PITPnm2 are reported to play important roles at ER-plasma membrane junctions as well. In this case, PtdIns-loaded PITPnm1 is proposed to sense PLC-mediated PtdIns(4,5)P₂ hydrolysis at the plasma membrane via its recruitment to the plasma membrane—a recruitment specified via a distinct PtdOH-binding site exhibited by PITPnm1 (Chang and Liou, 2015). This recruitment is driven by conversion of PLC-generated DAG to PtdOH, and it is this pool that recruits PITPnm1 for PM resupply with PtdIns transported from the ER by PITPnm1. This model is based on observations that: 1) PITPnm1 translocates to MCSs during PLC-activation, 2) levels of PtdIns(4,5)P₂ are reduced in PITPnm1-depleted cells (Kim et al., 2013, 2015; Chang et al., 2013), 3) PITPnm-depleted cells show blunted DAG and Ca²⁺ responses (Kim et al., 2013, 2015; Chang et al., 2013), 4) PtdOH accumulates in PITPnm1-depleted cells, and 5) PITPnm1 removes PtdOH from the PM via its PITP-domain (Kim et al., 2015). Since levels of PtdIns and PtdIns4P were also lower in PITPnm1-depleted cells it is suggested that PITPnm1 plays a role in basal regulation of lipid pools (Kim et al., 2015). PITPnm1 and PITPnm2 are proposed to work in concert in this role but in different capacities. PITPnm1 powers PtdIns resupply during receptor-stimulated phosphoinositide hydrolysis whereas PITPnm2 supplies PtdIns in resting cells (Chang and Liou, 2015).

The proposed role of PITPnm1 at MCSs is consistent with some data from functional characterizations of the *Drosophila* RdgB α with regard to its role in fly photoreceptor-cell homeostasis and maintenance of an appropriate light response (Chang et al., 1997; Hotta and Benzer, 1969; Guo and Yu, 1997). Basal levels of PtdIns(4,5)P₂ are lower in the retina of *Drosophila* RdgB α PITP loss-of-function mutants. Furthermore, RdgB α -deficient retina are unable to replenish PtdIns(4,5)P₂ levels at the photoreceptor PM following light-stimulation, and elevated PtdOH levels suggest alterations in PtdOH-signaling (Yadav et al., 2015). Interpretation of those data is complicated, however. Rhodopsin levels are reduced in these mutants, perhaps as a mechanism to cope with hyper-active PLC signaling, and mutant flies are unable to terminate signaling following a single light pulse (Milligan et al., 1997b; Trivedi and Padinjat, 2007). The inability to terminate signaling is not easily consistent with RdgB α acting in a simple PtdIns supply role. Acting in this capacity, lack of RdgB α would be predicted to terminate signaling prematurely following PtdIns(4,5)P₂ depletion (Grabon et al., 2019).

Perhaps the most striking finding is that the RdgB α PITP domain alone is sufficient for full execution of RdgB α functions in vivo—i.e. that some 80% of the RdgB α (including the FFAT, DDHD and LNS2 domains discussed above) is functionally dispensable. The data are truly remarkable as expression of the RdgB α PITP domain alone fully rescues the retinal degeneration and photoresponse defects of *rdgb* null flies (Milligan et al., 1997b; Vihtelic et al., 1993). These data are at not easily reconciled with the basic tenets of the membrane contact models as proposed for the PITPnm proteins, as it is not obvious how the PITP domain by itself could efficiently engage in a MCS.

3.4. PITPnm function from the perspective of the organism

Since RdgB α deficits in *Drosophila* result in a dramatic retinal degenerative disease, the PITPnm proteins have been considered as attractive candidates for identification of molecular mechanisms underlying mammalian retinopathies (Ocaka et al., 2005). To date, however, there is no evidence to support this case for PITPnm1 or PITPnm2—despite the fact that PITPnm1 is able to complement fly RdgB α deficiency (Lu et al., 1999; Lev et al., 1999; Allen-Baume et al., 2002). Mammalian PITPnm1 is widely expressed. High levels of expression are detected within the inner ear, particularly in the inner hair cells of the organ of Corti, from late embryonic stages until adulthood. PITPnm1 is also transiently expressed in the outer hair cells during early postnatal stages (Carlisle et al., 2013). While ablation of the PITPnm1 gene was originally concluded to result in preimplantation lethality in mice (Lu et al., 2001), a later study reported this gene to be non-essential for murine development—in agreement with studies in flies and worms that establish PITPnm1

counterparts in those organisms are also non-essential for viability. PITPnm1-null mice are viable, fertile and without hearing defects. The only reported defect is a reduction in circulating cholesterol levels in male homozygotes (Carlisle et al., 2013). PITPnm1 might also be dispensable in humans since 5% of the population express a truncated PITPnm1 protein encoding only the PITP domain (Lek et al., 2016). To date, the available data only indicate presence of the truncation in heterozygotes, it is currently unclear if the homozygous condition in humans is lethal or if those individuals have yet to be identified (Grabon et al., 2019).

PITPnm2 exhibits a more-restricted and neuronal-specific expression pattern than PITPnm1 (Lu et al., 1999; Lev et al., 1999; Allen-Baume et al., 2002) but, like the case of PITPnm1 nullizygous mice, PITPnm2 knockout mice are also viable, fertile and exhibit no obvious phenotype. Moreover, PITPnm2 deficient mice do not display photoreceptor deficits—even at an advanced age (Lu et al., 2001). The extent to which the lack of phenotype in *Pitpnm1* null mice reports a potential functional redundancy with Pitpnm2 or Pitpnm3 remains to be determined (Carlisle et al., 2013). Mutations in the PITP-domain-lacking PITPnm3 however, are associated with the inherited retinal dystrophy cone rod dystrophy 5 (Cord 5) disease which is characterized by severe vision loss, and arteriovenous brain malformations (BAVM) (Kohn et al., 2007, 2010). BAVM is a rare condition resulting in abnormal connections between the arteries and veins of the brain. While typically asymptomatic, this syndrome can lead to hemorrhaging and seizures.

3.5. PITPs as prototypes for other signaling nanoreactors?

The PtdIns ‘presentation’ model in effect views the PITP as a nanoreactor that solves the substrate accessibility problem for PtdIns 4-OH kinases, and provides a novel mechanism for addressing the biological problem of diversifying the biological outcomes of PtdIns4P signaling. Recent work suggests a nanoreactor-type lipid presentation mechanism applies also to other aspects of PIP signaling. Like PITPs, the mammalian tumor necrosis factor- α -induced protein 8-like (TIPE-proteins [also called TNFAIP8-like, or TNFAIP8L]) exhibit phospholipid-transfer activity in vitro, and are proposed to act as nanoreactors that present phosphoinositides to the appropriate enzymes for modification (Fayngerts et al., 2014).

The mammalian TIPE protein family is comprised of four members: TNFAIP8 (tumor necrosis factor- α -induced protein 8), TIPE1 (TNFAIP8-like 1, or TNFAIP8L1), TIPE2 (TNFAIP8L2), and TIPE3 (TNFAIP8L3). These proteins play critical roles in inflammation, immunity, autophagy, cell death, and tumorigenesis (Goldsmith and Chen, 2017a; Bordoloi et al., 2018; Sun et al., 2008). As such, functional derangements in TIPE proteins are implicated in the pathology of human disorders such as: 1) inflammatory diseases such as atherosclerosis, colitis, and arthritis; 2) infectious disease such as *Listeria*, and Hepatitis-B and -C; 3) liver fibrosis; 4) neuromuscular and neurodegenerative disease, including Parkinson’s disease, and Myasthenia gravis, an autoimmune, neuromuscular disease; 5) choroidal neovascularization (CNV); 6) diabetes; 7) restenosis; and 8) cancers of the lung, esophagus, cervical, ovary, pancreas, colon, and in lymphoma (Fayngerts et al., 2014; Bordoloi et al., 2018; Goldsmith and Chen, 2017b). All known members of the family are implicated in tumorigenesis and are reported to display dysregulated expression profiles (frequently upregulation) in a number of tumor states (Bordoloi et al., 2018; Padmavathi et al., 2018). TIPE protein signaling is implicated in all stages of tumor development including: initiation, promotion, and progression (reviewed (Padmavathi et al., 2018)). Importantly, the TIPE family offer prognostic, diagnostic, and therapeutic potential for cancer and other disease states (Bordoloi et al., 2018; Padmavathi et al., 2018). A clear understanding of the biology of TIPE proteins is therefore of critical importance. Studies investigating ligand-binding by TIPE proteins promise to inform the development of small molecular inhibitors allowing therapeutic intervention of TIPE protein regulated pathways.

The ligand-binding mechanisms of TIPE proteins is an understudied area of research. However, key similarities between START-like PITPs and TIPE proteins indicate that PITP studies will likely prove informative in this area. All TIPE protein family members are able to bind PtdIns(3,4)P₂, PtdIns(3,5)P₂, PtdIns(4,5)P₂, PtdIns4P, PtdIns(3,4,5)P₃, and PtdOH. TIPE proteins are currently proposed

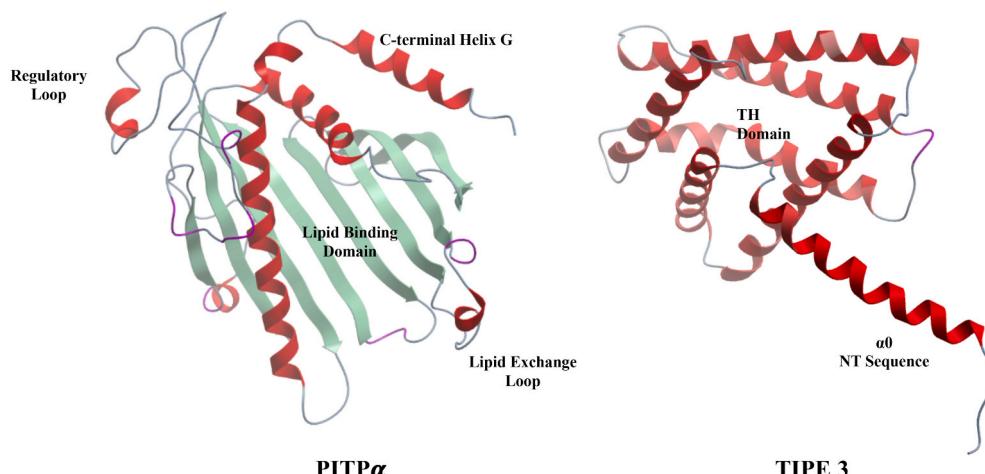


Fig. 5. Crystal structures of (a) PITP α and (b) TIPE3 are shown. The positions of the lipid-binding domain, the TH-domain, and regulatory regions are highlighted.

to be PtdIns(4,5)P₂ and PtdIns(3,4,5)P₃ transfer proteins on the basis of their abilities to extract and transfer PtdIns(4,5)P₂ and PtdIns(3,4,5)P₃ between distinct vesicle populations *in vitro* (Fayngerts et al., 2014). In this regard, TIPE3 is postulated to control the distribution and abundance of PtdIns(4,5)P₂ and PtdIns(3,4,5)P₃ by presenting lipid substrate to the kinase and enhancing PtdIns 3-OH kinase (PI3K) activity (Fayngerts et al., 2014). The ability of TIPE3 to enhance activity *in vitro* suggests that, rather than acting as a bona fide transfer protein, TIPE3 functions as a presentation module in a manner similar to that of PITPs (Fayngerts et al., 2014). In this capacity, TIPE3 presents PtdIns(4,5)P₂ to PI3K resulting in localized production of PtdIns(3,4,5)P₃.

3.6. TIPE protein structure

Structural insights suggest similarities between TIPE and PITPs. Crystal structures are available for TIPE2 (PDB ID 3F4M) and TIPE3 (PDB ID 4Q9V). Like the Sec14-like and START-like PITPs, both TIPE proteins possess a single hydrophobic phospholipid-binding pocket (Fayngerts et al., 2014; Zhang et al., 2009). Moreover, the TIPE proteins contain a distinct and characteristic structural fold (Fig. 5). The TIPE2-homology (TH) domain is evolutionarily conserved and found across the eukaryotic kingdom. It consists of six antiparallel α -helices (α 1– α 6) and has a large centrally-located hydrophobic cavity (20 Å deep, 10 Å wide). Structural and mutagenesis data suggest that the lipid acyl chains partition into the hydrophobic cavity formed by the TH-domain α 1– α 6 helices—with the result that the inositol head group is solvent accessible (Zhang et al., 2009). Despite the distinct nature of the TIPE-fold, computer modeling suggests the phospholipid-binding mode follows a similar strategy to that of the START-like PITPs in which the inositol head group is disposed towards the protein surface while the acyl chains are buried within the hydrophobic pocket (Grabon et al., 2017, 2019). Computer modeling studies further suggest that the negatively charged phosphoinositide headgroup engages positively charged amino acids of the α 0 via electrostatic interactions (Antony et al., 2016). This α 0 helix, along with residues at the entrance of the binding-pocket cavity, is positioned appropriately to function as a flexible “lid” regulating phospholipid access and exchange through a mechanism similar to that provided by the PITP helical gate.

Analyses of TIPE proteins indicate other features shared with PITPs (Fig. 5). Like START-like PITPs, TIPE2 presents a hydrophobic phosphoinositide binding-domain (TH-domain). Furthermore, TIPEs display a bipolar distribution of surface electrostatic charge as do START-like PITPs (Fig. 6). In this regard, the TIPE electropositive charge is concentrated towards the mouth of the TH-domain while electronegative charge is enriched at the back of the protein—forecasting how the TIPE protein docks onto the membrane surface and how it engages PIPs. The physiological relevance of PIP binding is supported by naturally-occurring mutations in the TIPE3 TH-domain that impair PIP binding and result in significant diminutions in biological activity (Fayngerts et al., 2014). Structural determination of the full-length TIPE bound to PIPs will provide further insight into the precise nature of TIPE-PIP binding, and promises more instructive comparisons of PITP and TIPE binding modes.

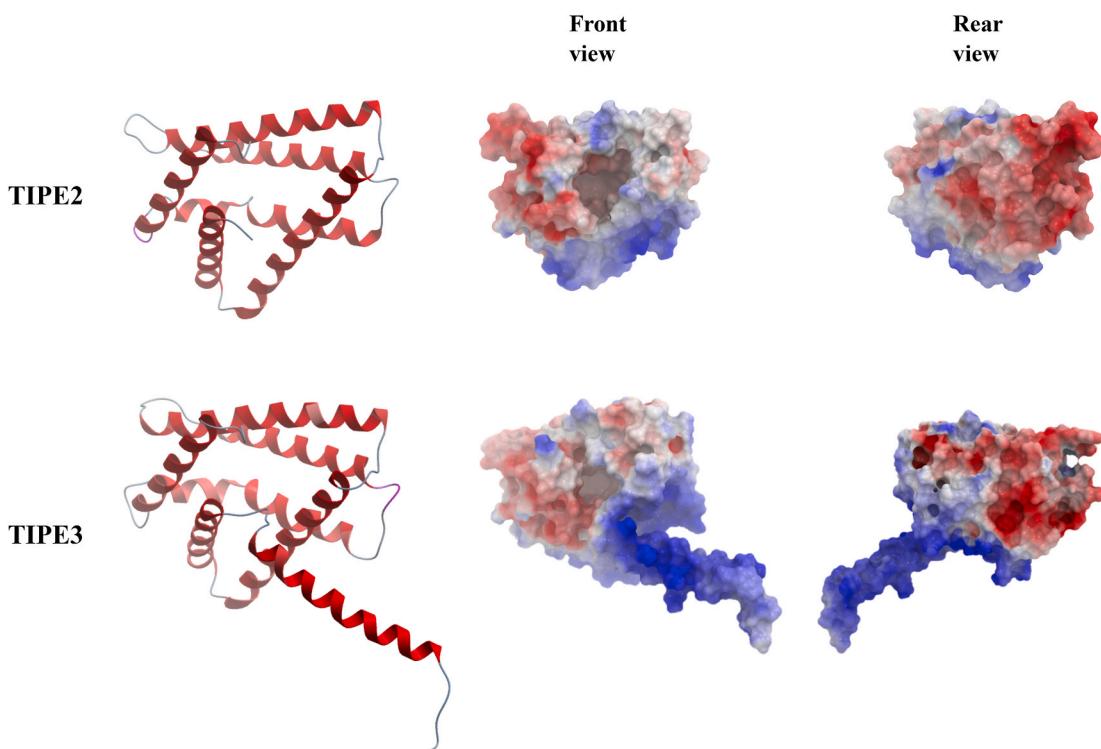


Fig. 6. Structural models of TIPE2 (top panels) and TIPE3 (bottom panels). Electrostatic surface potentials of each protein (front and rear view) are indicated (middle and right). Blue and red regions indicate electropositive and electronegative surface potentials, respectively.

Despite the high homologies shared by the TH-domains, and similarities in phospholipid-binding specificities, TIPE proteins execute diverse and even opposing functions. While the conserved TH-domain is responsible for their lipid binding activities, the function of at least one of the family members is regulated by other protein domains. The TIPE3 structure consists of an N-terminal α 0 helix, absent from TIPE2, as well as six additional helices (α 1– α 6) common to both proteins (Fayngerts et al., 2014). This unique 19 amino acid N-terminal sequence is not present in other TIPE family members, and this element is functionally critical for cell growth and survival. By contrast, a form of TIPE3 deleted for the N-terminal region behaves as a dominant negative (Fayngerts et al., 2014).

4. Nuclear inositol signaling

While this review focuses on the roles of PIPPs in regulating cytoplasmic PIP signaling, it is now clear that the nucleus runs a distinct phosphoinositide cycle (Martelli et al., 2004; Visnjic and Banfic, 2007). Pioneering studies to this effect documented specific modulations of PtdIns(4,5)P₂ synthesis in purified nuclei that were not apparent in bulk phosphoinositide pools (Cocco et al., 1987). Such compartment-specific regulation is also observed *in vivo* as evidenced by demonstrations that agonist stimulation of the cytoplasmic PIP cycle does not activate the nuclear PIP cycle and vice versa (Martelli et al., 2004). This compartment-specific regulation reflects the fact that nuclei host their own specific cohorts of phosphoinositide metabolizing enzymes. The nuclear PIP and soluble inositol-phosphate products generated by those enzymes regulate a myriad of processes that include chromatin remodeling and gene transcription, nucleolar processes, cell survival, and mRNA processing and export (Tsui and York, 2010). As example of its complexity, the nucleus harbors four isoforms of PLC (γ , β , ζ , and δ), all of which hydrolyze PtdIns(4,5)P₂, but each PLC isoform couples to a distinct biological outcome (Visnjic and Banfic, 2007).

While the evidence for a nuclear PIP cycle is compelling, the data indicate the PIP pools in the nuclear matrix, and nuclear matrix lipid pools in general, are small (Tribble et al., 2016). The scale suggests that essentially all lipids in the nuclear matrix can be accommodated by binding to proteins. In that regard, nuclear PIPs localize to distinct endonuclear compartments such as the nucleolus, nuclear lipid islets, nuclear speckles, and nuclear matrix. PtdIns(4,5)P₂ is detected in nuclear lipid islets, membrane-less PIP₂-containing structures, and this lipid interacts directly with components of the transcription processing machinery, chromatin remodeling, or splicing (Sztacho et al., 2019). Besides the nuclear enzymes involved in the PIP cycle, intranuclear proteins such as lamin B, DNA and RNA polymerases, and transcription factors also associate with PIPs. This association has functional consequences as PIPs enhance the enzymatic activities of certain nuclear proteins such as DNA polymerase (Cocco et al., 1994). These regulatory actions are achieved by the interaction of nuclear PIPs with proteins via PIPNs binding domains (PH, PX, ENTH, etc) and short polybasic PIP-binding motifs or regions (PBR). The PBRs are a predominant theme for how proteins engage PIPs in the nucleus (Reviewed in (Jacobsen et al., 2019)).

A major question that remains unresolved in the nuclear PIP field is how PtdIns is imported into the nuclear matrix. One possibility is that the inner nuclear membrane is the site at which engagement of PtdIns with PtdIns-kinases occurs, but the idea that PIPPs or TIPEs could play a role is a plausible one. While PIP α localizes to the nucleus of mammalian cells, and its ability to bind PtdIns is a contributing factor to the targeting of this PIP to the nucleus, dynamic lipidomics experiments suggest this PIP does not significantly affect the rate of PtdIns import into the nuclear matrix (Tribble et al., 2016). Nonetheless, the question of how PtdIns is imported into the nucleus, and the potential roles of lipid transfer proteins in either PtdIns import, or in facilitating nuclear metabolism of PtdIns and PIPs, is one worthy of attention.

5. Conclusions

The highly diverse biological activities of phosphoinositides collectively describe a major intracellular signaling system in eukaryotic cells. It is therefore no surprise that derangements in phosphoinositide metabolism are recognized as the basis underlying the pathologies associated with an ever-increasing roster of diseases in mammals—including humans. However, while much attention is presently being invested in understanding the mechanisms by which the inositol lipid kinases and the opposing inositol lipid phosphatases are regulated, the mechanisms by which phosphoinositide signaling is diversified from a rather simple chemical code to an impressive array of biological outcomes remains incompletely understood. In that regard, PIPPs are taking a rightful place at the center stage—not only as molecular nanoreactors that potentiate PtdIns 4-OH kinase signaling, but also as adaptors that link various arms of the lipid metabolome to the activation of PtdIns 4-OH kinases. This interface defines an unappreciated mode of PtdIns kinase control that is central to mechanisms for diversifying PtdIns4P signaling. Moreover, the TIPE class of lipid-binding proteins forecasts this PIPP-like nanoreactor mode of lipid kinase regulation extends beyond the PIP/PtdIns 4-OH kinase interface to other PtdIns- and phosphoinositide kinases. This new frontier represents a fertile ground for future work in both: (i) understanding mechanisms of phosphoinositide signaling, and (ii) leveraging that information for purposes of translating fundamental science relating to the rational design of new pharmaceuticals for clinical purposes.

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Advances in Biological Regulation

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Erratum regarding missing Declaration of Competing Interest statements in previously published articles

Declaration of Competing Interest statements were not included in the published version of the following articles that appeared in previous issues of *Advances in Biological Regulation*.

The appropriate Declaration/Competing Interest statements, provided by the Authors, are included below.

“Nuclear organization mediates cancer-compromised genetic and epigenetic control” (*Advances in Biological Regulation*, 2018; 69C: 1–10) 10.1016/j.jbior. 2018.05.001 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“New advances in targeting aberrant signaling pathways in T-cell acute lymphoblastic leukemia” (*Advances in Biological Regulation*, 2019; 74C) 10.1016/j.jbior. 2019.100649 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“The regulation of normal and neoplastic hematopoiesis is dependent on microenvironmental cells” (*Advances in Biological Regulation*, 2018; 69C: 11–15) 10.1016/j.jbior. 2018.06.003 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“A synthetic biological approach to reconstitution of inositide signaling pathways in bacteria” (*Advances in Biological Regulation*, 2019; 73C) 10.1016/j.jbior. 2019.100637 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“ZEB2 in T-cells and T-ALL” (*Advances in Biological Regulation*, 2019; 74C) 10.1016/j.jbior. 2019.100639 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“Altered chondrocyte differentiation, matrix mineralization and MEK-Erk1/2 signaling in an INPPL1 catalytic knock-out mouse model of opismodysplasia” (*Advances in Biological Regulation*, 2019; 76C) 10.1016/j.jbior. 2019.100651 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“Galectins as regulators of cell survival in the leukemia niche” (*Advances in Biological Regulation*, 2018; 71C: 41–54) 10.1016/j.jbior. 2018.09.003 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“Lipid transfer proteins and instructive regulation of lipid kinase activities: Implications for inositol lipid signaling and disease” (*Advances in Biological Regulation*, 2020; 78C) 10.1016/j.jbior. 2020.100740 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“The inflammatory microenvironment that promotes gastrointestinal cancer development and invasion” (*Advances in Biological Regulation*, 2018; 68C: 39–45) 10.1016/j.jbior. 2018.02.001 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

“Modulation of sulfur assimilation metabolic toxicity overcomes anemia and hemochromatosis in mice” (*Advances in Biological Regulation*, 2020; 76C) 10.1016/j.jbior. 2020.100694 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

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“Lipidomics-based assays coupled with computational approaches can identify novel phospholipase A2 inhibitors” (*Advances in Biological Regulation*, 2020; 76C) 10.1016/j.jbior. 2020.100719 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

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“The function of PLC γ 3 in developing mouse mDA system” (*Advances in Biological Regulation*, 2019; 75C) 10.1016/j.jbior. 2019.100654 Declaration of competing interest: The authors were contacted after publication to request a Declaration of Interest statement.

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1. "Polyphosphoinositides in the nucleus: Roadmap of their effectors and mechanisms of interaction" [Advances in Biological Regulation, 2019; Volume 72C, 631: 7-21] 10.1016/j.jbior.2019.04.001

Declaration of competing interest: The Authors have no interests to declare.

2. "Phosphoinositide spatially free AKT/PKB activation to all membrane compartments" [Advances in Biological Regulation, 2019; Volume 72, 632: 1-6] 10.1016/j.jbior.2019.04.002

Declaration of competing interest: The Authors have no interests to declare.

3. "ABCC3 is a novel target for the treatment of pancreatic cancer" [Advances in Biological Regulation, 2019; Volume 73, 634] 10.1016/j.jbior.2019.04.004

Declaration of competing interest: The Authors have no interests to declare.

4. "Pancreatic cancer tumorspheres are cancer stem-like cells with increased chemoresistance and reduced metabolic potential" [Advances in Biological Regulation, 2019; Volume 72, 627: 63-77] 10.1016/j.jbior.2019.02.001

Declaration of competing interest: The Authors have no interests to declare.

5. "Lipid transfer proteins and instructive regulation of lipid kinase activities: Implications for inositol lipid signaling and disease" [Advances in Biological Regulation, 2020; Volume 78, 100740] 10.1016/j.jbior.2020.100740

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6. "Abilities of berberine and chemically modified berberines to interact with metformin and inhibit proliferation of pancreatic cancer cells" [Advances in Biological Regulation, 2019; Volume 73, 633] 10.1016/j.jbior.2019.04.003

Declaration of competing interest: The Authors have no interests to declare.

7. "ZEB2 in T-cells and T-ALL" [Advances in Biological Regulation, 2019; Volume 74, 100639] 10.1016/j.jbior.2019.100639

Declaration of competing interest: The Authors have no interests to declare.

8. "Nonsteroidal anti-inflammatory drugs and glucocorticoids in COVID-19" [Advances in Biological Regulation, 2021; Volume 81, 100818] 10.1016/j.jbior.2021.100818

Declaration of competing interest: The Authors have no interests to declare.

9. "Lipidomics-based assays coupled with computational approaches can identify novel phospholipase A2 inhibitors" [Advances in Biological Regulation, 2020; Volume 76, 100719] 10.1016/j.jbior.2020.100719

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10. "MicroRNAs and their involvement in T-ALL: A brief overview" [Advances in Biological Regulation, 2019; Volume 74, 100650] 10.1016/j.jbior.2019.100650

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