Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Mitochondrial acyltransferases and glycerophospholipid metabolism

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ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 23 June 2016
Accepted 28 June 2016
Available online xxxx

Keywords:
Glycerolipid
Remodeling
Phosphatidic acid
Acyltransferase
Mitochondrial associated membrane
Phospholipid

ABSTRACT

Our understanding of the synthesis and remodeling of mitochondrial phospholipids remains incomplete. Two isoforms of glycerol-3-phosphate acyltransferase (GPAT1 and 2) and two isoforms of acylglycerol-3-phosphate acyltransferase (AGPAT4 and 5) are located on the outer mitochondrial membrane, suggesting that both lysophosphatidic acid and phosphatidic acid are synthesized in situ for de novo glycerolipid biosynthesis. However, it is believed that the phosphatidic acid substrate for cardiolipin and phosphatidylethanolamine biosynthesis is produced at the endoplasmic reticulum whereas the phosphatidic acid synthesized in the mitochondria must be transferred to the endoplasmic reticulum before it undergoes additional steps to form the mature phospholipids that are trafficked back to the mitochondria. It is unclear whether mitochondrial phospholipids are remodeled by mitochondrial acyltransferases or whether lysophospholipids must return to the endoplasmic reticulum or to the mitochondrial associated membrane for reesterification. In this review we will focus on the few glycerolipid acyltransferases that are known to be mitochondrial. This article is part of a Special Issue entitled: Lipids of Mitochondria edited by Guenther Daum.

1. Introduction

Mitochondria are endosymbionts, derived from ancient oxygen consuming bacteria that set up housekeeping within anaerobic eukaryotic cells [1,2]. Over the eons virtually all mitochondrial genes were transferred to the nucleus and only 13 protein-encoding genes remain, all of which encode for oxidative phosphorylation complex subunits that are translated within the mitochondria. Thus, the phospholipids that comprise the inner and outer membranes of mitochondria are synthesized by enzymes that are encoded by nuclear DNA. Most of these synthetic enzymes are located on the endoplasmic reticulum (ER) or on a specialized ER region called the mitochondrial-associated membrane (MAM). Thus, their phospholipid products require specialized systems to traffic from their site of synthesis to the mitochondrial membranes themselves. In this review we will focus on the few acyltransferases that are mitochondrial and that initiate phospholipid synthesis or remodel mitochondrial phospholipids.

The first step in the synthesis of phospholipids is catalyzed by one of four glycerol-3-phosphate acyltransferase (GPAT) isoforms. Their catalytic sites face the cytosol where they have access to long-chain acyl-CoAs and glycerol-3-phosphate. GPAT3 and −4 are located on the ER, and GPAT1 and −2 are present on the outer mitochondrial membrane (OMM) [3]. Similarly, among the several isoforms purported to be lysophosphatidic acid acyltransferases (LPAAT/AGPAT) [4], only AGPAT4 and 5 are located on the OMM [5,6]. Although the locations of most of the phospholipid synthetic genes remain insufficiently characterized, it is generally held that the terminal enzymes for the syntheses of phosphatidylcholine (PC), phosphatidylserine (PS), and phosphatidylinositol (PI) are located on the ER or on the MAM. One might consider the MAM to be a membrane hub enriched for lipid synthesis [7], because it contains cholesterol acyltransferase (ACAT) [8], acyl-CoA synthetase-4 (ACSL4) [9], phosphatidylethanolamine (PE) methyltransferase (PEMT) [10], cardiolipin (CL) acyltransferase (ALCAT1) [11], and PS synthase1 and −2 (PSS1, PSS2) [12]. The PSS isoforms synthesize the PS that is used for PE synthesis via PS decarboxylase [13]. MAM also contains lysophospholipid acyltransferases such as LPIAT1 [14] and Ale1, a lysoPE acyltransferase member of the mBOAT (membrane-bound O-acyltransferase) family that is located on the ER in vertebrates but on MAM in yeast [15]. When overexpressed, lysoPC acyltransferase 1 (LPCAT1) is found in both the ER and mitochondria, but it is not known whether these are the normal in vivo locations [16]. The fact that the terminal synthetic enzymes for PC, PS, and PI are present on ER or MAM membranes means that the products of mitochondrial GPAT and AGPAT (LPA and PA, respectively) must first be transferred to the ER, perhaps via liver fatty acid binding protein [17,18], in order to provide diacylglycerol to complete PC and PE synthesis before being transported and incorporated into mitochondria membranes (Fig. 1).

Contrasting with the synthesis of PC, for example, the syntheses of PE, PG, and CL differ in that phosphatidic acid (PA) and other

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http://dx.doi.org/10.1016/j.bbalip.2016.06.023
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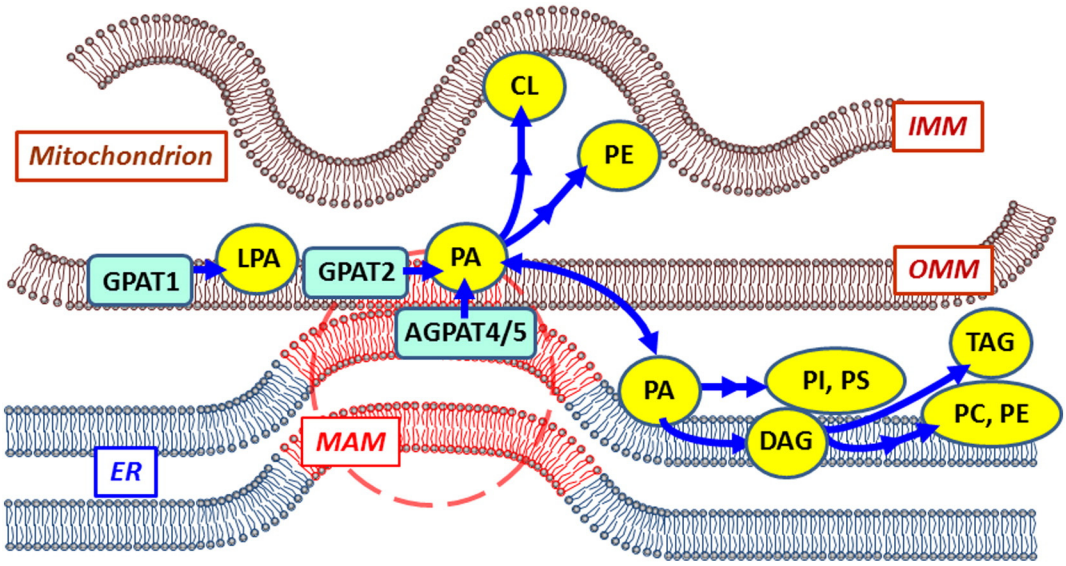

Fig. 1. Possible routes of PA transfer from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM) or the endoplasmic reticulum (ER). LPA, lysophosphatidic acid; PA phosphatidic acid; CL, cardiolipin; DAG, diacylglycerol; MAM, mitochondrial associated membrane; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; TAG, triacylglycerol.

downstream substrates such as CDP-diacylglycerol must be transported to the mitochondrial membranes where the final steps occur. In yeast, Ups1 transfers PA between mitochondrial membranes for CL synthesis [19], but this transport is not known to occur in other eukaryotic cells. Several modes of transport have been proposed for phospholipids and their precursors [20–22], but experimental data are best for yeast PS which is likely transported via tethering of the ER-mitochondria encounter structure (ERMES) [23,24]. Transport systems will be discussed elsewhere in this issue, but the question remains as to whether phospholipids whose synthesis is initiated on the OMM differ from those whose synthesis begins at the ER; specifically, do the acyl chains of mitochondrial and ER phospholipids differ, and does PA synthesized on the OMM contribute to CL synthesis?

After the initial synthesis of a phospholipid, its acyl-chains are heavily remodeled. The Ca^{2+}-independent PLA2 family member, iPLA2γ is mitochondrial [25], and mitochondria from mice deficient for iPLA2γ have a profound decrease in oxygen consumption [26], suggesting that phospholipid remodeling is essential for mitochondrial respiration. Although it is not known whether the lysophospholipid that is formed must return to the ER for reacylation, human cPLA2γ in mitochondria does expresses transacylase activity and could reesterify LPC [27]. Arguing against a transacylase role for iPLA2γ is a study in which a knockout of iPLA2γ in Taz-deficient mice did not prevent the decrease in tetralinoleoyl-CL [28]. Several lysophospholipid acyltransferases have been identified but their locations have not been confirmed. Modifications of CL are the exception; the final steps in CL synthesis take place on the inner mitochondrial membrane [22] as does deacylation by the CL deacylase (Cld1) in yeast and reacylation by the transacylase Taz1 on the IMM side facing the intermembrane space [21]. CL remodeling is discussed elsewhere in this issue.

Three families of intrinsic membrane proteins catalyze glycerolipid esterification. The 11 members of the mBOAT family in humans [29] esterify neutral lipids (e.g. DGAT1, ACAT1), reacylate lysophospholipids [30], and acylate proteins such as Wnt proteins, hedgehog, and ghrelin [31], but none of the mBOAT enzymes is known to be located on mitochondrial membranes. The seven members of the acylglycerol acyltransferase (AGAT) family are located on the ER where they esterify monoacylglycerol (MGAT) or diacylglycerol (DGAT2) or synthesize wax esters (AWAT) [32]. A third family contains motifs that denote a PlsC region [4,33,34]. Members of the PlsC family esterify glycerol-3-P, LPA, lysophospholipids, and dihydroxyacetone-P [3]. The dihydroxyacetone-P acyltransferase (DHAPAT; gene: *Gnpat*) is the only PlsC member with a peroxisomal location. We will focus on those PlsC family members known to be located on the OMM, GPAT1, GPAT2, AGPAT4 and AGPAT5, and we will address questions about deacylation-reacylation activities that modify fully formed mitochondrial phospholipids, although these lysophospholipid acyltransferases are thought to be located on the ER.

2. Glycerol-3-P acyltransferase-1

2.1. Structure and location

In eukaryotic cells GPAT1, an 828 amino acid protein, is closely related to the *Escherichia coli* GPAT (*PslB*) in both size, membrane orientation, and active site motifs which are located in the N-terminus portion [34]. GPAT1 is located on the outer mitochondrial membrane with its N- and C-termini facing the cytosol [35]. The active site residues are followed by two transmembrane domains with an 81 amino acid loop that faces the intermembrane space. Although their active site motifs are similar, GPAT1 is twice as large as the ER GPAT isoforms, which contain about 445 amino acid residues, and the AGPAT isoforms, which range between 283 and 524 amino acid residues. The C-terminal portion of GPAT1 interacts with its active site region and probably has a regulatory function, but this has not been studied except to show that all activity is lost when any portion of the C-terminal end is truncated [36].

2.2. Regulation

GPAT1 is regulated both transcriptionally and post-transcriptionally. Gene expression (*Gpam*) is upregulated by SREBP1c and ChREBP when dietary carbohydrate intake and plasma insulin are high [37,38]. In fact, in *ob*/*ob* mice in which massively steatotic livers result from upregulation of SREBP1c [39], GPAT1 appears to be largely responsible. Both shRNA knockdown of *Gpam* [40] and the double knockout of *ob*/*ob*:*Gpam*$^{-/-}$ dramatically ameliorate the fatty liver [41]. Decreased DNA methylation improves SREBP-1c recruitment, and when pregnant female mice are fed a high-fat/high-sucrose diet, the livers of their pups show decreased *Gpam* promoter methylation, increased GPAT1 expression, and increased liver triacylglycerol (TAG) content [42]. Qiagen also lists binding sites for LCR-F1,Pax-2b, Pax-2a, Pax-2, HNF-3β, GATA-2, c-Myc, Max1, ZIC2/Zic2, and FOXO3, but regulation by

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these transcription factors has not been studied. Multiple unstudied post-translational modifications are also listed. (http://www.phosphosite.org/proteinAction?id=16689&showAllSites=true#appletMsg). Casein kinase-2 phosphorylates rat liver GPAT1, but the site and significance of the modification was not shown [43]. Treating rat primary adipocytes with insulin increases GPAT1 Vmax and Km for both its substrates, and mass spectrometry identified phosphorylation at serine 632 and serine 639. These sites correspond to casein kinase-2 consensus sequences that are conserved in vertebrate GPAT1, but not in GPAT1 from fly, fungal or plant species [44].

2.3. Function

GPAT1 contributes about 10% of total GPAT activity in most cells, but in liver it constitutes 30–50% of activity [3]. The relative amount of GPAT1 contribution is likely due to its gene expression regulated by SREBP1c and ChREBP [37,38], because in SREBP1c null mice, fasting and refeeding do not upregulate GPAT1 mRNA expression [45]. SREBP1c and ChREBP also upregulate the enzymes required for *de novo* fatty acid synthesis, ACC, FASN, ACLY, and SCD1. As part of a transcriptionally-regulated pathway of de novo FA synthesis that produces palmitate as its primary product, it is not surprising that GPAT1 prefers saturated fatty acyl-CoAs, particularly palmitoyl-CoA. Because GPAT1 esterifies the newly formed acyl-CoAs, its co-regulation with de novo FA synthesis diminishes access of newly formed acyl-CoAs to CPT1 and prevents their conversion to acyl-carnitines that would be imported into the mitochondria and undergo β-oxidation. Thus, concomitant fatty acid synthesis and oxidation are avoided. Even under conditions in which high insulin and glucose promote the formation of the allosteric CPT1 inhibitor, malonyl-CoA, CPT1 remains sufficiently active to conduct de novo synthesized FAs towards mitochondrial oxidation, as demonstrated by the increase in fatty acid oxidation in liver from *Gpat1*$^{-/-}$ mice [46].

GPAT1 in primary rat hepatocytes is inhibited 22–34% by 5-amino-4-imidazolecarboxamide riboside (AICAR), whose phosphorylated metabolite is an activator of AMP-activated kinase, and purified recombinant AMPKα1 and AMPKα2 inhibit hepatic mitochondrial GPAT in a time-and ATP-dependent manner [47]. On the other hand, treating rats with AICAR for 6 weeks did not decrease GPAT1 activity, despite a reduction in the content of liver TAG [48].

In addition to palmitate synthesized de novo, GPAT1 is also required to partition diet-derived long-chain fatty acids towards TAG synthesis and away from mitochondrial oxidation [46]. Because of its preference for saturated fatty acids, GPAT1 contributes to the relatively high amount of 16:0 at the *sn*-1 position of liver phospholipids. In the absence of GPAT1, PE and PC contain about 21% less 16:0 at the *sn*-1 position and about 40% more 20:4ω6 at the *sn*-2 position [49]. Similar changes are observed in mitochondrial PC and PE in *Gpat1*$^{-/-}$ liver, but no alteration is observed in the acyl-composition of mitochondrial cardiolipin [50]. Altered phospholipid composition and TAG content are also observed in hearts from *Gpat1*$^{-/-}$ mice. The GPAT1 isoform contributes about 30% of total GPAT activity in the heart, and the content of TAG in knockout mice fed a high sucrose diet for 2 weeks or a high fat for 3 months is markedly lower than that of controls [51].

2.4. GPAT1 function in specialized tissues

GPAT1 has been studied in T cells where its activity declines with aging [52]. The activity is required for normal T cell proliferation and cytokine production [53,54], and Jurkat T cells deficient in GPAT1 had diminished IL-2 production and increased apoptosis [55]. GPAT1 deficiency increases mortality and pathology when mice are infected with Coxsackievirus B3 [56], and in EBV-infected B cells, several upregulated miRNAs targeted GPAT1 to downregulate both mRNA and protein [57]. The mechanism remains unexplored, but increased GPAT1 mRNA expression in breast cancer is reportedly associated with improved survival [58].

2.5. GPAT1 in other eukaryotes

GPAT1 homologs are present in fish, marsupials, platypus, birds, amphibians, turtles, worms and flies. These remain poorly investigated except for flies, worms and *Rhodnius prolixus*, the insect vector of Chagas' disease. In *Rhodnius* a single copy gene was found (*RpGpat*) whose molecular mass and characteristics are closely related to mitochondrial isoforms [59]. *RpGpat* transcription is induced at the onset of digestion and is required for glycerolipid production and TAG storage. A GPAT1-like activity was also described in the hepatopancreas of the shrimp *Macrobrachium borellii*. This organ, which expresses the highest TAG synthetic activity, contains the complete de novo biosynthetic pathway of TAG in mitochondria rather than microsomes. Although a mitochondrial 70-kDa protein cross-reacts with an anti-rat-GPAT1 antibody, the gene encoding this protein has not been identified [60]. In *Caenorhabditis elegans*, the mitochondrial GPAT, Acl-6, is essential for mitochondrial fusion, and *acl-6* null mitochondria are fragmented [61]. Injected LPA reverses this phenotype, suggesting that production of LPA by GPAT is critical for the fusion process; human GPAT1 silencing in HeLa cells leads to a similar phenotype of fragmented mitochondria [61].

2.6. Plants

Plants express numerous GPAT isoforms within chloroplasts, ER and mitochondria. The soluble chloroplast GPAT from *Cucurbita moschata* (squash) (PDB: 1K30_A) offers the only crystal structure for any GPAT [62,63]. Although this plastidial GPAT preferentially uses acyl-carrier protein rather than acyl-CoA as its acyl-donor, like other plastid GPATs from *Zea mays* and *Arabidopsis* (At1g32200), it contains the 4 motifs of the PlsC domain that are present in all vertebrate, yeast, and bacterial GPAT isoforms [3,34]. The tertiary structure of *C. moschata* identified the conserved H(×4)D motif in one of two major domains that also contained a cleft lined by hydrophobic residues thought to be the binding site for the acyl-ACP or acyl-CoA substrate, as well as the phosphate portion of glycerol-3-phosphate [63]. Membrane-bound GPAT isoforms are present in plant mitochondria and ER [64,65]. The 6 GPAT isoforms in ER have been investigated to relate substrate specificities to cold tolerance [66]. In *Arabidopsis*, AtGPAT9 synthesizes TAG [67], whereas several isoforms of AtGPATs 1–8 express both *sn*-2 acyltransferase and phosphatase activities that result in the production of *sn*-2-acylglycerols; these are involved in the synthesis of extracellular wax-like polymers such as cutin and suberin [65,68]. Three GPAT isoforms, AtGPAT1–3, form a separate clade [68], and may be located in mitochondria [65], but the mitochondrial location has been strictly verified only for AtGPAT1. Little information is available for plant mitochondrial GPATs. GPAT1–3 are said to depend on acyl carrier protein [65], but can use acyl-CoA substrates, including 20:0-CoA and 22:0 dicarboxylic acid-CoA [68]. AtGPAT1 is required for tapetal differentiation and nutrient secretion essential for pollen grain development. Although AtGPAT1 was originally believed to be important for glycerolipid biosynthesis, its absence did not change seed oil content [69]. *AtGpat2* and *AtGpat3* mutants appeared phenotypically normal [68].

2.7. Yeast and fungi

Although a GPAT activity was measured in yeast mitochondria, all the known yeast and fungi GPATs are located in the ER and/or on lipid droplets. A separate group of peroxisomal proteins termed GDPAT express both GPAT and DHAP activities [70]. Because yeast and fungi perform fatty acid oxidation in peroxisomes, it was speculated that a mitochondrial GPAT1 was not required to compete with CPT1 to control acyl-CoA availability for β-oxidation [70].

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3. Glycerol-3-P acyltransferase-2

3.1. Structure and location

GPAT2 is the most enigmatic of the mammalian GPATs. GPAT2 was first described in livers from Gpat1-null mice [71], and the mouse isoform was cloned based on its homology to GPAT1 [72]. The two proteins are similar in structure, molecular weight, and location in the outer mitochondrial membrane. Protease-protection studies suggested that murine GPAT2 has two transmembrane segments with the N-terminal and C-terminal domains facing the cytosol, similar to the topography of GPAT1 [73]. The amino acid sequences of GPAT1 and −2 are 33% identical and 64% homologous, with the greatest homology in the active site region, which is located within the cytosolic N-terminal domain. These two isoforms are distinguished from other members of the PlsC acyltransferase family by their long C-terminal domains.

3.2. Regulation

In spite of their structural similarities, the behavior of GPAT2 differs markedly from that of GPAT1. Whereas GPAT1 is preferentially expressed in lipogenic tissues, GPAT2 is primarily expressed in the testis, specifically in pachytene spermatocytes, and pathologically, in some human cancer-derived cells. *Gpam*, like the ER isoforms, *Gpat3* and *-4*, is up-regulated when 3T3-L1 cells differentiate to adipocytes; however, the expression of *Gpat2* is down-regulated [74]. *Gpat2* expression does not depend on the nutritional status of the animal, since rat liver from fasted or fasted-then-refed rodents shows no differences in *Gpat2* expression [72], indicating that neither SREBP1 nor ChREBP regulates its transcription. Conversely, *Gpat2* mRNA expression is activated in vitro in TM4 cells by retinoic acid, and demethylation of its promoter increases its mRNA abundance during sexual maturation of mouse testis [74].

3.3. Function

GPAT2 is highly selective for arachidonoyl-CoA as a substrate, and esterifies both glycerol-3-phosphate and 1-acylglycerol-3-phosphate. Physiologically, its expression and activity are linked to arachidonoyl-CoA incorporation into TAG in spermatogenic germ cells [75], although the function of TAG storage in these cells continues to be unclear. Human *Gpat2* belongs to a group of genes termed 'cancer-testis genes, which are important during spermatogenesis and fertilization for functions that include chromosome pairing, acrosin packaging, and regulation of specific gene expression [76]. *Gpat2* is overexpressed in several types of cancer and in cancer-derived human cell lines, in which the level of GPAT2 expression correlates with the histological grade of the tumor and promotes the tumorigenic phenotype [77]. GPAT2 is also involved in the primary biogenesis of piwil-interacting RNAs (piRNAs), a group of non-coding RNAs that are expressed in the spermatogenic cells to protect the genome from retrotransposons. GPAT2 physically interacts with piwil-homologous proteins, and mutating the acyltransferase activity signature H(×4)D motif does not affect either interaction or function in mouse ovarian follicle cells [78]. This function appears to be evolutionarily conserved. In *Drosophila*, when the gene CG5508 that encodes a mitochondrial GPAT is mutated, primary biogenesis of piRNAs is impaired [79]. Consistent with murine GPAT2, a mutant in CG5508 that deletes the acyltransferase active site is still functional for piRNA biogenesis; thus, this function does not appear to depend on the synthesis of LPA [79].

These features strongly suggest that GPAT2 has a second enzymatic activity and does not act strictly as a "classical" acyltransferase related to the synthesis of energy-rich molecules such as TAG or of membrane phospholipids. Perhaps the atypical PlsC motifs 2 and 3 in GPAT2, which are similar to sequences in some chloroplast GPAT isoforms [72], relate to an alternative function.

4. Acyl-glycerol-3-P acyltransferases

AGPATs, also called lysophosphatidic acid acyltransferases (LPAAT), are a family of enzymes that were annotated based on sequence homology to AGPAT1 and −2. Eleven putative AGPATs were named, but AGPAT6 and AGPAT9/10 have been redesignated as GPAT4 and -3, respectively. Of the remaining AGPAT isoforms, several have lysophospholipid acyltransferase activity, but only AGPAT4 and AGPAT5 are known to be located in mitochondria.

4.1. AGPAT4

Human AGPAT4 was first cloned and annotated as lysophosphatidic acid acyltransferase-delta (GeneBank direct submission access number AY358506). Murine *Agpat4* mRNA expression is high in the brain and moderate to low in skeletal muscle, gut, kidney, spleen and lung [80]. In brain, the function of AGPAT4 has been related to the biosynthesis of docosahexaenoic acid-rich glycerophospholipids [81]. The mitochondrial localization of AGPAT4 was confirmed by confocal microscopy, and its function has been linked to PE, PC, and PI remodeling because in *Agpat4* null mouse brain, each of these phospholipids decreased, particularly PI whose content in brain diminished by 50% [5]. Interestingly, the mRNAs of other brain *Agpat* isoforms (1, 2 3, 5, 9) were upregulated.

4.2. AGPAT5

Murine *Agpat5* mRNA is primarily expressed in brain, skeletal muscle and heart and at high levels in testis and prostate [80]. Localization to mitochondria was shown by over-expressed GFP-tagged protein. Unlike AGPAT4, AGPAT5 is active with multiple lysophospholipid substrates, including LPI, LPE, LPC and LPS [6]. The presence of these two AGPATs in mitochondria suggests that endogenously synthesized PA may have a specific role within the mitochondria; perhaps its fusogenic function is involved in the processes of mitochondrial fusion and fission [82].

4.3. Non-mammalian AGPATs

Plant AGPATs are all hydrophobic, membrane bound, and, like plant GPAT isoforms, present in chloroplasts, mitochondria and ER [64]. AGPAT activity was characterized in the outer mitochondrial membranes of potato tubers and pea leaves [83], but the mitochondrial isoforms contributing to this activity have not been identified. Several *C. elegans* and *Drosophila melanogaster* AGPAT genes have been identified [84], but their functions and subcellular locations have not been studied. The 4 *Rhodnius prolixus* (insect) AGPATs are all predicted to be located in the ER [59].

5. Monolysocardiolipin acyltransferases

When CL is initially synthesized, its acyl-chains are not specific, but because the final molecular species of CL in tissues such as heart and skeletal muscle are predominantly tetralinoleoyl, interest in CL remodeling has grown. In addition, the devastating cardiomyopathic problems observed in patients with Barth syndrome have suggested that major remodeling must occur, however CL-specific acyltransferases have proved elusive. ALCAT1 has acyltransferase activity for lysoCL as well as for lysoPI and lysophosphatidylglycerol (lysoPG), but ALCAT is located on the ER, so its role in CL remodeling is unclear [85,86]. However, because some CL is present on the cytosolic side of the OMM [11], CL might be available to an ER-MAM acyltransferase. An extensive purification scheme identified the α-subunit of the trifunctional protein of fatty acid β-oxidation as a monolysoCL acyltransferase [87]. In heart mitochondria from heterozygous mice, the in vitro acylation of MLCL was significantly reduced; CL mass and was reduced and CL acyl-composition was altered to produce diminished amounts of tetralinoleoyl-CL. Acyl-

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CoA substrates would be available within the mitochondrial matrix by action of CPT2 which converts acyl-carnitines back to acyl-CoAs. Because the over-expression or absence of MLCLAT1 or ALCAT1 does not result in CL with specific changes in its acyl-chains [11], these acyltransferases may be unimportant for CL remodeling. Over-expression of ALCAT1 results in CL species with acyl-chains that are more sensitive to oxidative damage, thought to be a cause of mitochondrial dysfunction, whereas mice deficient in ALCAT1 had improved function of complex 1 and insulin signaling [88]. The best evidence for CL remodeling comes from studies of the transacylase TAZ, which is discussed elsewhere in this issue.

6. Effects on cell and mitochondrial phospholipids

It is believed that phospholipid acyl-chain composition stabilizes membrane fluidity and affects permeability and the functions of intrinsic membrane proteins [11,36,37]. In addition, mitochondrial phospholipids, like those of the plasma membrane, may provide a reservoir of potential lipid signals such as LPA, PA, diacylglycerol, and eicosanoid precursors. A long-standing question concerns the relative contributions to acyl-chain composition of the de novo synthesis pathway and that of the recycling pathway. The preponderance of saturated fatty acid at the *sn*-1 position of phospholipids results from the preference of GPAT1 for saturated fatty acyl-CoAs [3]. Positional analysis showed that liver PE and PC contained 21% less palmitate in the *sn*-1 position and 36 and 40% more arachidonate, respectively, at the *sn*-2 position. PC and PE in liver from *Gpat1*$^{-/-}$ mice contained 35% less palmitate than controls, and when the phospholipids from isolated mitochondria were examined, a similar alteration in fatty acid composition was present [50]. The amount of TAG in liver and its acyl-composition is also, in part, due to GPAT1 activity. The GPAT1 deficient liver from mice fed a chow diet contains 37% less TAG than controls, and 44% less palmitate together with compensatory increases in stearate, oleate, and eicosapentaenoate [49].

Cardiolipin (CL) is of particular interest as it forms stable interactions with specific proteins of the respiratory complexes on the IMM. Although the tetralinoleoyl-CL species is prominent in heart and skeletal muscle, the tetralinoleoyl-CL is not the major species in other tissues [89]. CL synthesis and remodeling is covered elsewhere in this issue, but it is clear that at least part of its acyl composition results from activation of specific long-chain fatty acids by one or more acyl-CoA synthetases. Thus, diet can alter CL acyl species, and mice with deficient cardiac ACSL1, an enzyme located on the OMM, have altered acyl-composition of both total and mitochondrial PC and PE in heart, as well as prominent decreases of 18:2 in heart CL [89,90].

Integration of CL with electron transport chain complexes is well-established, but whether other phospholipids also have specific roles is unknown. It has been suggested that mitochondria must maintain a specific PE content, for example, to control mitochondrial stability [91]. Thus, in both CHO cells [92] and in yeast [93], decreases in PE content result in mitochondrial fragmentation and diminished ATP production.

7. Perspective

Major unanswered questions related to mitochondrial acyltransferases concern their role(s) in glycerophospholipid biosynthesis within the mitochondria versus the whole cell. The SREBP1c and ChREBP upregulation of *Gpat1* mRNA and protein and the preference of GPAT for palmitoyl-CoA coordinates with upregulated de novo fatty acid synthesis to divert newly synthesized fatty acids from futile cycling into the mitochondria as substrates for β-oxidation. In addition, the altered *sn*-1 acyl-composition of both total cellular and mitochondrial phospholipids suggests that the LPA product of GPAT1 or the PA product of the sequential mitochondrial AGPAT must be transferred to the ER to provide the substrate for phospholipid synthesis. In addition, despite the perceived importance of phospholipid remodeling, the effect of GPAT1 on the *sn*-1 acyl-composition is paramount, with GPAT1 determining the relative saturated to unsaturated acyl composition of PC and PE in heart and liver [49–51].

An important question concerns the origin of the PA required for the terminal steps of cardiolipin synthesis within the mitochondria (Fig. 1). GPAT1 and its associated mitochondrial AGPATs could provide PA substrate, but most reports assume that the PA precursor for CL comes from the ER. The fact that cardiolipin content and composition are normal in *Gpat1*$^{-/-}$ mice, supports this idea; either PA must predominantly originate from ER enzymes or the ER GPAT/AGPAT enzymes can compensate when mitochondrial production of PA fails. Another unresolved problem is the location of mitochondrial phospholipid remodeling. Phospholipases are present in the mitochondria [94–96], but apart from CL remodeling, only AGPAT5 on the OMM might catalyze the reacylation of mitochondrial lysophospholipids. Further work on the locations and functions of the remaining AGPAT isoforms will help to answer these questions.

Funding

This work was supported by the National Institutes of Health (DK56599, DK59935) and by ANPCyT-PICT3214 and CONICET-PIP0310, Argentina.

Transparency Document

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

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Please cite this article as: M.R. Gonzalez-Baro, R.A. Coleman, Mitochondrial acyltransferases and glycerophospholipid metabolism, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.06.023

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Please cite this article as: M.R. Gonzalez-Baro, R.A. Coleman, Mitochondrial acyltransferases and glycerophospholipid metabolism, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.06.023

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Please cite this article as: M.R. Gonzalez-Baro, R.A. Coleman, Mitochondrial acyltransferases and glycerophospholipid metabolism, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.06.023