BBA - Molecular and Cell Biology of Lipids 1865 (2020) 158462

Contents lists available at ScienceDirect

BBA - Molecular and Cell Biology of Lipids

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

Review

Phospholipid turnover and acyl chain remodeling in the yeast ER

Jana Patton-Vogt[a], Anton I.P.M. de Kroon[b,*]

[a] Department of Biological Sciences, Duquesne University, Pittsburgh, PA, USA
[b] Membrane Biochemistry & Biophysics, Bijvoet Center and Institute of Biomembranes, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Acyl chain exchange
Membrane phospholipids
Acyltransferase
Membrane lipid homeostasis
Phospholipid degradation

ABSTRACT

The turnover of phospholipids plays an essential role in membrane lipid homeostasis by impacting both lipid head group and acyl chain composition. This review focusses on the degradation and acyl chain remodeling of the major phospholipid classes present in the ER membrane of the reference eukaryote *Saccharomyces cerevisiae*, *i.e.* phosphatidylcholine (PC), phosphatidylinositol (PI) and phosphatidylethanolamine (PE). Phospholipid turnover reactions are introduced, and the occurrence and important functions of phospholipid remodeling in higher eukaryotes are briefly summarized. After presenting an inventory of established mechanisms of phospholipid acyl chain exchange, current knowledge of phospholipid degradation and remodeling by phospholipases and acyltransferases localized to the yeast ER is summarized. PC is subject to the PC deacylation-reacylation remodeling pathway (PC-DRP) involving a phospholipase B, the recently identified glycerophosphocholine acyltransferase Gpc1p, and the broad specificity acyltransferase Ale1p. PI is post-synthetically enriched in C18:0 acyl chains by remodeling reactions involving Cst26p. PE may undergo turnover by the phospholipid: diacylglycerol acyltransferase Lro1p as first step in acyl chain remodeling. Clues as to the functions of phospholipid acyl chain remodeling are discussed.

1. Introduction

The ER is a highly dynamic organelle that is involved in many aspects of the biogenesis of cellular membranes, including the production and distribution of most cellular lipids. Most membrane lipids (or their lipid precursors) are synthesized *de novo* by enzymes localized in the ER membrane, and can be transported to other cellular membrane compartments by vesicular trafficking and lipid transfer at membrane contact sites. For proper function of these and a multitude of other processes it is imperative that the ER membrane is flexible while maintaining barrier function. Membrane flexibility is a reflection of physical parameters such as membrane fluidity and intrinsic curvature that, to a large extent, are determined by membrane lipid composition. The lipid matrix of the ER membrane is mainly composed of diacyl glycerophospholipids enriched in unsaturated acyl chains, with up to 10 mol% sterol [1].

Membrane fluidity depends on the ratio of saturated-to-unsaturated acyl chains and on the membrane's content of phosphatidylethanolamine (PE) and sterol [2], whereas membrane intrinsic curvature is determined by the proportion of lipids with non-bilayer propensity, diunsaturated PE molecular species first and foremost [3]. To maintain membrane physical parameters in an optimal range, glycerophospholipid head group and acyl chain composition need to be regulated in concert, *i.e.* at the phospholipid molecular species level. The ER membrane harbors sensors that monitor membrane physical properties and signal the transcriptional machineries governing fatty acid desaturation and *de novo* phospholipid and sterol biosynthesis to make adjustments as necessary (reviewed by [4,5]). In addition to transcriptional regulation of membrane lipid composition, lipid biosynthetic enzymes are regulated by posttranslational modification such as phosphorylation (see *e.g.* [6]), and acetylation [7].

The synthesis of membrane lipid components, as well as the regulation of those processes, have been extensively studied in yeast [8,9] and eukaryotes in general [10]. Far fewer studies have addressed the role of phospholipid turnover, let alone the regulation of those events, in membrane lipid homeostasis. Several processes contribute to the turnover of the main membrane phospholipids of the ER, *i.e.* phosphatidylserine (PS), phosphatidylinositol (PI), PE, and phosphatidylcholine (PC) [11]. First of all, PS and PE serve as biosynthetic precursors of PE and PC, respectively, making those turnover/conversion reactions the most important quantitatively. Superimposed on the lipid headgroup conversions, the molecular species selectivity (*i.e.* selectivity at the level of the specific acyl chains esterified at the *sn*-1 and *sn*-2 positions of the glycerol backbone) of the decarboxylation of PS to PE

* Corresponding author.
E-mail address: a.i.p.m.dekroon@uu.nl (A.I.P.M. de Kroon).

https://doi.org/10.1016/j.bbalip.2019.05.006
Received 13 March 2019; Received in revised form 1 May 2019; Accepted 15 May 2019
Available online 27 May 2019

[12] and of the triple methylation of PE to PC [13] impacts the membrane's biophysical properties. Since the conversion of PS to PE is for the most part localized outside the ER [14,15], interorganellar lipid transport out of and back into the ER and the local supply of substrate species also play a role.

PE and PI are subject to turnover in several additional biosynthetic reactions. PE serves as precursor in an essential step of the synthesis of the glycosylphosphatidylinositol (GPI) anchor that attaches a subset of plasma membrane proteins to the membrane [16,17], and it becomes covalently bound to Atg8 in the assembly of autophagosomes [18]. Whether these conversions are PE molecular species-selective and affect the molecular species composition of the PE pool is unknown.

PI is the biosynthetic precursor in the synthesis of phosphoinositides, GPI anchors and yeast sphingolipids. The phosphoinositides, phosphatidylinositol phosphate (PIP) and phosphatidylinositol bisphosphate (PIP2) show roughly similar fatty acyl chain compositions as PI in several mammalian cell lines and tissues [19] as well as in yeast [20]. These studies suggest a single rapidly interconverting metabolic pool, which could be interpreted to argue against pronounced molecular species selectivity by the kinases and phosphatases involved. In support of molecular species-selective substrate use, inactivation of the PI-kinases Vps34 and Pik1 or the phosphoinositide phosphatase Sac1 in yeast mutants was found to affect the molecular species profile of PIP [21]. However, the molecular species profile of the bulk membrane lipid PI was largely unaffected in these mutants, underscoring the low abundance of phosphoinositides.

The PI-derived moiety of GPI-anchors is subject to acyl chain remodeling during the assembly of GPI-anchored proteins in the ER and Golgi [17], but no data exists to suggest that GPI anchor synthesis is substrate selective at the level of PI molecular species. In the synthesis of yeast sphingolipids, PI serves as head group donor [22], generating diacylglycerol. To the best of our knowledge no PI molecular species preference has been reported for the Golgi-localized inositol phosphorylceramide synthase, Aur1p. Similarly, no preference for certain PC molecular species has been reported in the synthesis of sphingomyelin in mammalian cells [23].

Finally, bulk membrane phospholipids are subject to turnover by phospholipases and transacylases as part of lipid acyl chain remodeling or degradation. This review will focus on the role of these reactions in membrane lipid homeostasis in the reference eukaryote *Saccharomyces cerevisiae*, with emphasis on the acyl chain remodeling reactions that the bulk membrane phospholipids PC, PI and PE undergo in the ER membrane. First, we will put acyl chain remodeling (also referred to as acyl chain editing or retailoring) in a broader perspective and briefly summarize its discovery and occurrence in eukaryotes.

2. Occurrence and functions of phospholipid acyl chain remodeling in eukaryotes

Phospholipid acyl chain exchange was first reported in a pioneering study by W.E. Lands [24]. He discovered that lysophosphatidylcholine (lysoPC) formed in rat liver microsomes by the action of a phospholipase A_2 (PLA_2), is reacylated by an acyltransferase dependent on the presence of acyl-CoA. These sequential reactions are known as the Lands' cycle, which was proposed to adapt the molecular species profile of PC to obtain the desired thickness and fluidity of cellular membranes [25]. The substrate specificity of the acyltransferases involved leads to the enrichment of saturated acyl chains at the *sn*-1 and unsaturated acyl chains at the *sn*-2 position of the glycerol backbone [26].

Mammalian cells host a multitude of intracellular phospholipases A and acyltransferases, often with tissue-specific distributions, that catalyze phospholipid acyl chain exchange [27–29]. Several of these enzymes play key roles in essential processes, such as the generation of lysophospholipid and eicosanoid messengers in signal transduction. Polyunsaturated fatty acyl chains (PUFAs) including arachidonic acid (C20:4), mainly enter the pool of membrane phospholipids by acyl chain remodeling *via* the Lands' cycle (reviewed by [30]). Mobilization of PUFAs from the phospholipid pool by highly regulated phospholipases presents an essential step in inflammatory responses of the immune system, in which arachidonic acid is converted to eicosanoids (reviewed by [31]). Mobilization is followed by regeneration of the phospholipid.

In recent years, acyltransferases catalyzing acyl chain remodeling have been implicated in processes where maintenance of the proper physical state of the (ER) membrane appears crucial. For example, genetic studies in mice have shown that the ER-localized lysophosphatidylcholine acyltransferase LPCAT3 with a preference for PUFA-CoA is required for VLDL assembly in hepatocytes, and for the regulation of cholesterol biosynthesis and, as a consequence, intestinal stem cell proliferation (reviewed in [32]). The lysophosphatidylcholine acyltransferase LPCAT1 expressed in lung alveolar type II cells, is an important contributor to the synthesis of dipalmitoyl-PC (PC 16:0/16:0), an essential component of pulmonary lung surfactant [33]. Although their names suggest otherwise, most acyltransferases are promiscuous with regard to the lysophospholipid acceptor [30].

In plant cells phospholipid remodeling is crucial for the production of polyunsaturated fatty acids. The chloroplast produces saturated and monounsaturated fatty acids that are exported to the cytosol, and after activation to acyl-CoA, channeled into glycerophospholipids and triacylglycerol [34,35]. A major proportion of C18:1-CoA is incorporated at the *sn*-2 position of lysoPC by acyl-CoA:lysophosphatidylcholine acyltransferase (LPCAT) in the ER. PC then serves as substrate for further desaturation of the acyl chain at the *sn*-2 position by the desaturases FAD2 and FAD3, yielding linoleic (18:2$cis^{9,12}$) and α-linolenic (18:3$cis^{9,12,15}$) acids, which are released for use in *de novo* lipid synthesis [36]. The latter step, regenerating lysoPC, is mediated by phospholipase A activity (Lands' cycle), phospholipid:diacylglycerol acyltransferase (PDAT) or by the reversed LPCAT reaction, yielding free fatty acid, triacylglycerol or acyl-CoA, respectively [35].

Phosphatidylcholine deacylation and reacylation has been proposed to facilitate lipid transport at membrane contact sites between ER and the chloroplast outer envelope membrane [37]. Transfer of more polar lysoPC and acyl-CoA between membranes would be energetically more favorable than of intact PC.

In the model eukaryote *Saccharomyces cerevisiae*, remodeling of PC in microsomes was discovered by Yamada and colleagues [38]. Phospholipid acyl chain exchange was demonstrated *in vivo* in yeast by the fast, on a time scale of minutes, incorporation of radiolabeled oleic and palmitic acid supplied in the culture medium into the major membrane phospholipids [39]. While studies in yeast have often paved the way for understanding mechanisms and functions of the homologous processes in so-called higher eukaryotes, this does not (yet) apply to lipid acyl chain remodeling, with the notable exception of Taz1p (tafazzin)-mediated remodeling of cardiolipin in mitochondria [40].

3. Definition and mechanisms of phospholipid (acyl chain) remodeling

We define phospholipid acyl chain remodeling, or phospholipid remodeling in short, as comprising reactions in which one or both phospholipid acyl chains are exchanged by deacylation and subsequent reacylation, with a lysophospholipid or glycerophosphodiester as intermediate. This implies that the phospholipid headgroup stays attached to the glycerol backbone in acyl chain remodeling reactions, *i.e.* the glycerophosphodiester moiety remains intact. Thus, the recycling of choline (or ethanolamine) derived from PC (or PE) degradation back into PC (or PE) *via* the CDP-choline (or CDP-ethanolamine) route is considered *de novo* phospholipid biosynthesis rather than lipid remodeling. Moreover, phosphatidic acid (PA) can only be remodeled with lysoPA as intermediate since reacylation of its glycerophosphomonoester moiety, glycerol-3-phosphate, is indistinguishable from *de novo* synthesis.

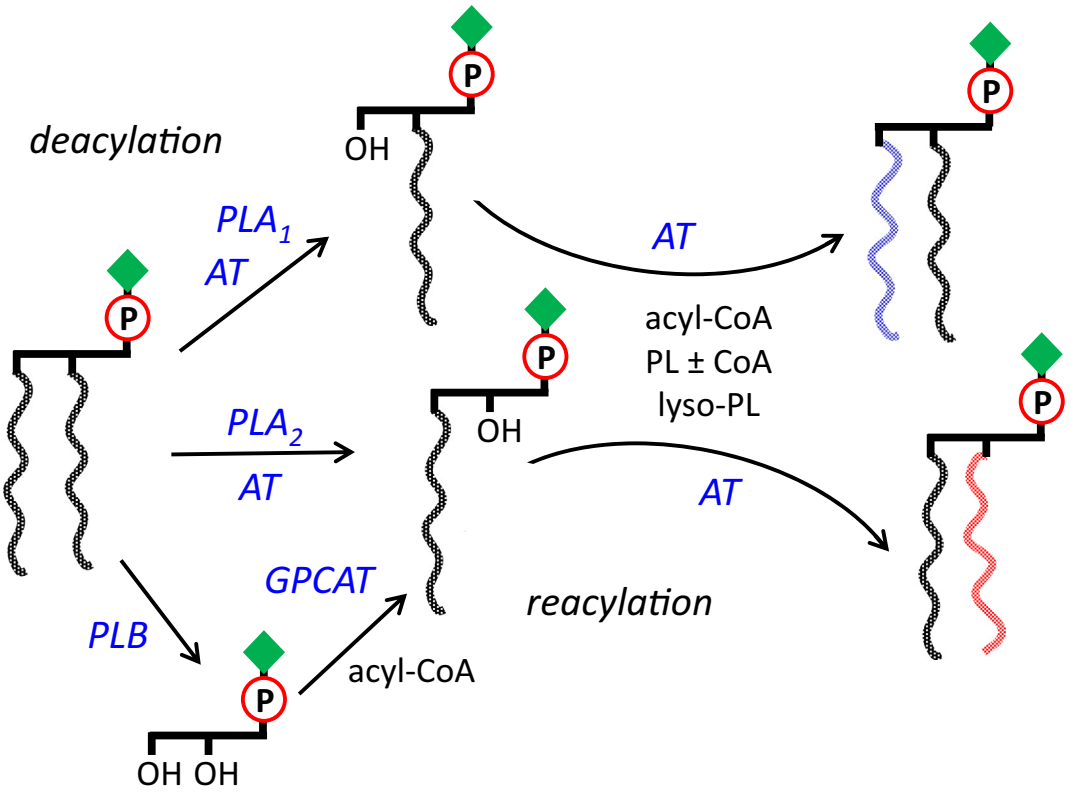

Fig. 1. Phospholipid acyl chain remodeling reactions in eukaryotes, as found for phosphatidylcholine (PC). PC is first deacylated by a phospholipase A_1 (PLA_1), A_2 (PLA_2), or B (PLB), yielding *sn*-1 lyso-PC, *sn*-2 lyso-PC or glycerophosphocholine (GPC), respectively. Acyltransferases (AT) may generate lyso-PC in transacylation reactions. Subsequently GPC is reacylated to *sn*-2 lyso-PC by glycerophosphocholine acyltransferase (GPCAT), and lyso-PC's are reacylated by AT that use acyl-CoA's, phospholipids (in CoA-dependent or independent reactions) or lyso-phospholipids as acyl donor.

In addition to the acyl-CoA dependent Lands' cycle introduced above, several other mechanisms of acyl chain remodeling have been described (Fig. 1; reviewed in [28]). These include CoA-dependent transacylation reactions in which an acyl chain is transferred from a diacyl phospholipid to a lysophospholipid in the presence of CoA. This transacylation consists of the reverse (*i.e.* ATP-independent acyl-CoA synthesis) and forward reactions of acyl-CoA-dependent acyltransferases, with acyl-CoA serving as short-lived intermediate. In CoA-independent transacylation an acyl chain is directly transferred from a diacyl- or lysophospholipid donor to a lysophospholipid without requirement for any cofactor. The lecithin:cholesterol acyltransferase (LCAT) transfers the *sn*-2 acyl chain from PC to cholesterol generating lysoPC and cholesteryl ester in mammalian systems. Likewise, a phospholipid:diacylglycerol acyltransferase (PDAT) transfers an acyl chain from a phospholipid to diacylglycerol (DAG) generating an *sn*-2 lysophospholipid and triacylglycerol in plants and yeast [41]. Recently, the exchange of both phospholipid acyl chains with a glycerophosphodiester as intermediate was reported for PC. This reaction involves acyl-CoA:glycerophosphocholine acyltransferase (GPCAT) activity and was first demonstrated in plants and yeast [42,43].

The enzymes involved in phospholipid remodeling at the ER mostly contain conserved motifs that predict their generalized function. Most acyltransferases and transacylases catalyzing reacylation belong to the acylglycerophosphate acyltransferase (AGPAT) family or to the membrane bound O-acyltransferase (MBOAT) family. The characteristic AGPAT domain contains four conserved motifs [44], and is widespread, but not found in viruses or archaea. This family comprises taffazin as well as 1-acyl-*sn*-glycerol-3-phosphate acyltransferases [28,45,46], including mammalian LPCAT1 mentioned above. The AGPAT family is a member of the larger Acyltransferase Clan (CL0228) which includes several families of acyltransferases, including DAGAT and LipA acyltransferases [45,46].

Members of the MBOAT superfamily (Clan CL0517) are found in all kingdoms of life and are characterized by the ability to transfer organic acids onto hydroxyl groups of membrane-embedded targets [47]. Many, but not all MBOAT-containing enzymes, utilize acyl-CoA as the acyl donor and targets include lipids, amino acids residues within proteins, and other hydroxyl group-containing compounds [47,48]. All confirmed MBOAT proteins (including mammalian LPCAT3 mentioned above) contain a conserved histidine residue that appears important for catalysis [47,49]. A recent paper presents the crystal structure of DltB, an MBOAT that catalyzes the alanylation of cell-wall teichoic in Gram-positive bacteria [50], providing the most detailed structural information on this class of enzymes to date. The structure reveals an extracellular funnel extending into the membrane with the conserved histidine located at the bottom. A narrow tunnel connects the histidine to the cytoplasm suggesting a mechanism of cross-membrane catalysis.

4. ER-based phospholipid turnover by acyl chain remodeling and degradation

Here we will review current knowledge of degradation and acyl chain remodeling of PC, PE and PI, the bulk phospholipid constituents found in the yeast ER membrane [11], and the enzymes involved. Since PC is at the end of the phospholipid biosynthetic pathways, and has a relatively long half-life compared to PE and PI, which also serve as biosynthetic intermediates to other lipids [51], PC turnover has been most extensively characterized.

4.1. PC

PC turnover, acyl chain remodeling, and biosynthesis are

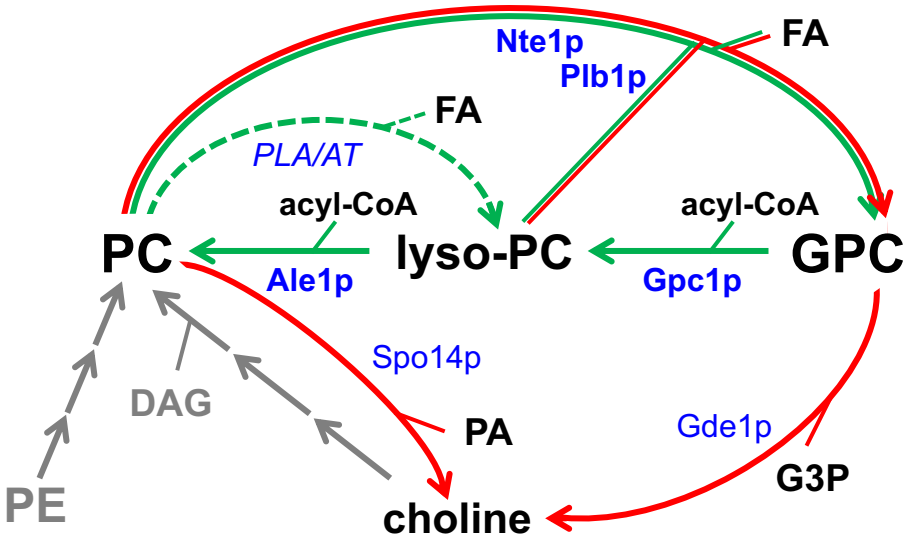

Fig. 2. Phosphatidylcholine (PC) turnover in the yeast ER. Turnover reactions degrading PC are indicated by red arrows, acyl chain exchange reactions (PC-DRP) by green arrows, and the enzymes involved in blue, with those localized to the ER in bold. The putative conversion of PC to lyso-PC by a phospholipase A (PLA) or transacylase (AT) referred to by the dashed green arrow has not been demonstrated *in vivo*. The methylation of phosphatidylethanolamine (PE) and the CDP-choline pathway both synthesizing PC *de novo* are indicated in grey. DAG, diacylglycerol; FA, fatty acid; G3P, glycerol-3-phosphate; GPC, glycerophosphocholine.

intertwined (Fig. 2). At any point in time, the PC molecular species profile observed in cellular membranes reflects both the molecular specificity of the biosynthetic routes and post-synthetic acyl chain exchange [52–54]. Beginning with the basics, the fatty acids esterified to the *sn-1* and *sn-2* positions of the glycerol backbone in PC are mainly C16 and C18 with one or no double bonds, although shorter chain fatty acids occur in lesser amounts. As a result, four major PC species occur: PC 32:1 (monounsaturated) consisting of C16:0 and C16:1, PC 32:2 (diunsaturated) consisting of C16:1 and C16:1, PC 34:2 (diunsaturated) consisting of C16:1 and C18:1, PC 34:1 (monounsaturated) consisting of either C16:0 and C18:1 (this being the predominant acyl chain combination) or C16:1 and C18:0 [53,55]. In general, the unsaturated species predominate at the *sn-2* position [39,56]. PC biosynthesis occurs through the PE methylation and the CDP-choline pathways. The methylation pathway produces primarily diunsaturated species and the CDP-choline pathway a more heterogeneous set of PC molecules [52] that appears to reflect the available pool of diacylglycerol species [57]. In choline-free media, the CDP-choline pathway does not contribute to net synthesis, but rather utilizes choline released through PC turnover events for re-synthesis [58].

Phospholipase D (encoded by *SPO14/PLD1*) produces choline and PA, the choline being converted to choline-phosphate by Cki1p during the first step of the CDP-choline pathway [59]. Other than cardiolipin-specific Cld1p [60] and Ddl1p, a PLA_1 with a broad substrate specificity [61,62], both of which are localized to mitochondria, no dedicated phospholipases A have been identified in yeast. The ER-localized PDAT Lro1p and the mitochondrial CoA-independent transacylase Taz1p were shown to convert PC into *sn*-1 lysoPC *in vitro* [41,63,64]. However, whether these reactions also occur *in vivo* remains to be established.

PC turnover *via* the activity of phospholipases of the B type, primarily Plb1p and Nte1p, results in the formation of free fatty acids and glycerophosphocholine (GPC, Fig. 2) [65,66]. Plb1p is a protein of 73 kDa consisting of 664 amino acids [65]. Although first thought to be plasma membrane-associated and secreted, it was later shown to be primarily ER-associated, as well as secreted from the cell [67]. Plb1p contains no predicted transmembrane domains, suggesting that it enters the ER lumen and associates transiently with the membrane to perform its enzymatic activities. Plb1p contains the Pfam [45,46] defined PLA2_B domain (PF01735). This family includes lysophospholipase/phospholipase B (EC:3.1.1.5) [65] and cytosolic phospholipase A2 [68] activities (EC:3.1.4). The phospholipase Nte1p consists of 1679 amino acids with a predicted MW of 187 kDa [66]. It derives its name from its similarity to the human neuropathy target esterase gene [66,69]. Nte1p is ER-associated and has four predicted transmembrane domains. It contains cyclic nucleotide-binding domains (PF00027) as well as a patatin-like phospholipase domain (PF01734). The patatin domain is found widely across eukaryotic and prokaryotic organisms and contains the consensus serine lipase motif, Gly-X-Ser-X-Gly [70,71]. Radiolabeling showed that Nte1p deacylates PC derived from CDP-choline rather than PC synthesized by the methylation of PE [66], in agreement with the observation that the supply of choline induces deacylation of PC [72]. An explanation for these intriguing findings is lacking, and requires future experiments that distinguish between the stimulatory effects of choline on PC synthesis on the one hand and PC degradation on the other. To date there have been no indications that the phospholipases that turn over PC exhibit molecular species selectivity.

Some of the GPC produced is released extracellularly [72,73] and can be transported back into the cell *via* the Git1p permease under low phosphate conditions [74]. Git1p, which transports both GPI (Section 4.2) and GPC, provides a mechanism for adding exogenous radiolabeled GPC in order to track its metabolism [74]. Through a series of such experiments, GPC has been shown to have two potential metabolic fates. The first metabolic fate does not impact remodeling as defined here, but does impact synthesis. The glycerophosphodiesterase encoded by Gde1p hydrolyzes GPC to produce glycerol-3-phosphate and choline [74,75]. The choline released through Gde1p activity can be incorporated into the CDP-choline pathway for PC biosynthesis (Fig. 2).

The second metabolic fate for GPC, its acylation to lysoPC, directly impacts PC remodeling. This atypical acyltransferase activity, one acting on GPC instead of glycerol-3-phosphate, was first detected in yeast [43] and plant [42] extracts. Identification of *GPC1*, the GPC acyltransferase (GPCAT)-encoding gene, took longer, as it required a biochemical screen of a portion of the yeast knockout collection due to the lack of similarity of Gpc1p to other known acyltransferases [76]. Unlike other enzymes involved in lipid remodeling in yeast, Gpc1p has no domains that would have predicted its role as an acyltransferase [54,76]. Gpc1p consists of 432 amino acid residues and has a MW of 53 kDa. The protein has 8 predicted transmembrane segments and a DUF2838 domain (PF10998). DUF2838 is one of several domains of unknown function (DUFs) collected in the Pfam database. The results of high throughput analysis suggest that Gpc1p localizes to the ER [77]. Gpc1p homologs are widely distributed in eukaryotes, including fungi, plants, animals, algae and protists [76]. Notably, Gpc1p homologs are not found in prokaryotes nor in the animal subclades of chordates and arthropods. Gpc1p homologs cloned from *Arabidopsus thaliana, Ricinus communis* (castor bean) and *Brassica napus* (oilseed rape) were shown to also have GPCAT activity when expressed in yeast [76], suggesting that other homologs will also have this function.

Once Gpc1p has formed lysoPC, the lysophospholipid acyltransferase, Ale1p, is primarily responsible for the second acylation step to produce PC, although other acyltransferases may be involved [54,76]. Ale1p is an acyl-CoA-dependent acyltransferase that consists of 619 amino acids (MW 72 kDa) and belongs to the MBOAT family (PF03062). Ale1p preferentially esterifies unsaturated acyl chains at the *sn*-2 position of a variety of lysophospholipids *in vitro* [78–82]. However, deletion of *ALE1* hardly affects the molecular species profiles of the major phospholipid classes [78]. In support of a role for Ale1p in PC remodeling, *ale1Δ* cells contain more lysoPC than wild type [80], and accumulate lysoPC when supplied with GPC [54]. Ale1p is ER-localized and enriched in mitochondria-associated membranes (MAM) [81]. It contains multiple membrane spanning regions and its conserved His residue was localized to the ER lumen like that of other yeast MBOAT enzymes [49]. If the conserved His residue is part of the active site, this would imply that the acylation of lysoPC occurs in the ER lumen. We speculate that the cytosol-facing tunnel found in the crystal structure of DltB and most likely conserved in other MBOAT proteins [50], allows access of cytosolic acyl-CoA to the enzyme's active site at the bottom of the luminal funnel.

The identification of Gpc1p, coupled with *in vitro* and *in vivo* experiments in various mutant backgrounds, defined a novel route for PC biosynthesis. Perhaps more importantly, it provided the last player in a post-synthetic PC deacylation/reacylation remodeling pathway (PC-DRP) by which both acyl chains can be exchanged [54,76]. Indeed, prior to the identification of Gpc1p, an enzyme with such an activity was predicted through experiments in which post synthetic acyl chain remodeling of PC was detected [52,83]. In particular, pulse-chase studies in a *pct1Δ* mutant in which the CDP-choline route is inactivated, using deuterium labeled (*methyl*-D3)-methionine followed by ESI-MS/MS analysis, detected a post-synthetic increase in monounsaturated PC species (PC 32:1, PC 34:1) at the expense of diunsaturated PC species (PC 32:2, PC 34:2) that stems from the preferential incorporation of C16:0 at the *sn*-1 position [52,56]. Gpc1p activity appears to be primarily responsible for this remodeling at the *sn*-1 position to more saturated species based on experiments with strains lacking and overexpressing the gene [54]. Accordingly, *in vitro* assays show that microsomal Gpc1p has a preference for C16:0-CoA as acyl donor [76]. Similar assays revealed that Gpc1p acylates GPC at about tenfold reduced rate when lysoPC is supplied as acyl donor instead of acyl-CoA [76].

The overexpression of the GPAT *SCT1* increases cellular C16:0 content, and strongly enhances the incorporation of C16:0 into PC by acyl chain remodeling in *pct1* cells, thus providing a more sensitive read-out of PC remodeling by ESI-MS/MS [53]. Under these conditions, deletion of the *PLB1* gene was found to reduce the rate of PC remodeling and the cellular lysoPC content [56], implicating Plb1p in PC-DRP.

4.2. PI

PI synthase encoded by the *PIS1* gene uses CDP-DAG and inositol to synthesize PI [84]. Compared to the other phospholipid classes PI is strongly enriched in saturated acyl chains, which are present at 50% of total [55,85], some 10% being stearic acid (C18:0). A major fate of PI is its deacylation by Plb3p to produce free fatty acids and intracellular and extracellular GPI [51,73,86]. Under conditions of low phosphate availability, extracellular GPI is taken up by the Git1p transporter [87]. There is no evidence that GPI can be reacylated or contributes to PI remodeling. Whether the deacylation of PI is molecular species-selective is not known.

The enrichment of C18:0 results from acyl chain remodeling by the acyl-CoA dependent acyltransferase Cst26p/Psi1p [88]. Cst26p/Psi1p consists of 397 amino acids, has a MW of 46 kDa, and is localized to the ER [8]. It has 3 predicted transmembrane domains and contains the acyltransferase domain (PF01553). Deletion of *CST26* causes the virtual disappearance of stearic acid from the *sn*-1 position of PI, and accordingly, microsomes isolated from the mutant lack acyltransferase activity for *sn*-2-acyl-1-lysoPI [88]. Interestingly, the deletion mutant has an overall reduced cellular C18:0 content, indicating the loss of a metabolic sink for C18:0 chains [89]. The loss in C18:0 is compensated for by a rise in the proportion of C16:0 that appears to preferentially end up in PC [88]. The phospholipase or transacylase generating 2-acyl-lysoPI remains elusive.

Deletion of *CST26* was recently reported to exhibit strong negative genetic interactions with deletion of *ELO2* and *ELO3,* genes that encode the acyl-CoA elongases responsible for the synthesis of C26:0-CoA required for sphingolipid synthesis [90]. It turned out that Cst26p is important for synthesizing a minor molecular PI species with C26:0 attached at the *sn*-1 position [91]. In *elo2Δ* or *elo3Δ*, Cst26p most likely generates PIs with a very long saturated acyl chain at *sn*-1 that compensate for the lack of mature sphingolipids [90].

The majority of PI and derived phosphoinositides in mammalian cells consists of the 1-stearoyl-2 arachidonoyl molecular species [92]. The post-synthetic incorporation of C18:0 at the *sn*-1 position of PI by Psi1p homologs (AGPAT8/ALCAT1) has been conserved in higher eukaryotes including *C. elegans* and mice [93,94]. An acyltransferase belonging to the MBOAT family, LPIAT1 (MBOAT7) incorporates C20:4 at the *sn*-2 position of PI *via* the Lands' cycle [95].

4.3. PE

Data on the degradation and remodeling of PE in yeast is scarce. A Ca^{2+}-dependent PE-hydrolyzing phospholipase D activity was reported that has not yet been assigned to an ORF [96,97]. Turnover of PE to glycerophosphoethanolamine (GPE) has been reported in a *cho2opi3* strain that accumulates PE due to inactivation of the methylation of PE to PC [72]. Plb1p that hydrolyzes PE *in vivo* [65], and/or the broad specificity phospholipase Plb2p [86] may be involved. Ale1p is the major acyltransferase acylating lysoPE [81], and accordingly, *ale1Δ* cells contain more lysoPE than wild type [80].

Remodeling of exogenously supplied short-chain PE 10:0/10:0 by exchange of both acyl chains was demonstrated in a *psd1Δ psd2Δ* strain with impaired PE synthesis [98]. Whereas Plb1p, Plb2p, Plb3p, Nte1p, Ddl1 and the potential phospholipase Spo1p were not required for the remodeling, Ale1p and, to a less extent, Slc1p, the major lysoPA acyltransferase [78], were involved in the incorporation of C16:1 and C18:1 acyl chains at the *sn*-2 position.

The involvement of additional enzymes in PE turnover and remodeling may be inferred from data obtained *in vitro*. Microsomal Gpc1p acylates GPE [76], presumably at the *sn*-1 position. The dual function enzyme Tgl3p with both triacylglycerol lipase and acyltransferase activity, acylates *sn*-2 lysoPE *in vitro* [99]. The PDAT Lro1p uses PE and PC as acyl chain donor *in vitro* [41,63], with a preference for PE [100]. Based on the observations that both the synthesis of triacylglycerol and the activity of Lro1p are decreased in mutants impaired in PE biosynthesis *via* the Kennedy pathway, Lro1p was proposed to preferably deacylate PE *in vivo* [101].

Lro1 consists of 661 amino acids with a MW of 75 kDa, and contains an LCAT (lecithin: cholesterol acyltransferase) domain (PF02450). This family also encompasses enzymes with phospholipid:diacylglycerol acyltransferase (PDAT) activity (EC 2.3.1.158) that, like Lro1, transfer acyl groups from the *sn*-2 position of a phospholipid to diacylglycerol, thus forming an *sn*-1 lysophospholipid. The LCAT family is part of the Alpha/Beta (AB) hydrolase clan. The AB hydrolase fold, is found in a wide range of enzymes [102]. Lro1p has been localized to the ER membrane, contains a single transmembrane domain, and has a large luminal domain containing the active site [103].

In mammals, LPEAT1, an MBOAT, and LPEAT2, an AGPAT, acylate lysoPE using unsaturated acyl-CoA as preferred acyl donor [28]. Both have been implicated in the synthesis of cone-shaped PE, required for organogenesis [30] and osteoclast fusion [104], respectively.

5. Functions of phospholipid acyl chain remodeling in yeast

In the absence of any strong phenotypes associated with the inactivation of enzymes implicated in phospholipid acyl chain remodeling in the ER, we can only speculate about its biological functions. The most obvious function for phospholipid acyl chain remodeling is the fine-tuning of membrane lipid composition at the molecular species level to ensure optimal membrane physical properties and to sustain specific lipid functions. The latter may be exemplified by the changes in the cellular distribution of PI(4)P and PI(4,5)P_2 impacting cell polarity that were observed in a *cst26* deletion mutant [20]. Inactivation of Cst26p not only depletes PI of C18:0 acyl chains, but PIP and PIP_2 as well. Furthermore, acyl chain remodeling may serve to remove acyl chains that have been damaged, *e.g.* by oxidation.

Phospholipid acyl chain remodeling of PC by PC-DRP has been proposed to buffer acyl chain composition [56], based on the increased channeling of C16:0 into PE-derived PC by, presumably, Gpc1p-mediated acyl chain remodeling under conditions of Sct1p overexpression. Studies in which free fatty acids were supplied in the culture medium provided further clues as to the buffering function of acyl chain remodeling. Yeast *dga1Δ lro1Δ* mutants lack the ability to store excess acyl chains in triacylglycerol, and as a consequence exhibit sensitivity to unsaturated but not to saturated fatty acids supplied in the culture medium [105,106]. Exogenous C16:0 was found to be efficiently incorporated in the phospholipid fraction, PC and PS in particular, in the absence of TAG synthesis [106]. Accordingly, if *dga1Δ lro1Δ* cells are disturbed in PC synthesis by deletion of either of the phospholipid methyltransferase-encoding genes *CHO2* or *OPI3* they become sensitive to C16:0 [106].

Interestingly, PC deacylation *via* Plb1p is regulated in coordination with sphingolipid biosynthesis. Abrogation of sphingolipid biosynthesis *via* deletion of the Ypk1 kinase or treatment with myriocin results in increased Plb1p expression and increased PC turnover. Moreover, deletion of *PLB1* exacerbates the phenotype of a *ypk1Δ* mutant, while overexpression of *PLB1* (but not of *NTE1*) rescues cells defective in Ypk1p and Ypk2p, suggesting that increased PC turnover (or remodeling) mitigates the consequences of defects in sphingolipid biosynthesis [67].

Studies on the physiological importance of Gpc1p are just beginning, but it is, like other genes involved in lipid metabolism in yeast, upregulated by inositol limitation [8]. In addition, *gpc1Δ* mutants growing in inositol-free medium display a defect in stationary phase viability [54]. Thus, PC remodeling to more saturated molecular species may be important for maintaining long-term survival under certain culture conditions.

6. Conclusion and future directions

Acyl chain remodeling of the bulk membrane phospholipids PC and PI has been unequivocally demonstrated in yeast, and several of the enzymes involved have been identified. As detailed in Section 5, we are beginning to catch the first glimpses of possible functions of acyl chain remodeling. Many questions remain: *e.g.*, what is the added value of PC-DRP given that choline-recycling *via* the CDP-choline pathway also increases the saturated acyl chain content of PC [52]? How are PC-DRP and recycling of choline *via* the CDP-choline route regulated? The membrane topology of Plb1p, Ale1p and Lro1p raises the question of whether acyl chain remodeling is restricted to the luminal leaflet of the ER membrane, and prompts elucidation of the active site and membrane topology of Gpc1p and Cst26p. Which additional enzymes are involved?

With the availability of dynamic lipidomics approaches and the ease of obtaining yeast mutants, there are no technical obstacles to increase our insight into yeast acyl chain remodeling and its role in membrane lipid homeostasis. We expect it to soon reach and surpass knowledge about acyl chain remodeling in higher eukaryotes.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgments

We thank the (former) members of our research groups for useful discussions and their input in the research described here. This work was supported by the Division of Chemical Sciences in the Netherlands with financial aid from The Netherlands Organization for Scientific Research (NWO) and by National Institutes of Health Grant R15 GM104876 (to J. P.-V.).

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