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Minireview

Phospholipid transfer proteins in perspective

Karel W.A. Wirtz*

Bijvoet Center for Biomolecular Research, Section of Lipid Biochemistry, Utrecht University, Padualaan 8, 3584CH Utrecht, The Netherlands

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Abstract Since their discovery and subsequent purification from mammalian tissues more than 30 years ago an impressive number of studies have been carried out to characterize and elucidate the biological functions of phosphatidylcholine transfer protein (PC-TP), phosphatidylinositol transfer protein (PI-TP) and non-specific lipid transfer protein, more commonly known as sterol carrier protein 2 (SCP-2). Here I will present information to show that these soluble, low-molecular weight proteins constitute domain structures in StArR-related lipid transfer (START) proteins (i.e. PC-TP), in retinal degeneration protein, type B (RdgB)-related PI-TPs (e.g. Dm RdgB, Nir2, Nir3) and in peroxisomal β-oxidation enzyme-related SCP-2 (i.e. 3-oxo-acyl-CoA thiolase, also denoted as SCP-X and the 80-kDa D-bifunctional protein). Further I will summarize the most recent studies pertaining to the physiological function of these soluble phospholipid transfer proteins in metazoa.

Keywords: Phospholipid transfer proteins; PC-TP; PI-TP; SCP-2; Cholesterol; Metazoa

1. Introduction

Transfer and exchange of phospholipids and cholesterol was initially observed in the serum between lipoproteins [1] as well as between chylomicrons and lipoproteins [2]. Given the low off-rate of these hydrophobic molecules at the lipid–water interface this spontaneous lipid redistribution did not reflect monomer transfer through the aqueous phase, but was interpreted to be due to collisions between particles. Apart from this rather unspecific, non-mediated transfer it was subsequently shown that plasma contains lipid transfer proteins, specifically cholesterol ester transfer protein (CETP) [3] and phospholipid transfer protein (PLTP) [4] both acting as specific mediators of lipid transfer between lipoproteins and lipoproteins and cells. CETP plays a key role in the conversion of very low density lipoprotein (VLDL) into low density lipoprotein (LDL) by replacing triglyceride for cholesterol ester. Among other activities PLTP is intimately involved with the modification of high density lipoprotein (HDL) and the removal of phospholipid and cholesterol from peripheral tissues by HDL.

Prior to the discovery of these plasma lipid transferring proteins it was observed that the membrane-free cytosol from mammalian tissues facilitated the transfer of phospholipids between subcellular organelles like mitochondria and microsomes [5]. In view of the experience with plasma lipoproteins it was assumed that the cytosol also contained lipoprotein-like structures which by collision with the organelles would give rise to lipid exchange and, thereby, act as mediators of lipid transfer between different organelles. However, the cytosol depleted from these cellular 'lipoproteins' kept its phospholipid transfer activity providing the first evidence that mammalian cells may contain proteins that mediate phospholipid transfer between membrane interfaces [6]. This observation has been the starting point of extensive efforts to purify these phospholipid transfer proteins (PL-TPs) from mammalian sources [7]. To date, three different classes of mammalian phospholipid transfer proteins (PL-TPs) are known; (i) phosphatidylcholine transfer protein (PC-TP), (ii) phosphatidylinositol transfer protein (PI-TP) and (iii) the non-specific lipid transfer protein, more commonly denoted as sterol carrier protein 2 (SCP-2) which is able to transfer a wide range of phospholipids including sterols. The 3D-structure of these proteins has been elucidated showing that despite a lack of primary structure homology, each protein has a hydrophobic cavity suited to accommodate a specific lipid ligand [8–10]. The exposure of this lipid binding site at the membrane interface is a prerequisite for these proteins to act as carriers of phospholipids and cholesterol (in the case of SCP-2) between membranes. Orthologues of PL-TPs have been identified in a great variety of organisms among which zebra fish, *Caenorhabditis elegans*, *Drosophila melanogaster*, yeast and plants. Despite many years of research the biological role of these PL-TPs is still much of an enigma. Here I will present the most current information on how these PL-TPs relate to other proteins and what cellular functions they may fulfill.

2. Intracellular phospholipid transfer proteins and domain structures

PC-TP. This 28-kDa protein is highly specific for phosphatidylcholine (PC) [11]. It belongs to the START (steroidogenic acute regulatory protein related transfer) domain superfamily of hydrophobic ligand-binding proteins. Since its 214-residue amino acid sequence makes up the actual START domain, PC-TP represents the minimal START protein structure. In

*Fax: +31 30 2522478.
E-mail address: k.w.a.wirtz@chem.uu.nl

Abbreviations: PC, phosphatidylcholine; PI, phosphatidylinositol; SPM, sphingomyelin; PIP_2, phosphatidylinositol 4,5-bisphosphate

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addition to PC-TP, this START protein superfamily comprises at least another 30 human proteins among which the steroidogenic MLN64, steroidogenic acute regulatory protein (StAR), p122-Rho GTPase activating protein, Goodpasture antigen-binding protein (GPBP) and a acyl-CoA thioesterase (KIAA0707) [12]. From the superposition of the structures known to date it is clear that the overall fold of PC-TP is similar to the START domain of MLN64 [9]. On the other hand, START domain proteins express different lipid affinities. StAR and MLN64, both involved in steroidogenesis, bind and transfer cholesterol [13], StarD10, a protein overexpressed in breast cancer, binds and transfers PC and phosphatidylethanolamine [14] whereas a splicing variant of GPBP is involved in the intracellular trafficking of ceramide [15]. It is to be noted that START proteins (e.g. PH domain proteins, RhoGAP proteins and PC-TP-like proteins) are also found in *C. elegans* and in *Drosophila*. An extensive family of START domain proteins is present in plants the majority of which belong to a novel class of putative lipid/sterol-binding homeodomain (HD) transcription factors [16]. These HD-START proteins may provide a mechanism by which lipid ligands can modulate transcription in plants.

SCP-2. This 13.2-kDa basic protein is also known as nonspecific lipid transfer protein (nsL-TP) for reasons that in vitro this protein lacks specificity facilitating the transfer of sterols and a great variety of phospholipids between membranes [17,18]. Extensive lipid binding studies emphasize the non-specific character of SCP-2 in that the lipid binding cavity can accommodate fatty acids, fatty acyl-CoA esters, PC, cholesterol, dehydroergosterol as well as their fluorescently labeled analogues [19]. The mammalian SCP-2 domain constitutes the C-terminal part of the 58-kDa peroxisomal 3-oxoacyl-CoA thiolase, also denoted as SCP-X [20,21] and of the 80-kDa D-bifunctional protein expressing 17β-hydroxysteroid dehydrogenase, fatty acid-CoA dehydrogenase and fatty acid-CoA hydratase activity [22]. Like SCP-2 either peroxisomal enzyme transfers 7-dehydrocholesterol and PC from small unilamellar vesicles to acceptor membranes in vitro. SCP-2 is formed by cleavage of SCP-X or from pre-SCP-2 both of which proteins are encoded by the gene *SCP-X* which has two separate promoters [23]. Owing to the AKL peroxisomal targeting sequence both SCP-X and pre-SCP-2 are imported into the peroxisomes by the Pex5p-mediated PTS1 pathway where these proteins are processed posttranslationally [24]. Despite the presence of the PTS-1 targeting signal, substantial amounts of SCP-2 are found in the cytosol possibly due to the modulation of the C-terminal PTS1, i.e. cleavage of the leucine residue [19,24,25]. At this point it is not known to what extent SCP-X and pre-SCP-2 contribute to the cytosolic SCP-2. On the other hand, overexpression of the cDNA encoding the 58-kDa SCP-X in transfected mouse L-cell fibroblasts provided clear evidence that apart from the peroxisomal localization significant amounts of SCP-X/SCP-2 were extraperoxisomal [26]. SCP-X carrying the SCP-2 domain is also commonly expressed in insects (e.g. mosquito *Aedes aegypti*, *Drosophila melanogaster*, cotton leafworm *Spodoptera littoralis*). In the mosquito SCP-X was predominantly found in peroxisomes and SCP-2 in the cytosol [27]. SCP-2 is also expressed in the peroxisomes of *Arabidopsis thaliana* being 54% similar to human SCP-2 [28]. Similarly, a SCP-2 domain has been detected at the carboxy-terminal end of UNC-24 a protein which is required for *C. elegans* to display normal locomotion [29]. It was suggested that this domain (64% similar to human SCP-2) may be tethered to the plasma membrane by the juxtaposed stomatin-like domain of UNC-24, and as such could be involved in lipid transfer between closely apposed membranes.

PI-TP. Mammalian cells express two soluble, 35-kDa PI-TPs, i.e. PI-TPα and PI-TPβ, which are highly homologous (>98% sequence identity). Initially purified from bovine brain cytosol, both isoforms act as carriers of phosphatidylinositol (PI) and PC between membranes in vitro, yet PI-TPβ can also transfer sphingomyelin (SPM) [30,31]. Another soluble PI-transferring protein is the 38-kDa retinal degeneration Bβ (MrdgBβ) which consists of a PI-TP-like domain (41% identical to PI-TPα) and a small carboxy-terminal domain [32]. MrdgBβ was identified by homology to the retinal degeneration protein (type B) in *Drosophila*, denoted as Dm rdgB [33]. Mammalian homologues of Dm RdgB are rdgB1 (Nir2) (1244 amino acids) and rdgB2 (Nir3) (1349 amino acids) both of which proteins carry an amino-terminal PI-TP domain and a highly conserved carboxy-terminal segment containing the tyrosine kinase Pyk2-binding domain [34]. The PI-TP domains of Nir2 and Nir3 are 45% identical to PI-TPα, 72% identical with each other and 65% identical with the *Drosophila* homologue. Recently the genomic organization of both soluble and membrane-associated *Drosophila* and human PI-TP-domain-containing genes was determined [35]. Phylogenetic analysis indicated that the gene lineage of PI-TPα and PI-TPβ and the membrane-associated Dm RdgB, Nir2 and Nir3 arose at a very early stage in human evolution. Apart from *Drosophila* [36], PI-TPs are also found in zebrafish [37], *C. elegans* and yeast [38] and as an amino-terminal domain of the COW1 protein in *Arabidopsis* [39]. It is to be noted that the COW1 PI-TP domain is 32% identical to the yeast PI-TP (Sec14 protein) which has neither sequence nor structural homology with metazoan PI-TPs.

3. PC-TP and phosphatidylcholine transport to the plasma membrane

Initially it was proposed that PC-TP is involved in the transfer of PC from its site of biosynthesis, the endoplasmic reticulum, to other subcellular organelles deficient in PC biosynthesis [7,40]. Isotope labeling studies showed that the translocation of newly synthesized PC to mitochondria and plasma membrane in living cells was very rapid with a half-time of equilibration of a few minutes, yet no conclusion could be drawn as to whether PC-TP was responsible for this rapid equilibration [41,42]. In view of its relatively high expression in liver and lung type II cells it was proposed that PC-TP may be involved in supplying PC to the canalicular membrane for secretion into bile or the production of lung surfactant. However, none of these functions appeared to be affected in *Pc-tp*$^{-/-}$ mice [43]. Although disruption of the *Pc-tp* gene did not affect the output of PC, bile salts and cholesterol into bile of *Pc-tp*$^{-/-}$ mice fed a chow diet, the secretion of these biliary components was impaired when these mice were fed a high-fat, high-cholesterol lithogenic diet [44]. This may indicate that under conditions of a dietary challenge PC-TP deficiency may result in a defect in the trafficking of the biliary components to the canilicular membrane. Although the role

of PC-TP in this trafficking process is unresolved, recent evidence indicates that PC-TP may participate in the regulation of hepatic cholesterol homeostasis possibly at the level of acyl CoA:cholesterol acyltransferase located in the endoplasmic reticulum [45]. Another line of evidence suggests that PC-TP is involved in the metabolism of HDL by modulating its particle size and rates of hepatic clearance in mice [46]. Moreover, PC-TP overexpressed in Chinese hamster ovary cells appears to contribute to the accelerated apolipoprotein A-1 (apoA-1)-mediated lipid efflux possibly by replenishing the plasma membrane with PC which becomes available during pre-β-HDL particle formation via ATP binding cassette A1 (ABCA1) [47]. One of the important questions is whether intracellular PC-TP activity is connected to HDL metabolism as controlled by plasma PLTP activity. A main function of plasma PLTP is the enlargement of HDL particles which is accompanied by the release of lipid-poor apoA-1 [48]. PLTP also plays a key role in the removal of excess cholesterol and phospholipids from peripheral cells via ABCA1 by HDL apolipoproteins [49,50]. These studies strongly suggest that the cellular function of PC-TP may be intimately linked to plasma PLTP activity. On the other hand, the lack of a clear phenotype in *Pc-tp*$^{-/-}$ mice may indicate that other START proteins (e.g. StarD7, StarD10 and Goodpasture antigen-binding protein) effectively fulfill the function of PC-TP (also denoted as StarD2) in these mice [12].

4. SCP-2 in cholesterol and fatty acid metabolism

In view of the occurrence of SCP-2 both in the cytosol and the peroxisomes it is reasonable to assume that these two SCP-2 pools are involved in different cellular processes. There is ample evidence that cytosolic SCP-2 plays a role in intracellular non-vesicular cholesterol transport to the plasma membrane as well as in the cellular uptake of cholesterol and fatty acids (for an extensive review, see [19]). As for peroxisomal SCP-2 it appears likely that this protein is involved in the peroxisomal β-oxidation of fatty acids possibly by facilitating the presentation of substrates to the enzymes involved. So it was shown that in situ SCP-2 was associated with acyl-CoA oxidase, the 41-kDa 3-oxoacyl-CoA thiolase (thiolase A) and bifunctional enzyme [25]. Based on in vitro evidence it was also proposed that the association of SCP-2 with the β-oxidation complex could be important for the protection of unsaturated fatty acid intermediates against oxidative attack by hydroxyl radicals generated in the peroxisomes from H_2O_2 [51]. A role in the cellular defense against oxidative damage is in line with SCP-2 and SCP-X being upregulated by the daf-16-like Forkhead transcription factor FOXO3a [51]. Previously these transcription factors have been shown to protect against oxidative stress by increasing the levels of the antioxidant enzymes MnSOD and catalase [52]. In addition to thiolase A which is responsible for the thiolytic cleavage of straight chain 3-oxoacyl-CoAs, peroxisomes contain a 58-kDa thiolase (SCP-X) which can be converted into a 46 kDa-thiolase by enzymatic removal of the carboxy-terminal SCP-2 domain [53]. This SCP-2/thiolase catalyzes the thiolytic cleavage of the 3-oxoacyl-CoA derivatives of the tetramethyl-branched chain pristanic acid. In agreement with this function, phytanic acid, the precursor of pristanic acid, accumulated 10-fold in SCP-2/SCP-X knockout mice [54]. Similarly, SCP-2/thiolase is critical for the thiolytic cleavage step of the steroid side chain of cholesterol as step in the conversion into bile acids [55]. Accordingly, bile and serum of SCP-2/SCP-X knockout mice displayed a pronounced accumulation of a characteristic derivative of the 3α,7α,12α-trihydroxy-24 keto-cholestanoyl-CoA bile acid precursor, the putative substrate of the SCP-2/thiolase. Subsequent studies on SCP-2/SCP-X knockout mice supported a role of SCP-2 in cholesterol metabolism, biliary lipid secretion and intracellular cholesterol distribution [56]. Recently, cytosolic SCP-2 was found to directly interact with caveolin-1, thereby fulfilling a function in targeting, among other lipids, PI to caveolae at the cell surface plasma membrane [57]. Given the long and winding road to understanding SCP-2 function one may expect that SCP-2 plays an intricate role in various aspects of intracellular lipid metabolism still to be discovered.

5. PI-TP is essential for intracellular signaling

The ability of PI-TPα and PI-TPβ to specifically bind and transfer PI and, be it with a lower affinity, PC and SPM (only PI-TPβ) is intriguing for the fact that the metabolism of these particular phospholipids is linked to lipid signaling pathways, thereby raising the question to what extent PI-TPs play a role in these pathways. In line with the hypothesis that PI-TP transfers PI from intracellular stores to the plasma membrane as part of the receptor-controlled phosphoinositide signaling pathway [58] ample evidence is now available that addition of PI-TPs to permeabilized cells stimulates the production of inositol phosphates (for reviews, see [59,60]). In these reconstitution studies PI-TPα and PI-TPβ appear to be equally effective. Given that PI-TPα localizes predominantly to the nucleus and cytoplasm and PI-TPβ to the Golgi complex [61–63] one wonders how in situ this intracellular localization can be reconciled with their proposed roles in phosphoinositide signaling at the plasma membrane. An explanation for this anomaly becomes the more pressing as murine embryonic stem (ES) cells deficient in PI-TPα developed normally during embryogenesis expressing all functions which were proposed to require PI-TPα [64]. On the other hand, PI-TPβ gene ablation failed to give viable ES cells again emphasizing that PI-TPα and PI-TPβ fulfill different cellular functions [64]. Very interestingly, *PI-TPα*$^{-/-}$ mice died early after birth stemming from complicated organ failure including spinocerebellar disease, hypoglycemia and intestinal and hepatic steatosis [65]. At an earlier stage, the phenotype of the *vibrator* mouse was found to be linked to a single mutation in intron 4 of the PI-TPα gene [66]. In mice homozygous in the *vibrator (vb)* allele, brain PI-TPα levels were fivefold reduced. These mice displayed progressive action tremor and degeneration of neurons in brain and spinal cord which led to early juvenile death. Either of the above studies failed to provide a satisfactory explanation as to why PI-TPα deficiency had such dire consequences for the survival of the mice. Recently evidence was provided that PI-TPα may be linked to the activation of a PI-specific phospholipase A_2 thereby being involved in the release of arachidonic acid and the subsequent production of an eicosanoid-like factor(s), that stimulates cell growth and inhib-

its apoptosis [67,68]. Given that this 'survival' factor protected cultured primary neurons against induced cell death it was proposed that the normal development of *PI-TPα*$^{-/-}$ mice embryos depended on a maternal supply of this factor lack of which caused early death after birth [69]. In support of this proposal, zebrafish embryos microinjected at the one-cell stage with PI-TPα-antisense oligonucleotides appeared to develop normally, yet displayed a loss of spinal-cord neurons and defects in motor-axon outgrowth [37]. In the latter study, however, this lack of axon outgrowth was interpreted to indicate that netrin-1 which is an extracellular signal for neurite extension, requires PI-TPα for its activity. Similarly, the moderate effect of netrin-1 on neurite outgrowth in cortical explants from homozygous vibrator mouse embryos (PI-TPα^{vb} mutant) as compared to wild-type explants was thought to be due to a lack of PI-TPα. This interpretation was based on the observation that netrin-1 was found to stimulate binding of PI-TPα to the netrin receptor DCC (deleted in colorectal cancer) in cultured mouse cortical neurons thereby increasing phospholipase C-induced hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2). Increased PIP_2 hydrolysis was not observed when netrin-1 was added to cortical neurons isolated from homozygous vibrator mice which are virtually devoid of PI-TPα. Hence, it was concluded that PI-TPα is required for netrin-1 stimulated PIP_2 hydrolysis thereby generating inositol phosphate signaling molecules which play an essential role in neurite outgrowth [37].

Different from mammals, *Drosophila* contains one soluble PI-TP encoded by *giotto (gio)* [36]. This 35-kDa protein, denoted as Gio, is about 60% identical to mammalian PI-TPs, yet based on phylogenetic analysis, Gio is closer to the β- than to the α-isoform. Very interestingly, neuroblasts and spermatocytes from *gio* mutants display cytokinesis failures. Moreover, evidence was obtained that Gio is involved in membrane-vesicle fusion as *gio* mutations in spermatocytes caused an abnormal accumulation of Golgi-derived vesicles. A mammalian membrane-associated PI-TP-like protein, Nir2, also plays an important role in membrane trafficking and cytoskeletal remodeling [70]. By delivering PI to specialized membrane sites containing PI 4-kinase both Gio and Nir2 are proposed to promote phosphatidylinositol 4-phosphate synthesis which would then lead to the formation of PIP_2, a lipid shown to be important in cytokinesis. Probably inherent to the failure to properly carry out mitotic and meiotic cytokinesis, ablation of either the mouse PI-TPβ (mammalian Gio orthologue) or Nir2 gene resulted in early embryonic death [64,71]. Recently, Nir2 was shown to be important for maintaining a diacylglycerol (DAG) pool in the Golgi apparatus which is critical for controlling protein transport from the *trans*-Golgi network to the plasma membrane [72]. In analogy with yeast PI-TPβ (Sec14p) it appears that Nir2 maintains the Golgi DAG pool by regulating its consumption via the CDP-choline pathway [73].

At this point many questions still remain on how PI-TPs act in the cell. Do these proteins act by being targeted to specific sites in the cell as proposed for the action of netrin-1 [37] and/or do they then deliver substrates directly to enzymes like PI 4-kinases and PI-specific phospholipase A_2 [74,75]? Another interesting suggestion is that by binding either PI, PC or SPM, PI-TPs act as biosensors thereby regulating phospholipid metabolism at distinct sites in the cell [73,76].

6. Conclusion

The soluble PL-TPs (PC-TP, PI-TP, SCP-2) have the unique property of being able to extract and bind a single lipid molecule from a membrane interface. The importance of this feature is reflected in these PL-TPs being identified as domain structures in a host of proteins, both soluble and membrane-associated. As such these PL-TPs are involved in a wide variety of essential cellular processes forming an interface between the hydrophobic domain of the membrane and the enzymes/proteins that need monomeric lipids for expressing their activity. With genetic information available one is now able to map PL-TPs in the total protein network which will undoubtedly lead to new insights in how these proteins play key roles in cell function.

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