Progress in Lipid Research 61 (2016) 30–39

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review

The orchestra of lipid-transfer proteins at the crossroads between metabolism and signaling

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ARTICLE INFO

Article history:
Received 29 September 2015
Accepted 15 October 2015
Available online 1 December 2015

Keywords:
Signaling lipid
Biological membranes
Non-vesicular lipid trafficking
Metabolism
Transport
Lipid-transfer proteins
Lipid-binding domains
Membrane contact sites
Organelles
Systems biology
Biomolecular networks

ABSTRACT

Within the eukaryotic cell, more than 1000 species of lipids define a series of membranes essential for cell function. Tightly controlled systems of lipid transport underlie the proper spatiotemporal distribution of membrane lipids, the coordination of spatially separated lipid metabolic pathways, and lipid signaling mediated by soluble proteins that may be localized some distance away from membranes. Alongside the well-established vesicular transport of lipids, non-vesicular transport mediated by a group of proteins referred to as lipid-transfer proteins (LTPs) is emerging as a key mechanism of lipid transport in a broad range of biological processes. More than a hundred LTPs exist in humans and these can be divided into at least ten protein families. LTPs are widely distributed in tissues, organelles and membrane contact sites (MCSs), as well as in the extracellular space. They all possess a soluble and globular domain that encapsulates a lipid monomer and they specifically bind and transport a wide range of lipids. Here, we present the most recent discoveries in the functions and physiological roles of LTPs, which have expanded the playground of lipids into the aqueous spaces of cells.

Contents

Abbreviations: CERT, ceramide transfer protein; CETP, cholesteryl ester transfer protein; ER, endoplasmic reticulum; FABP, fatty acid-binding protein; FFAT, diphenylalanine in an acidic tract; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; GLs, glycerolipids; GLTP, glycolipid transfer protein; GLTPD1, glycolipid transfer protein domain-containing protein 1; GM2A, ganglioside GM2 activator protein; GPL, glycerophospholipids; LTD, lipid-transfer domain; LTP, lipid transfer protein; MCS, membrane contact site; ML, MD-2-related lipid-recognition; NLS, nuclear localization sequence; NPC, Niemann–Pick C; OSBP, oxysterol-binding protein; OSBPL1A, oxysterol-binding protein-related protein 1; OSBPL9, oxysterol-binding protein-related protein 9; PLEKHA8, pleckstrin homology domain-containing family A member 8; PPARD, peroxisome proliferator-activated receptor δ; PH, pleckstrin homology; PC, phosphatidylcholine; PI, phosphatidylinositol; PIP, phosphatidylinositol phosphate; PITP, PI-transfer protein; PITPNM1, membrane-associated PITP 1; PM, plasma membrane; PS, phosphatidylserine; RARA, retinoic acid receptor α; SL, sphingolipids; SCP2, sterol carrier protein 2; StAR, steroidogenic acute regulatory protein; START, StAR-related lipid-transfer; TGN, trans-Golgi network; TSPO, translocator protein; VAPA, vesicle-associated membrane protein-associated protein A.

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http://dx.doi.org/10.1016/j.plipres.2015.10.004

1. Introduction

The tight control of lipid biosynthesis and degradation in time and space largely accounts for the fine-tuned and differentiated lipid composition of eukaryotic membranes. Pathways of lipid metabolism need to be coupled to a variety of lipid transport systems as enzymes catalyzing sequential steps of a reaction often localize to membranes of distinct organelles. Moreover, lipids often exert their biological activity – as both structural elements and signaling molecules – at places distant from their site of synthesis [1]. The spontaneous dissociation of lipids from membrane bilayers into and through the aqueous space occurs very slowly and rapid, directed and regulated transport is achieved via vesicular and non-vesicular mechanisms. Over the past decades, lipid-transfer proteins (LTPs) have emerged as an important mechanism of non-vesicular lipid transport. They were initially identified in the 80th from various sources of animal and plant tissues, as cytosolic factors able to transfer lipids *in vitro* [2–5]. Their soluble, globular lipid-transfer domain (LTD) encapsulates interacting lipids (Fig. 1) and carries them through the aqueous space within cellular, tissue and whole body compartments. LTPs are widely distributed across cellular compartments and tissues. Accumulating evidence suggests that structural features of LTPs ensure the directionality of the transfer from a specific donor membrane to a specific acceptor membrane or protein, thereby placing LTPs at the interface between signaling and metabolism. This review highlights the state-of-the-art knowledge regarding the role of LTPs in the control of whole-body homeostasis. We provide an integrated map showing how these activities are compartmentalized and which metabolite(s) they involve. Finally, we zoom in on some of their structures and functions and critically discuss the impact of their activity on human health and disease.

2. Lipids and membranes of eukaryotic cells

2.1. Lipid diversity

Lipids are one of the most abundant classes of cellular metabolites [6] and are important for energy supply and storage, the construction of cellular membranes, trafficking, and signaling. The complete repertoire of lipids in eukaryotes comprises more than 1000 different species with diverse structures and functions [7]. About 5% of eukaryotic coding genes encode proteins involved in the metabolism and transport of lipids [8]. Lipid species are classified into seven categories according to their chemical structures and their pathways of biosynthesis: fatty acyls, glycerolipids (GLs), glycerophospholipids (GPLs), sphingolipids (SLs), sterol lipids, prenol lipids, and saccharolipids (see LIPID MAPS, http://www.lipidmaps.org/data/classification/LM_classification_exp.php).

The GLs (such as diacylglycerol and triacylglycerol) and GPLs are the products of fatty acids esterified on glycerol. GPLs alone represent ~75 mol% of total cellular lipids (reviewed in [9]) and their chemical structures, most commonly comprising two esterified fatty acids, make them key elements for the assembly of lipid bilayers. The types of head groups conjugated to the third glycerol hydroxyl group further categorize GPLs into classes that include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), and phosphatidic acid (PA). The phosphorylation of PI at the 3-, 4-, and 5-hydroxyl groups of the head group inositol ring gives rise to the series of phosphatidylinositol phosphates (PIPs), well known for their signaling function [10]. The GPLs are further subdivided into different species based on structural variations in the numbers of carbons and in the numbers and positions of unsaturations of the esterified fatty acids.

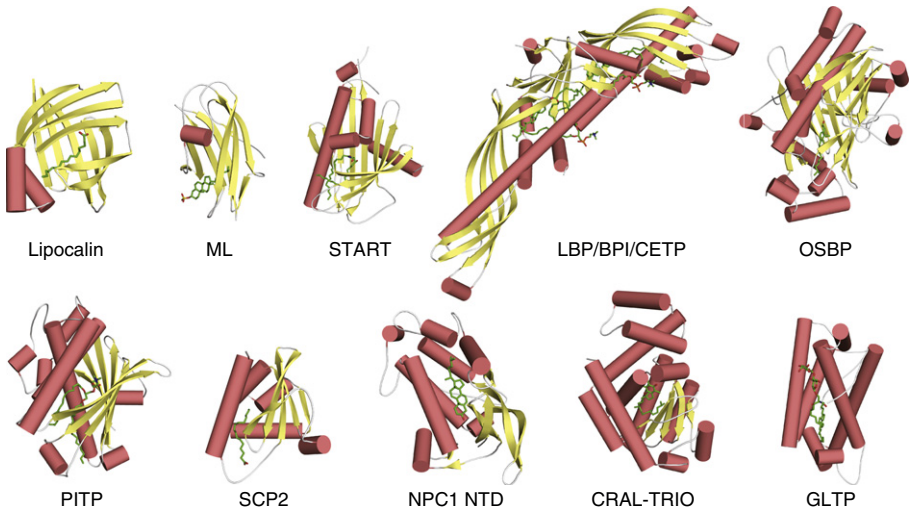

Fig. 1. Cartoon displays of the three-dimensional structures of ligand-bound LTDs. The LTDs displayed are: the lipocalin domain of the rat FABP2 in complex with palmitate (PDB entry code 2IFB); the ML domain of the bovine NPC2 in complex with cholesterol sulfate (PDB entry code 2HKA, chain B); the START domain of the CERT in complex with C16-ceramide (PDB entry code 2E3O); the LBP/BPI/CETP domain of the CETP in complex with two molecules each of cholesteryl ester and phosphatidylcholine (PDB entry code 2OBD); the OSBP domain of the yeast Osh4 in complex with ergosterol (PDB entry code 1ZHZ); the PITP domain of the rat PITP in complex with PC (PDB entry code 1 T27); the SCP2 domain of the yellow fever mosquito SCP2-like 3 in complex with palmitate (PDB entry code 3BKR); the NPC1 NTD of the NPC1 in complex with cholesterol (PDB entry code 3GKI); the CRAL-TRIO domain of the TTPA in complex with α-tocopherol (PDB entry code 1R5L); and the GLTP domain of the GLTP in complex with lactosylceramide (PDB entry code 1SX6). The helices and β-strands are colored salmon and yellow, respectively. The bound ligands are shown as sticks with the carbon, nitrogen, oxygen, and phosphate atoms colored green, blue, red, and orange, respectively (Figs. 2–4).

Other important categories of lipids are the sterol lipids, which have a common four-ring structure and comprise 12–14 mol% of the total cellular lipids (reviewed in [11]). SLs account for 8–12 mol% of total cellular lipids [9,11] and they share a sphingoid base backbone that can be conjugated to a fatty acid via an amide bond and to a variety of head groups including one or multiple sugar residues. Vitamin A and E belong to the category of prenol lipids. Vitamin A (retinol) and its derivatives (retinoids) have three structural determinants: a polar terminus, a conjugated side chain and a β-ionone ring. Retinol is the precursor for the synthesis of two important metabolites, retinal and retinoic acid, which have a role in vision [12] and gene expression [13], respectively. Vitamin E is a major fat-soluble antioxidant [14] and its most abundant form in mammals is α-tocopherol. It has a structure that comprises a chromanol ring, with four methyl groups and a phytyl side chain, and three chiral centres in the RRR configuration (reviewed in [15]).

2.2. Lipid compartmentalization

Cellular lipids are primarily assembled into membrane lipid bilayers, in which they form dynamic networks of interactions with each other and with proteins associated with the periphery or integrated into the membrane. A number of observations indicate that lipids are highly organized within the eukaryotic cell. Firstly, different lipid species are not evenly distributed among the various cellular membranes. For example, signaling lipids such as PS, PI(4,5)P_2, and PI(3,4,5)P_3 are predominantly found in the plasma membrane (PM), whereas PI(3,5)P_2 localizes to the endosomal membranes [7]. PIPs mediate and spatiotemporally organize both acute and constitutive signals through the recruitment of cytosolic proteins, such as protein kinases, to specific membranes. The uneven distribution of lipids also dictates the physical nature of eukaryotic membranes. For example, compared with those of the endoplasmic reticulum (ER) and Golgi apparatus, GPLs of the PM are composed of longer and more saturated fatty acids that make the PM generally thick and rigid (reviewed in [9]). Secondly, cellular membranes are laterally heterogeneous as lipids cluster and partition into lateral domains as a result of lipid–lipid interactions. For example, the PM forms sphingolipid- and sterol-rich lateral domains referred to as lipid rafts [16,17]. Finally, cellular lipids are distributed differently between the two leaflets of a lipid bilayer. Enzymes involved in lipid biosynthesis often perform these reactions in only one of the two leaflets. For instance, PIPs are synthesized at the cytosolic leaflets of membranes because soluble PI kinases are recruited to the membrane periphery from the cytosol. PS is synthesized in the ER, but is highly enriched at the cytosolic leaflet of the PM due to specific non-vesicular transport through the cytosol [18–20]. The exposure of PS at the cell surface acts as a signal for apoptosis [21].

3. Lipid-transfer proteins: variations on a common theme

3.1. Lipid recognition by lipid-transfer proteins

Within the human genome there are about 125 distinct genes that together encode at least ten families of LTPs. They are generally expressed in virtually all tissues in human (Fig. 2; Supplementary Table S1), but some families of LTPs, such as the lipocalins, show preferences for some cell types (e.g. the skin and soft tissues). Each family is defined by the distinct structural fold of their globular, water-soluble LTD (Fig. 1). For example, the MD-2-related lipid-recognition (ML) domains [22,23] and the lipocalin domains [24,25] mainly comprise β-strands that completely surround the binding cavity (Fig. 1). The binding pockets of the oxysterol-binding protein (OSBP), LBP/BPI/CETP, CRAL-TRIO, StAR-related lipid-transfer (START), sterol carrier protein 2 (SCP2), Niemann–Pick C1 (NPC1) N-terminal, and PI transfer protein (PITP) domains are defined by both β-strands and α-helices [26–32] (Fig. 1). By contrast, the secondary structure of the glycolipid transfer protein (GLTP) domain solely consists of helices [33] (Fig. 1).

Despite their apparent structural diversity, all LTDs exhibit striking similarities in their mode of lipid interactions. All have a polar outer surface and a deep hydrophobic or amphiphilic cavity shaped as a tunnel. Lipid molecules are accommodated inside this cavity and are shielded from the surrounding aqueous environment. Structures are available for the ten known LTD families and these represent snap-shots of the protein–lipid interactions that take place during physiological lipid transport (Fig. 1). These structures commonly show the LTD cavity enclosing the majority of the bound lipid and providing hydrophobic contacts to non-polar groups of the molecule. Once the lipid ligand is bound, a flexible motif referred to as a "lid" or a "cap" often blocks the cavity entrance, and sterically disables its dissociation. These "lids" sometimes consist of a single loop that, in the case of PITP, can swing open upon PC binding [32,34]. In the lipocalin domain, the lid forms a so-called helix–loop–helix motif (Fig. 1). Most LTD–lipid complexes are stoichiometric, involving a single lipid molecule, but there are a few interesting exceptions that show that some LTD can simultaneously bind to more than one ligand. For example, the LBP/BPI/CETP domain of the cholesteryl ester transfer protein (CETP) carries two molecules each of cholesteryl esters and PC, and the lipocalin domain of fatty acid-binding protein 1 (FABP1) binds two molecules of oleic acid [25].

The current knowledge of LTP–lipid interactions has already shed light on the interplay between LTPs and lipids from all categories (Fig. 3; Supplementary Table S2). Despite the fact that they share similar folds, members of the same LTD family show a surprisingly broad lipid-binding specificity (Fig. 3; Supplementary Table S2). For instance, the ML domain protein lymphocyte antigen 96 (LY96) binds bacterial lipopolysaccharide [35], whereas another ML domain protein, NPC2, binds cholesterol [36]. Similarly the lipocalin domain proteins have binding specificity for a variety of lipids and lipophilic molecules including retinoids, steroids and fatty acids (Fig. 3; Supplementary Table S2). The ligand-binding specificity is created by a series of polar groups on the ligands such as the head groups of GPLs and SLs that are often engaged in intermolecular hydrogen bonding to LTD residues at the interior of the cavity (e.g. the ceramide-transfer protein (CERT) START domain–ceramide complex [29]) or at the outer surface (e.g. the GLTP–lactosylceramide complex [33]). In addition, the volume and shape of the lipid-binding cavity also influence the LTD–lipid interactions and can sterically restrict the size of ligands. For example, the CERT START domain can bind different ceramide species, but not those with long amide-acyl chains that are too bulky for its small hydrophobic pocket [29]. For those LTPs in a spatially restricted compartment, LTP–lipid interactions are also influenced by the accessibility and availability of lipids. These LTPs can associate with non-physiological lipids when brought into an unnatural environment, for example upon heterologous expression [18,31,37]. The characterization of LTP–lipid interactions are thus a demanding and on-going task and, for the majority of LTPs, the identity of their cargoes remains elusive (Fig. 3, Supplementary Table S2).

3.2. Molecular architecture of lipid-transfer proteins defining their localization and function

LTPs frequently also harbor domains or motifs that specify their subcellular location (Figs. 3 and 4; Supplementary Table S3) or mediate interactions with downstream protein effectors, such as enzymes, transmembrane transporters, other LTPs or nuclear receptors (see below).

The function of many LTPs requires their precise targeting to specific organellar membranes through the recognition of membrane (or lipid) signatures. Membrane targeting sometimes involves transmembrane helices (for example in NPC1 [38]) or the lid of the LTDs. A good example is the ML domain of the ganglioside GM2 activator protein (GM2A), the lid of which interacts with the inner lysosomal membranes through two loops present at the entrance of the lipid-binding cavity [39] to facilitate the loading of its cargo (the GM2 ganglioside) [23]. However,

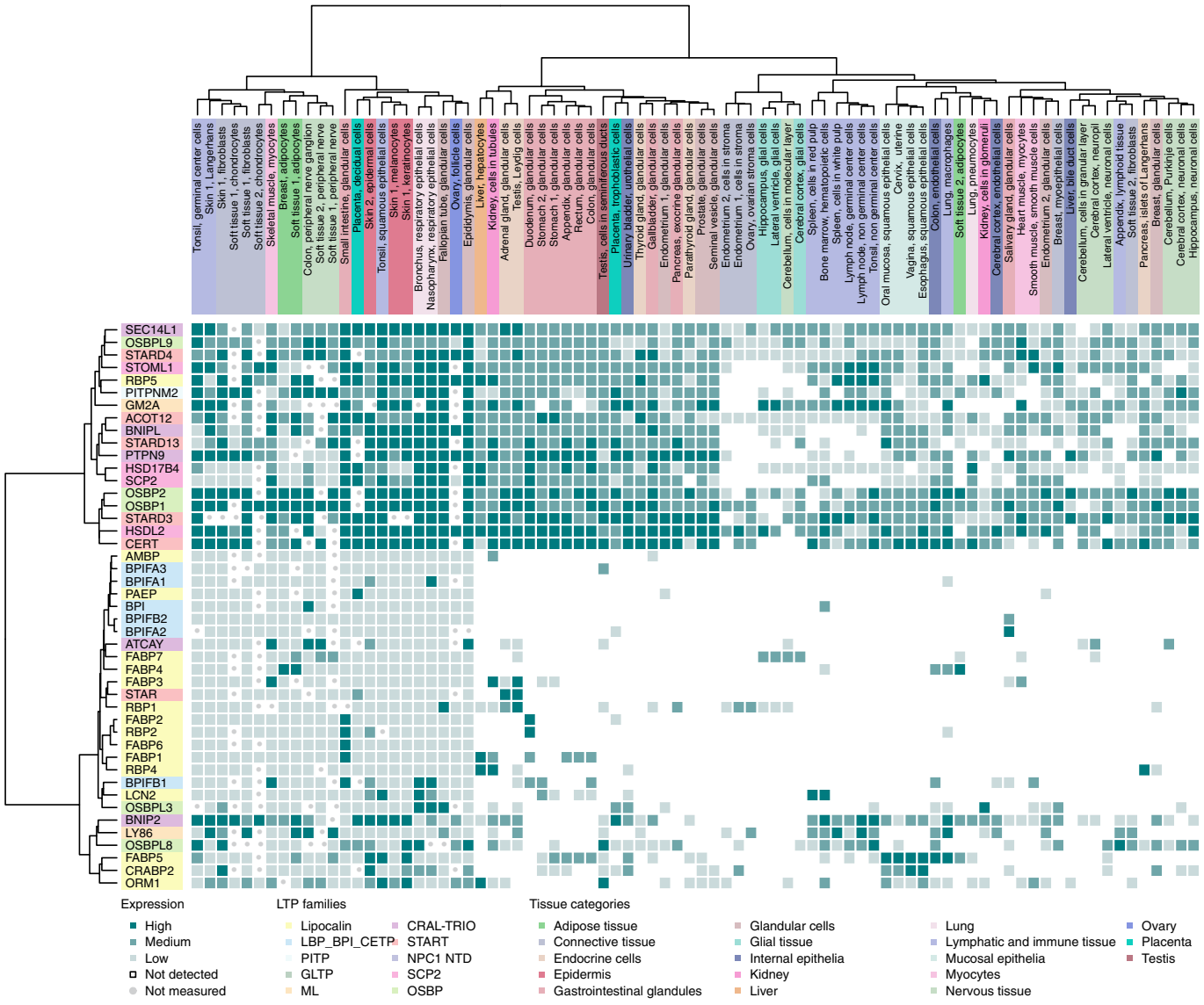

Fig. 2. Expression pattern of LTPs in human tissues. LTPs are generally expressed in virtually all tissues in human. Some of LTPs are pleiotropic across almost all the tissues, while others show a more specific occurrence. This pattern suggests that the expression of LTPs is closely related to the functions performed by different cell types. The heat map shows that, overall, each tissue expressed between 6 and 29 LTPs. LTP families and tissues with similar functions tend to cluster together e.g. gastrointestinal glandular cells, or lymphoid tissues. The data was extracted from the expert curated immunohistochemistry and RNA-seq dataset of the Human Protein Atlas (HPA; version 13) [108]. The LTPs are color coded according to their LTD families. The tissues are colored by functional and histological similarities. A total of 45 LTPs in 82 tissues have at least one high confidence expression value. According to the HPA, high confidence is determined based on a number of criteria considering the congruence of immunohistochemistry of multiple antibodies and RNA level evidences. HPA scores the level of expression as high, medium, low or not detected, based on evaluation of immunohistochemistry staining and RNA levels (FPKM values). Colored fields show the 3 levels of expression (protein abundance), and white fields the cases where the protein is considered to not be expressed, as it has been measured, but not detected. Fields marked with dots signify those cases where the protein hasn't been measured, and there is hence no information available on its expression. For the remaining 57 LTPs we missed high confidence expression data (lack of multiple good quality antibodies and/or supportive RNA level expression data). They were thus omitted. Both LTPs and tissues are clustered with unsupervised hierarchical clustering.

targeting often requires the presence of specialized domains, such as the pleckstrin homology (PH) or the Golgi dynamic (GOLD) domains that bind lipids and/or other proteins. Remarkably, PH domains – well known for their PIP-binding activity – are present in several families of LTPs: the OSBP, the START, the GLTP and the CRAL-TRIO domain families (Fig. 4). However, these PH domains are sometimes difficult to identify on the basis of sequence analyses alone. For example, the cryptic PH domain of neurofibromin (NF1, which belongs to the CRAL-TRIO domain family) was overlooked by the classical algorithm, and its detection required biochemical and structural analyses [37].

The precise, spatiotemporally regulated targeting of LTPs to specific subcellular membranes often requires the integration of multiple low-affinity interactions. This is well known for CERT and OSBP, the localization of which at MCSs between the Golgi and the ER requires the presence of both a PH domain and a diphenylalanine in an acidic tract (FFAT) motif [40,41]. In the case of OSBP, its PH domain simultaneously interacts with the trans-Golgi network (TGN) resident ADP-ribosylation factor 1 (ARF1) and PI(4)P [42], whereas its FFAT motif interacts with the ER transmembrane protein, vesicle-associated membrane protein-associated protein A (VAPA) [43–46]. LTPs also possess a signal peptide and are sorted to various subcellular compartments or are secreted (Fig. 3; Supplementary Table S3). Some possess a nuclear localization sequence (NLS). Interesting examples are the lipocalin domain proteins cellular retinoic acid-binding protein 2 (CRABP2), FABP4, and FABP5. The binding of these proteins to their lipid ligands induces intramolecular rearrangements that lead to the exposure of an otherwise hidden NLS and the targeting to acceptor proteins localized in the nucleus (described in more detail below).

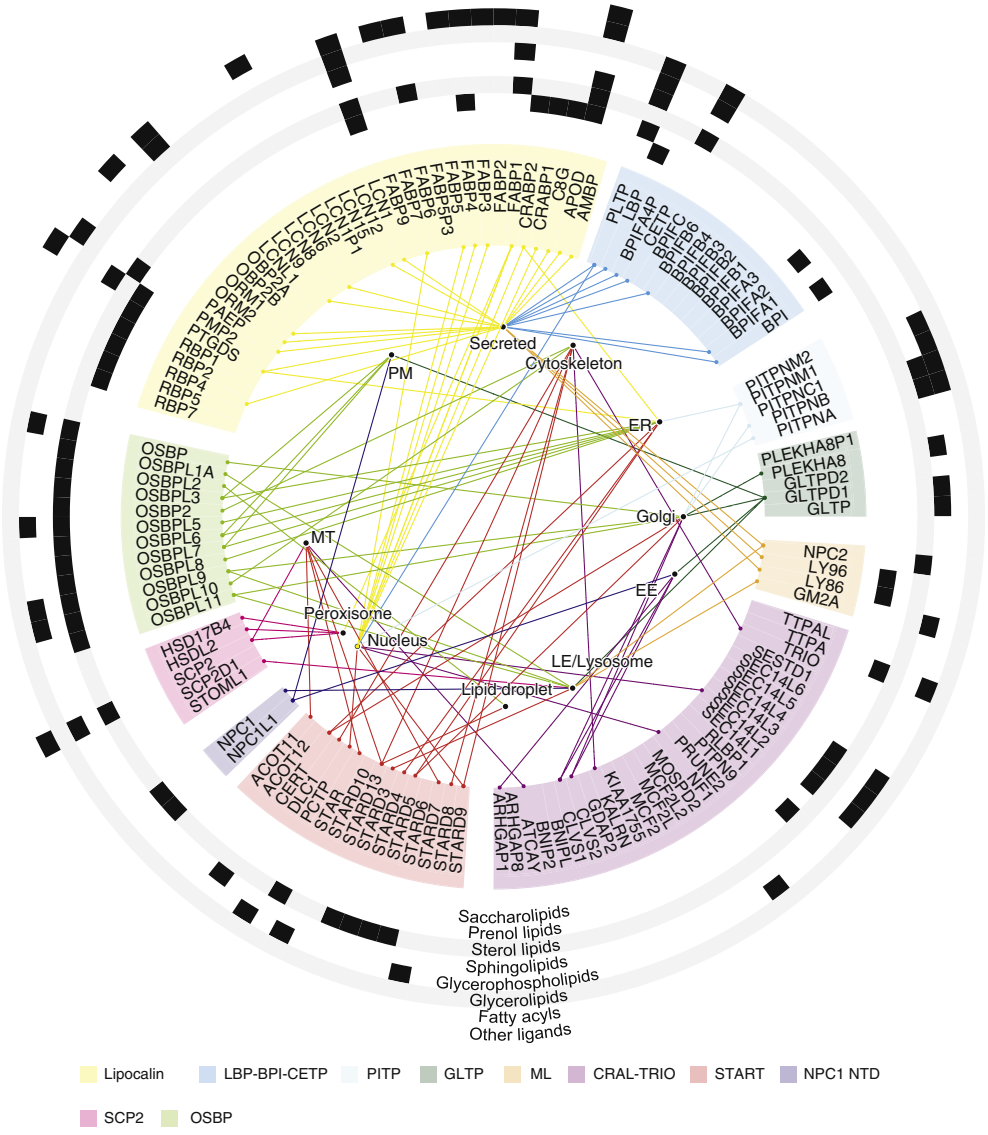

Fig. 3. Subcellular localizations and lipid-binding specificities of human lipid-transfer proteins. The members of the ten families of LTPs are displayed. The systematic manual annotation of their localization shows that these proteins are localized in virtually every compartment within the cell and, in some cases, they can be secreted. Moreover, within families they do not necessarily share the same binding specificity, while across families it is possible to find affinity for the same lipid. Colors are specific for each LTD family as indicated in the legend. Lines are drawn to indicate the reported subcellular localization of LTPs. Filled black squares at the outer circles indicate the reported lipid-binding activities of each LTPs. The data on lipid-binding activity and subcellular localizations – obtained from the UniProtKB database (http://www.uniprot.org/) and by a manual search of the relevant literature – can be found in Supplementary Tables S2 and S3, respectively. MT, mitochondria; PM, plasma membrane; EE, early endosomes; LE, late endosomes.

LTPs also comprise numerous additional signaling, protein–protein interaction, or catalytic domains that illustrate the broad functional diversity of LTPs (Fig. 4). Remarkable examples are members of the CRAL-TRIO and START domain families that frequently harbor signaling domains such as protein kinase (TRIO, KALRN), protein phosphatase (PTPN9), Src homology 3 (SH3)(KALRN, MCF2L, TRIO), RhoGAP (ARHGAP1, ARHGAP8, DLC1, STARD8, STARD13), RhoGEF (KALRN, MCF2, MCF2L, MCF2L2, TRIO) and RasGAP (NF1) domains, or metabolic domains such as the macro domain – a binding module for poly(ADP-ribose), a metabolite of NAD^+ (GDAP2) – and the 4-hydroxybenzoyl-CoA thioesterase domain (HotDog)(ACOT11, ACOT12).

4. Compartmentalized functions of lipid-transfer proteins

4.1. Lipid-transfer proteins transfer lipids between cellular membranes

One of the first proposed functions of LTPs was the non-vesicular transfer of lipids between biological membranes (Fig. 5). This activity was initially described some 30 years ago in *in vitro* reconstituted biochemical systems [47–49]. More recently, mechanisms of non-vesicular lipid transfer between membranes have also been demonstrated *in vivo* [18,50], in which the LTPs have important functions such as spatially organizing lipids and connecting lipid metabolic pathways that are distributed across distant organelle membranes [40,41,51,52]. LTPs have also been proposed to contribute to the still-elusive membrane-tethering mechanisms that drive the formation of MCSs [53,54]. In particular, they link the ER – the major site of lipid synthesis – to several other organelles such as the Golgi [41], the mitochondria [55,56] and the PM [18].

The ER and Golgi apparatus are populated by many LTPs such as OSBP, oxysterol-binding protein-related protein 9 (OSBPL9), glycolipid transfer protein domain-containing protein 1 (GLTPD1), pleckstrin homology domain-containing family A member 8 (PLEKHA8), the membrane-associated PITP 1 (PITPNM1) and CERT, and their lipid-transfer activities contribute to sterol lipid, GPL and SL homeostasis along the different compartments of the secretory pathways (ER/cis-

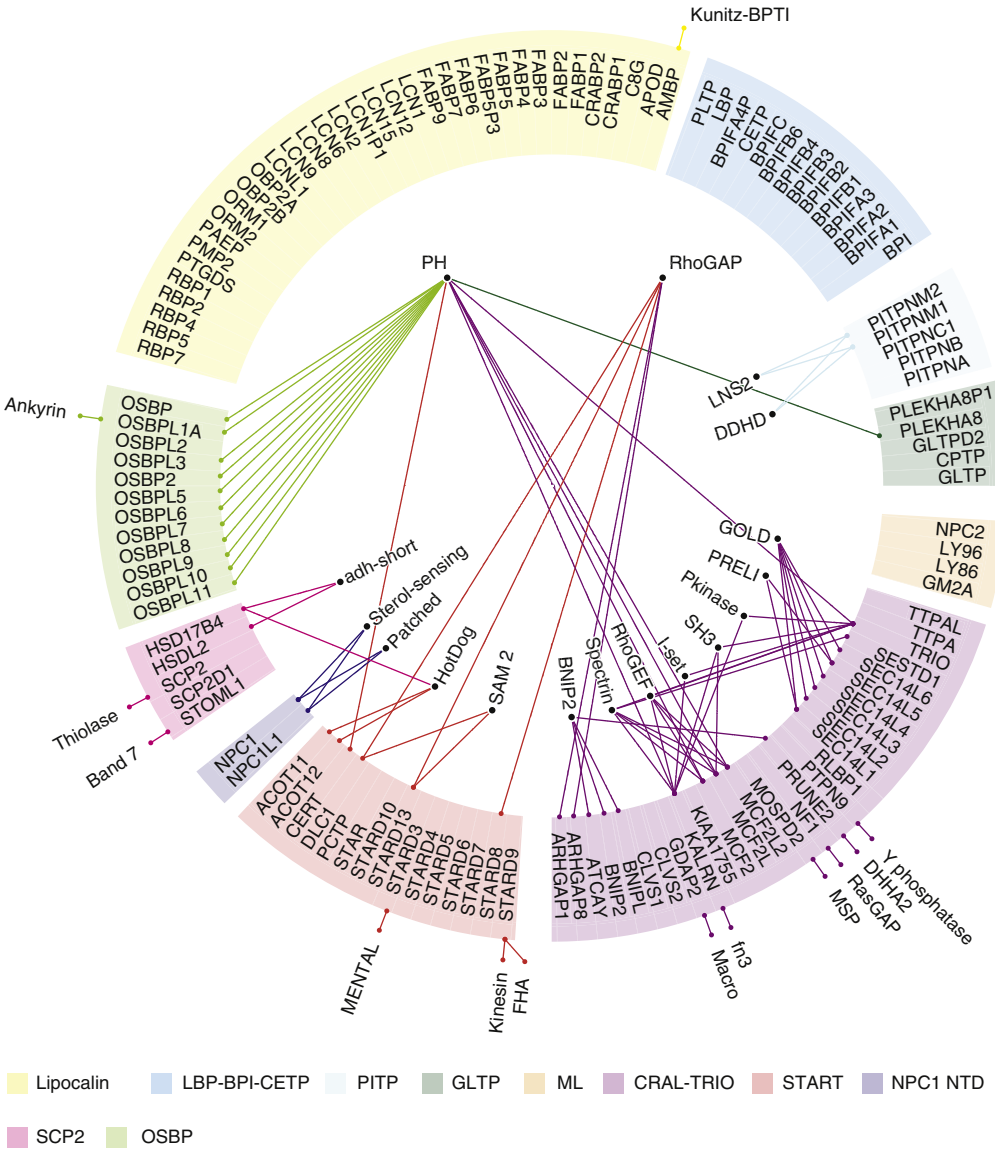

Fig. 4. Domain organizations of human lipid-transfer proteins. The members of the ten families of LTPs are displayed. We systematically searched protein databases for the domains that co-occur with the different LTD. Membrane-targeting domains, protein–protein interaction domains, or catalytic domains are often also present in LTDs. This is consistent with the view that LTDs are involved in many cellular functions. Colors are specific for each LTD family as in Fig. 3. Lines indicate additional domains present in LTPs. Domains shared by multiple LTPs are placed inside the circle of LTP names, whereas those unique for a single LTP are shown outside the circle. Data on domain organization can be obtained from Pfam (http://pfam.xfam.org/) and InterPro (http://www.ebi.ac.uk/interpro/) databases. Abbreviations used are; adh-short, short chain dehydrogenase; ankyrin, ankyrin-repeat; BNIP2, Bcl2−/adenovirus E1B nineteen kDa-interacting protein 2; GLTP, glycolipid transfer protein; GOLD, Golgi dynamics; FHA, Forkhead-associated; fn3, Fibronectin type III; I-set, Immunoglobulin I-set; Kunitz-BPTI, Kunitz/Bovine pancreatic trypsin inhibitor domain; MENTAL, MLN64 N-terminal; ML, MD-2-related lipid-recognition; MSP, Major sperm protein; NPC1 NTD, Niemann–Pick C1 N-terminal domain; OSBP, oxysterol-binding protein; PH, pleckstrin homology; PITP, phosphatidylinositol transfer protein; Pkinase, protein kinase; SAM 2, Sterile alpha motif type 2; SCP2, sterol carrier protein 2; SH3, src Homology-3; Spectrin, Spectrin-repeat; START, StAR-related lipid-transfer; Y phosphatase, protein tyrosine phosphatase.

Golgi and TGN/PM) [57]. For example, CERT transfers ceramide from the ER to the Golgi where it generates a pool of ceramide that acts as a precursor for the synthesis of sphingomyelin that is required at the PM [40]. In other cases, the lipid-transfer activity of LTPs contributes to the accumulation of lipids in different organelles and the building of lipid gradients such as the one observed along the secretory pathway. For instance, OSBP transfers cholesterol from the ER to the TGN against the concentration gradient of cholesterol, which increases along the secretory pathway, i.e. from the ER to the PM (the PM comprises 60% of the total cellular cholesterol [58,59]). The OSBP-mediated transfer of cholesterol is coupled to the OSBP-mediated reverse-transfer of PI(4)P from the TGN to the ER, where PI(4)P is dephosphorylated (to PI) by the phosphatidylinositide phosphatase SAC1. PI in the ER, in its turn, is transferred – via another LTP, PITPNM1 – to the Golgi apparatus [41,57,60] where it is phosphorylated by a PI 4-kinase [60]. According to this model, cycles of PI(4)P dephosphorylation (in the ER), PI transport and PI phosphorylation (in the TGN) provide the energy required for the OSBP-dependent cholesterol transfer and the accumulation of sterol along the secretory pathway. This mechanism is also conserved in *Saccharomyces cerevisiae*, in which the oxysterol-binding protein homolog 4 (Osh4)/Kes1 and a CRAL-TRIO domain protein, Sec14, act together to guarantee the net PC–sterol exchange sustained by the ATP hydrolysis catalyzed by the Golgi PI-kinase PIK1 [54].

Some LTPs also transport hydrophobic vitamins. For instance, the CRAL-TRIO domain protein α-tocopherol (a form of vitamin E) transfer protein (TTPA) is part of the machinery involved in the secretion of vitamin E from hepatocytes. TTPA mutations in humans cause ataxia with vitamin E deficiency (AVED) [61,62]. In hepatocytes, TTPA extracts

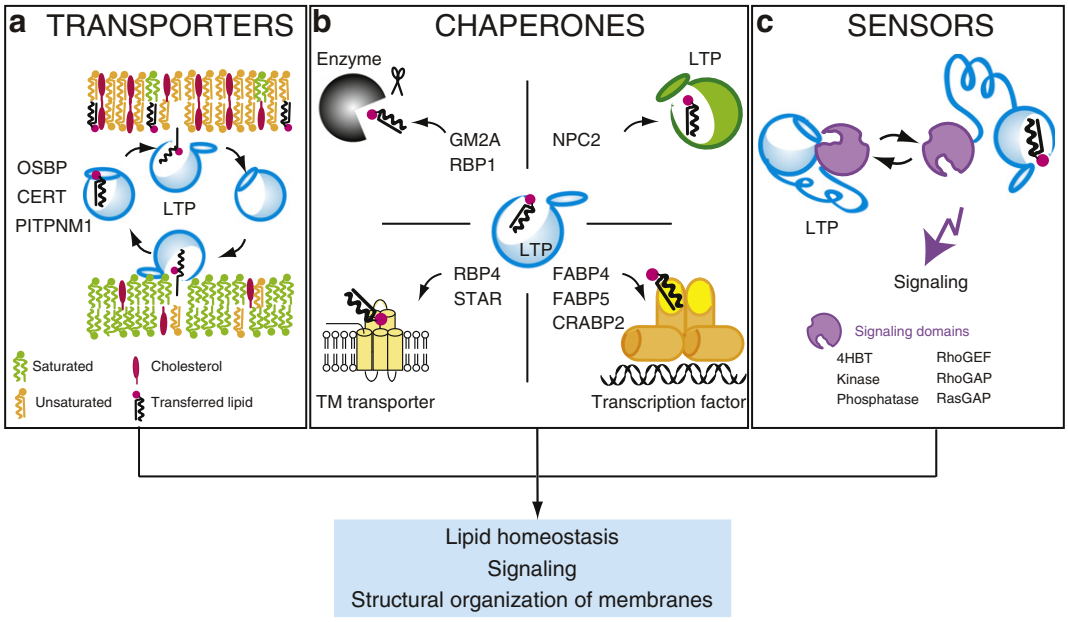

Fig. 5. Lipid-transfer proteins have multiple modes of action. a, LTPs can transfer lipids between cellular membranes and act as transporters. b, Some LTPs (chaperones) present lipids to an acceptor protein (e.g. enzymes, LTPs, transmembrane (TM) transporters or transcription factors). c, The LTD can be engaged in intramolecular interactions with other domains (illustrated here in purple) or proteins (not illustrated). Binding to the lipid cargo acts as a trigger that induces conformational changes and leads to the activation of signaling. This mechanism is sometimes coupled to the mechanisms described in a and b. LTPs have pleiotropic functions and can modulate lipid homeostasis, signaling and the structural organization of membranes.

α-tocopherol from endosomal membranes and releases it to the PM [63–65]. This implies specific interactions between the TTPA/vitamin E complex and the head group of a PM-localized PIP_2 – $PI(3,4)P_2$ or $PI(4,5)P_2$ – leading to the exchange of vitamin E for the PIP_2. The fate of the extracted, TTPA-bound PIP_2 is not yet clear. The recycling of TTPA – and the directionality of the vitamin E transfer – might imply the release of PIP_2 to an as yet unknown acceptor membrane or its channeling to metabolic enzymes such as a lipid kinase or phosphatase (the role of LTPs in the presentation of lipids to another protein is discussed in the next section).

LTPs also have important lipid-transfer functions in the extracellular milieu and in the bloodstream. Many LTPs are indeed secreted (Fig. 3, Supplementary Table S3). For example, the phospholipid transfer protein (PLTP) and CETP transfer GPLs and cholesteryl ester/triacylglycerol, respectively, between various lipoprotein particles, which are organized assemblies of proteins and lipids that move cholesteryl esters and triacylglycerol in the plasma. These LTPs modulate the size, lipid composition, identity and function of the lipoprotein particles [66].

4.2. Lipid-transfer proteins can act as chaperones and present lipids to other proteins

An interesting feature shared by some LTPs is their ability to transfer their lipid cargoes to acceptor proteins such as enzymes, transmembrane transporters, nuclear receptors, transcription factors or other LTPs (Fig. 5). They act as chaperones, presenting specific lipids to specialized downstream protein effectors. The dysfunction of these important pathways in humans frequently leads to disease, some examples of which are given below.

A number of LTPs can transfer lipids to downstream enzymes (Fig. 5). For example, GM2A is a lysosomal LTP that works as a specific, essential cofactor for the lysosomal glycosphingolipid-degrading enzyme, β-hexosaminidase A [67]. GM2A extricates GM2 gangliosides out of the inner lysosomal membranes and makes them accessible for the soluble β-hexosaminidase A [68–71]. A recessively inherited deficiency in GM2A leads to the AB variant of GM2-gangliosidosis, a disorder characterized by the neuronal accumulation of GM2 [72–74]. Another example, is the lipocalin domain protein, retinol-binding protein 1 (RBP1), that transfers retinol (vitamin A) from its trans-plasma membrane transporter (stimulated by retinoic acid 6, STRA6) to intracellular retinol-metabolizing enzymes such as the lecithin retinol acyltransferase (LRAT) [75] or the retinol dehydrogenase 16 (RDH16) [76–78].

Some LTPs transfer lipids to small molecule transporters or to other LTPs (Fig. 5). This represents the mode of action of the START domain protein steroidogenic acute regulatory protein (StAR), which transfers cholesterol from the cholesterol-rich outer mitochondrial membrane to the translocator protein (TSPO) [79–81]. TSPO further transfers cholesterol to the cholesterol-poor inner mitochondrial membrane, where cholesterol is a precursor for steroidogenesis [82]. Loss-of-function mutations in StAR lead to lipoid congenital adrenal hyperplasia [83–85], a potentially lethal disease arising from defects in the early stages of adrenal cortisol synthesis.

LTPs can also translocate from the cytoplasm to the nucleus and present their lipid cargoes to nuclear receptors, a class of transcription factors (Fig. 5). Two good examples are the epidermal FABP5 and CRABP2, which translocate to the nucleus upon binding to retinoic acid and tunnel it to the peroxisome proliferator-activated receptor δ (PPARD) and the retinoic acid receptor-activated receptor α (RARA), respectively [86–89]. The two nuclear receptors activate opposing signaling cascades: RARA activates a pro-apoptotic cascade, whereas PPARD promotes cell survival [90–92], cell proliferation and tumorigenesis [93]. The ratio between FABP5 and CRABP2 thus determines pro- and anti-apoptotic responses. Similarly, the adipocyte FABP4 binds a variety of ligands, including linoleic acid and troglitazone – a drug developed to treat type 2 diabetes – and present them to another nuclear receptor, the peroxisome proliferator-activated receptor γ (PPARG) [89].

4.3. Lipid-transfer proteins as lipid sensors, linking lipid metabolism to signaling

LTPs can also act as lipid sensors that undergo conformational changes following the binding of specific lipids. These structural changes regulate downstream biological processes such as signaling cascades,

cytoskeleton dynamics or the redistribution of organelles. Such LTPs acts as molecular probes that sense fluctuations in the levels of specific lipids in their environment and elicit the appropriate cellular adaptation. In many cases, the sensing mechanisms are tightly coupled to the lipid-transfer activity of the LTPs.

Some LTPs act as molecular scaffolds. A good example is OSBP, which exchanges cholesterol and PI(4)P between the ER and the TGN but also has a signaling function [41]. When the levels of cholesterol are high, OSBP – loaded with cholesterol – acts as a scaffold for both a serine/threonine (PP2A) and a tyrosine (PTPBBS family) phosphatase [94,95]. The resulting hetero-oligomer dephosphorylates pERK, and thus down regulates the MAP kinase signaling cascade. A decrease in the cellular cholesterol level induces cholesterol dissociation and conformational changes in OSBP that promote the disassembly of the heteroligomer [95]. In the case of the oxysterol-binding protein-related protein 1 (OSBPL1A), binding to cholesterol induces conformational changes that expose an otherwise hidden ankyrin repeat. OSBPL1A bound to cholesterol acts as a scaffold for both the small GTPase Ras-related protein RAB7A (through OSBPL1A's ankyrin repeat), the membrane lipid bilayer of late endosomes (LE) [96,97] (through OSBPL1A's PH domain) and the RAB7A-interacting lysosomal protein (RILP) (through RAB7A). The trimeric complex OSBPL1A–RAB7A–RILP recruits the $p150^{Glued}$ subunit of the dynein–dynactin motor and drives the LE to the minus end of the microtubules [98]. Conversely, upon cholesterol depletion, OSBPL1A is in its cholesterol-free conformation in which the ankyrin repeat is hidden but a FFAT motif is exposed. The FFAT motif interacts with the ER-resident protein VAPA [44,45], favoring the formation of LE-ER contacts and preventing the binding of the $p150^{Glued}$ subunit [97].

Many LTPs carry domains with enzymatic activities such as protein kinase, protein phosphatase, thioesterase, guanine nucleotide exchange factor (GEF) and GTPase-activating protein (GAP) [83] (see above) domains, which suggests the existence of mechanisms of intra-molecular regulation. In these cases, the co-occurrence of multiple domains in a single protein may contribute to rapid spatiotemporal regulation of signaling. In many cases, however, the exact mechanisms remain elusive. For example, ARHGAP1 belongs to the CRAL-TRIO domain family and also contains a RhoGAP domain [99]. This domain interacts with the prenyl group of the target GTPase (probably Rab5 and/or Rab11 localized on the endosome and on endocytic recycling compartments, respectively) and releases an auto-inhibitory intra-molecular interaction between the C-terminal RhoGAP domain and the CRAL-TRIO domain [100].

4.4. Lipid-transfer proteins often work together and are organized in functional, cellular networks

Some LTPs act in more complex networks. For example, NPC1 and NPC2 [101] are two lysosomal LTPs, mutations in which lead to the Niemann–Pick disease type C, an inherited, neurodegenerative disorder [102,103]. NPC2 is a soluble LTP that extracts cholesterol from the inner lysosomal membranes and transfers it to the N-terminal domain of NPC1, a transmembrane LTP located at the lysosomal delimiting membrane. This process – called "hydrophobic handoff" – is crucial for the export of cholesterol from the lysosomal compartment [104], but the molecular mechanism of cholesterol export after its delivery to the NPC1 N-terminal domain remains elusive. Another LTP, the oxysterol-binding protein-related protein 5 (OSBPL5), may contribute to the formation of LE–ER MCSs, bind the cholesterol delivered by NPC1 and transfer it to the ER [13].

Other interesting examples, are RBP1 and RBP4, two LTPs belonging to the lipocalin domain family. Both act in the same pathway involved in retinol homeostasis and signalling. RBP4 is a secreted LTP that binds and transfer retinol from the liver to extra hepatic organs [105], which are highly dependent on retinol for their function [106,107]. There, RBP4 transfers its cargo to the STRA6 transmembrane receptor. Retinol uptake by STRA6 triggers the Janus kinase 2 (JAK2) and signal transducer and activator of transcription 5 (STAT5) mediated signalling. Simultaneously, the intracellular the RBP1 binds the retinol taken up by STRA6 and transfers it to enzymes responsible for the conversion into esters – the storage form of many lipids – or into all-trans RA – important in regulating cellular proliferation, differentiation, and apoptosis (see above) [75].

5. Conclusion

The number of physiological roles reported for LTPs has greatly increased in the past decades. The current, yet incomplete, overview of the protein–lipid interaction networks of LTPs already includes all lipid categories and covers essentially all subcellular localizations as well as extracellular spaces. Such an overview has challenged our idea of the membranes of eukaryotic cells as a set of islands that isolate lipids, and has illuminated the movement of lipids along complex and interconnected networks of "highways" specialized in selective and directional transport. Lipid metabolic pathways that require LTPs for their proper functioning are no longer the exception, and it is now becoming apparent that LTPs constitute integrated parts of lipid metabolic networks. Further investigations into the physiological activities of LTPs will thus increase our understanding of the mechanisms of these metabolic networks and how they are regulated in health and disease.

Efforts in both biochemistry and structural biology have elucidated the lipid-binding mechanisms of many LTPs. Nevertheless, novel protein–lipid interactions are still being uncovered, even for members of well-studied LTP families, indicating that our understanding of the mechanisms of action of LTPs is incomplete. The fact that the lipid-binding specificity of LTPs is difficult to predict highlights the need for systematic and unbiased monitoring of the protein–lipid interactions of LTPs. Moreover, even though humans possess over one hundred LTP genes, this number is very small compared to that of the human lipid repertoire. Novel LTPs evolutionally unrelated to previously known LTPs continue to be reported, and the actual number of LTPs and LTP-interacting lipids in humans is likely to expand in the future.

The physiological roles of most human LTPs remain poorly assigned. Among the numerous compartmentalized LTP networks visualized in the integrated maps we provide here, physiological roles have been demonstrated for only a small subset. The complex series of transient interactions with cargoes, donors, acceptors, and/or downstream effectors together define the physiological role of an LTP, and mapping these requires extensive experimental efforts. This complexity is further increased by the fact that most LTPs are multi-domain proteins, in which each constituting domain can have different, inter-dependent functions.

Despite these challenges, recent advances in -omics and network analyses will no doubt support the effort in elucidating the physiological roles of LTPs and shed further light on their modes of action in health and disease.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.plipres.2015.10.004.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgments

We are grateful to the Gavin's group, in particular Kanchan Anand, Ivana Vonkova and Charlotte Gehin for inspiring comments and discussions on the manuscript.

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