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Review

Peroxisomal acyl-CoA synthetases ☆

Paul A. Watkins [a,b,*], Jessica M. Ellis [c]

[a] Hugo W. Moser Research Institute at Kennedy Krieger, Baltimore, MD, USA
[b] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[c] Department of Biological Chemistry, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

Peroxisomes carry out many essential lipid metabolic functions. Nearly all of these functions require that an acyl group—either a fatty acid or the acyl side chain of a steroid derivative—be thioesterified to coenzyme A (CoA) for subsequent reactions to proceed. This thioesterification, or "activation", reaction, catalyzed by enzymes belonging to the acyl-CoA synthetase family, is thus central to cellular lipid metabolism. However, despite our rather thorough understanding of peroxisomal metabolic pathways, surprisingly little is known about the specific peroxisomal acyl-CoA synthetases that participate in these pathways. Of the 26 acyl-CoA synthetases encoded by the human and mouse genomes, only a few have been reported to be peroxisomal, including ACSL4, SLC27A2, and SLC27A4. In this review, we briefly describe the primary peroxisomal lipid metabolic pathways in which fatty acyl-CoAs participate. Then, we examine the evidence for presence and functions of acyl-CoA synthetases in peroxisomes, much of which was obtained before the existence of multiple acyl-CoA synthetase isoenzymes was known. Finally, we discuss the role(s) of peroxisome-specific acyl-CoA synthetase isoforms in lipid metabolism. This article is part of a Special Issue entitled: Metabolic Functions and Biogenesis of Peroxisomes in Health and Disease.

1. Introduction

When peroxisomes were first identified over a half-century ago, they were considered by some to be vestigial organelles with little physiological significance. Work done over the last three to four decades has clearly demonstrated otherwise. In particular, peroxisomes carry out many essential processes involving fatty acid (FA) metabolism.

Essentially all cellular metabolic pathways in which FAs participate require that they first be activated to their CoA derivatives (Fig. 1). Among these pathways are the synthesis of triacylglycerol, phospholipids, plasmalogens, sphingolipids, and cholesterol esters, α-and β-oxidation of FA, FA elongation, conversion of FA to fatty alcohols, insertion and removal of double bonds, and protein acylation. Notable exceptions to the requirement for FA activation are the pathways for conversion of polyunsaturated FAs arachidonic acid and docosahexaenoic acid to bioactive eicosanoids and docosanoids, respectively. In addition, some bacteria, yeast, and plants use FA-acyl carrier protein thioesters instead of acyl-CoAs for certain metabolic processes [1–3].

The ACS reaction is ATP-dependent. In the first half-reaction, the FA substrate is adenylated, releasing inorganic pyrophosphate (PPi):

$$\text{Fatty acid} + \text{ATP} \rightarrow \text{Fatty acyl—AMP} + \text{PPi}$$

The ubiquitous enzyme inorganic pyrophosphatase, which can be found in soluble, mitochondrial, peroxisomal, and other subcellular fractions [4], rapidly cleaves PPi, effectively preventing reversal of this reaction. In the second half-reaction, CoA displaces AMP, forming a thioester bond to yield the activated FA:

$$\text{Fatty acyl—AMP} + \text{CoA} \rightarrow \text{Fatty acyl—CoA} + \text{AMP}$$

The length of FA carbon chains varies from 2 to more than 30, significantly affecting FA hydrophobicity and solubility. These factors likely influenced the evolution of distinct families of ACSs that activate short-, medium-, long-, and very long-chain FA substrates. This was nicely demonstrated more than 40 years ago by Aas, who measured rat liver mitochondrial and microsomal ACS enzyme activity with FA substrates ranging in chain length from 2 to 20 carbons [5]; four overlapping but distinct peaks of enzyme activity were observed. Although it was initially thought that there might be a single ACS responsible for activation of each FA chain length group, we now know the situation to be far more complex. Human and mouse genomes encode 26 ACSs [6], while the plant *Arabidopsis thaliana* has an estimated 64 acyl-activating enzyme genes [7].

Abbreviations: AA, Arachidonic acid (C20:4ω6); ACS, Acyl-CoA synthetase; CoA, Coenzyme A; FA, Fatty acid; FATP, Fatty acid transport protein; PGE_2, Prostaglandin E_2; PPAR, Peroxisome proliferator-activated receptor; VLCFA, Very long-chain fatty acid

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* Corresponding author at: Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205, USA. Tel.: +1 443 923 2754; fax: +1 443 923 2755.
E-mail address: watkins@kennedykrieger.org (P.A. Watkins).

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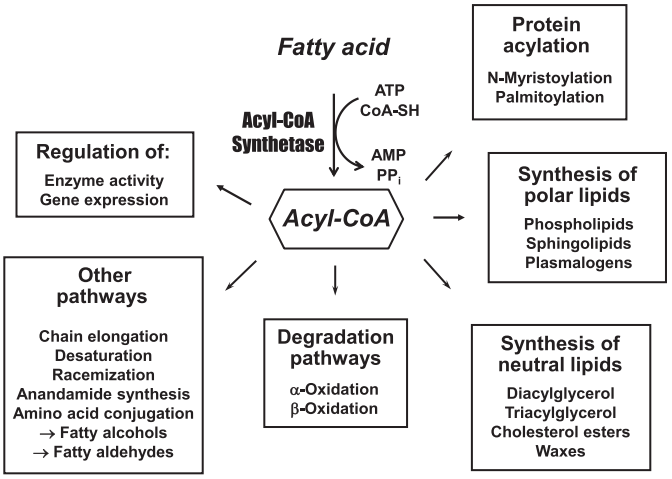

Fig. 1. Metabolic fates of activated FAs. Most pathways of cellular FA metabolism require prior activation of the FA by thioesterification to CoA. The ACS isoform that participates in a specific pathway is frequently dependent upon the tissue, cell type, subcellular location, and FA chain length. In addition to the pathways illustrated, fatty acyl-CoAs can be degraded by thioesterases that cleave the FA:CoA bond, and by nudix hydrolases that cleave the pyrophosphate bond within the CoA moiety.

Identification of ACSs was facilitated by the recognition of two highly conserved domains; all enzymes with documented ACS activity contain these motifs (Fig. 2) [6,8,9]. This has allowed the identification of several new putative ACSs, and has facilitated the assignment of proteins to structurally-related subfamilies. Additional conserved domains found in some, but not all, ACS subfamilies have been identified. Twenty-two of the mammalian ACSs can be grouped into five subfamilies, which include the aforementioned short-, medium-, long-, and very long-chain activating enzymes, as well as a family containing two proteins homologous to the *Drosophila melanogaster* "bubblegum" protein [6]. Uniform ACS nomenclature has been established for four subfamilies, the short-chain (ACSS), medium-chain (ACSM), long-chain (ACSL), and bubblegum (ACSBG) families

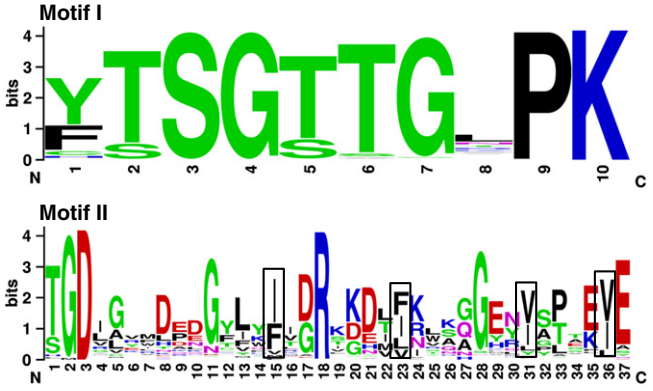

Fig. 2. Conserved domains in ACSs. Most ACS sequences contain 600–700 amino acids. All proteins known to have ACS enzymatic activity have two highly conserved motifs. *Top.* Motif I is a 10 amino acid sequence typically located 200–300 from the N-terminus. Motif I consensus: [YF]TSGTTGxPK. Motif I is an AMP-binding domain first described by Babbitt et al. [116]; mutations in this region decrease or abolish catalytic activity [117]. *Bottom.* Motif II contains 36–37 amino acids and the conserved arginine (R) at position 18 is always found approximately 260 residues downstream of Motif I [6]. Four positions where hydrophobic residues are found are enclosed in boxes. Motif II consensus: TGDxxxxxxxGxxx*h*x[DG]Rxxxx*h*xxxxGxx*h*xxx[EK]*h*E. Weblogo version 2.8.2, located at weblogo.berkeley.edu, was used to generate sequence logos in which the height of each letter indicates the amino acid conservation at that position. Data from 137 human, mouse, zebrafish (*Danio rerio*), fruit fly (*D. melanogaster*), worm (*C. elegans*), and yeast (*S. cerevisiae*) ACS sequences described in Ref. [6] were used to generate the logos. In the consensus sequences, x is any amino acid, and *h* indicates a hydrophobic residue.

Table 1
Acyl-CoA synthetase nomenclature.

ACS subfamily	Official symbol	Official name	Aliases
Short-chain			
	ACSS1	Acyl-CoA synthetase short-chain family member 1	ACAS2L, AceCS2
	ACSS2	Acyl-CoA synthetase short-chain family member 2	ACAS2, ACECS, ACS, ACSA
	ACSS3	Acyl-CoA synthetase short-chain family member 3	
Medium-chain			
	ACSM1	Acyl-CoA synthetase medium-chain family member 1	BUCS1, MACS1
	ACSM2a	Acyl-CoA synthetase medium-chain family member 2A	ACSM2
	ACSM2b	Acyl-CoA synthetase medium-chain family member 2B	ACSM2, HXMA
	ACSM3	Acyl-CoA synthetase medium-chain family member 3	SA, SAH
	ACSM4	Acyl-CoA synthetase medium-chain family member 4	
	ACSM5	Acyl-CoA synthetase medium-chain family member 5	
Long-chain			
	ACSL1	Acyl-CoA synthetase long-chain family member 1	ACS1, FACL1, FACL2, LACS, LACS1, LACS2
	ACSL3	Acyl-CoA synthetase long-chain family member 3	ACS3, FACL3
	ACSL4	Acyl-CoA synthetase long-chain family member 4	ACS4, FACL4, LACS4
	ACSL5	Acyl-CoA synthetase long-chain family member 5	ACS2, ACS5, FACL5
	ACSL6	Acyl-CoA synthetase long-chain family member 6	ACS2, FACL6, KIAA0837, LACS 6, LACS2, LACS5
Very long-chain	SLC27A1	Solute carrier family 27 (fatty acid transporter), member 1	ACSVL5, FATP, FATP1
	SLC27A2	Solute carrier family 27 (fatty acid transporter), member 2	ACSVL1, FACVL1, FATP2, VLACS, VLCS, hFACVL1
	SLC27A3	Solute carrier family 27 (fatty acid transporter), member 3	ACSVL3, FATP3, VLCS-3
	SLC27A4	Solute carrier family 27 (fatty acid transporter), member 4	ACSVL4, FATP4, IPS
	SLC27A5	Solute carrier family 27 (fatty acid transporter), member 5	ACSB, ACSVL6, FACVL3, FATP5, VLACSR, VLCS-H2
	SLC27A6	Solute carrier family 27 (fatty acid transporter), member 6	ACSVL2, FACVL2, FATP6, VLCS-H1
"Bubblegum"			
	ACSBG1	Acyl-CoA synthetase bubblegum family member 1	BG, BG1, BGM, GR-LACS, KIAA0631, LPD
	ACSGG2	Acyl-CoA synthetase bubblegum family member 2	BGR, BRGL
Other			
	AACS	Acetoacetyl-CoA synthetase	ACSF1
	ACSF2	Acyl-CoA synthetase family member 2	
	ACSF3	Acyl-CoA synthetase family member 3	
	AASDH	Aminoadipate-semialdehyde dehydrogenase	ACSF4

[10]; the mammalian genes/proteins are listed in Table 1. The six very long-chain ACS family genes are currently designated SLC27A1-6. Members of this subfamily were investigated as fatty acid transport proteins (FATPs) as well as ACSs; the official gene nomenclature (SoLute Carrier) reflects their putative transport function (Table 1). Four less structurally-related ACS enzymes are also represented in mammalian genomes.

In addition to FAs, other compounds containing acyl side chains are substrates for ACSs. For example, the final step in the synthesis of bile acids requires the removal of three carbons from the cholesterol side chain, converting 27-carbon precursors to 24-carbon mature bile acids [11]. In this process, a terminal carbon of the cholesterol aliphatic side chain is oxidized to a carboxylic acid, which must be activated to its CoA thioester before removal of a 3-carbon fragment via β-oxidation. Furthermore, many xenobiotic compounds, such as the hypolipidemic drug clofibrate and the non-steroidal anti-inflammatory drug ibuprofen, are ACS substrates [12]. Enzymes of the ACSM family are primarily responsible for xenobiotic activation [13]. Besides providing an acyl-CoA substrate for amino acid conjugation and elimination, xenobiotic-CoAs are substrates for lipid synthesis [12].

In addition to classifying ACSs by their substrate chain length preference, these enzymes have also been categorized by their subcellular locations. There are numerous literature references to a "mitochondrial medium-chain ACS" or a "microsomal long-chain ACS", without designating a specific enzyme. Many of these studies were done prior to the genomic era, at a time when our understanding of the diversity of the ACS subfamilies was far more limited.

2. Peroxisomal pathways requiring activated FAs

Because peroxisomal metabolic pathways are discussed in detail elsewhere in this special issue, they will be mentioned only briefly here. Peroxisomal reactions requiring acyl-CoA are depicted schematically in Fig. 3. Structures of peroxisomally relevant acyl-CoAs are depicted in Fig. 4.

2.1. β-Oxidation of very long-chain fatty acids (VLCFA)

Accumulation of VLCFA, particularly in the nervous system, is partly responsible for the pathologic manifestations seen in X-linked adrenoleukodystrophy and disorders of peroxisome biogenesis [14]. Detoxification of excess VLCFA occurs via the chain-shortening peroxisomal β-oxidation pathway [14]. VLCFA must be activated to their CoA derivatives before being degraded by the sequential action of peroxisomal enzymes acyl-CoA oxidase, D- (or L-) bifunctional protein, and 3-oxoacyl-CoA thiolase. Both bifunctional enzymes catalyze enoyl-CoA hydratase and hydroxyacyl-CoA dehydrogenase activities. Products include acetyl-CoA and a shortened (by two carbons) acyl-CoA; the latter becomes the substrate for subsequent rounds of β-oxidation (Fig. 3). Whether VLCFA are activated intraperoxisomally or outside the peroxisome (and then transported into the organelle as VLCFA-CoA) has been the subject of some debate [15–19].

2.2. α-Oxidation of phytanic acid

Failure to degrade excess amounts of the dietary 3-methyl branched-chain FA, phytanic acid (3,7,11,15-tetramethyl hexadecanoic acid) causes Refsum disease, an adult-onset peripheral neuropathy [20]. Phytanic acid also accumulates in the peroxisome biogenesis disorders, and in rhizomelic chondrodysplasia punctata [21]. Because phytanic acid has a methyl group on the 3-carbon, it cannot be degraded by β-oxidation. Instead, a single carbon is removed by α-oxidation. Activation of this branched-chain FA to phytanoyl-CoA is a requisite first step (Fig. 3). The sequential action of peroxisomal enzymes phytanoyl-CoA hydroxylase and 2-hydroxyacyl-CoA lyase release the carboxyl carbon as formyl-CoA and produce a branched-chain aldehyde, pristanal. Pristanal is then oxidized to pristanic acid (2,6,10,14-tetramethyl pentadecanoic acid), which can be degraded by the peroxisomal β-oxidation pathway for branched-chain carboxylic acids (see below). The CoA thioesters of long-chain 2-hydroxy FA are also shortened by one carbon by enzymes of the α-oxidation pathway [22]. Like the situation with VLCFA, it has not been unequivocally resolved whether phytanic acid, pristanic acid, or 2-hydroxy FA are activated extra- or intraperoxisomally [19,23].

2.3. β-Oxidation of branched-chain carboxylic acids

Pristanic acid levels are elevated in several peroxisomal disorders, including D-bifunctional protein deficiency and sterol carrier protein-X deficiency [14]. Pristanic acid must be activated to pristanoyl-CoA prior to further catabolism in the peroxisome. Because the first methyl branch is now on the 2-carbon, this FA can be degraded by β-oxidation. Although the reactions are similar to those involved in the degradation of VLCFA, the enzymes of branched-chain FA β-oxidation are somewhat different. Branched-chain acyl-CoA oxidase and sterol carrier protein-X thiolase catalyze the first and fourth enzymatic steps, respectively, while D-bifunctional protein facilitates

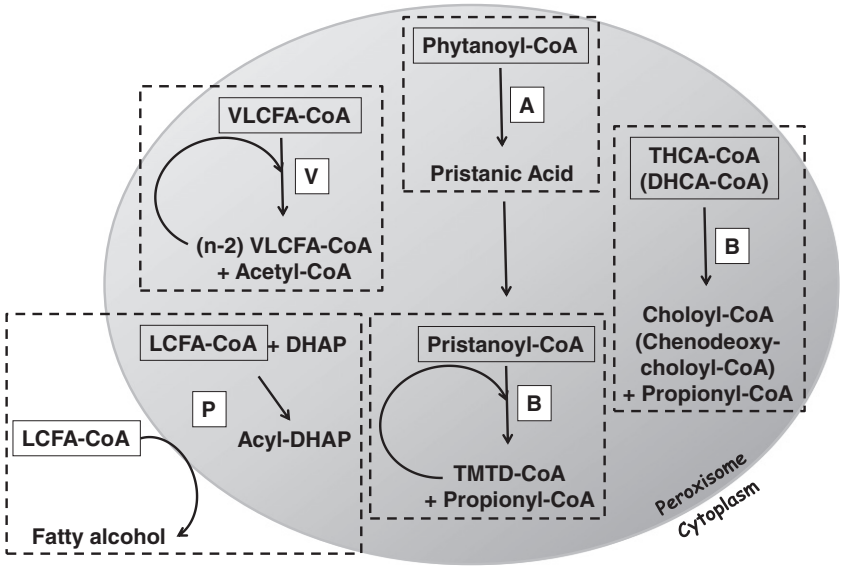

Fig. 3. Peroxisomal reactions requiring acyl-CoA. An acyl-CoA is required for several peroxisomal reactions. The pathways in which these reactions are found include VLCFA β-oxidation (V), branched-chain β-oxidation (B), α-oxidation (A), and plasmalogen synthesis (P). Racemization of *R*- and *S*-enantiomers of intermediates of the branched-chain β-oxidation pathways also require CoA thioesters (not illustrated). LCFA-CoA, long-chain fatty acyl-CoA; DHCA-CoA, dihydroxycholestanoyl-CoA; THCA-CoA, trihydroxycholestanoyl-CoA; TMTD-CoA, 4,8,12-trimethyltridecanoyl-CoA; DHAP, dihydroxyacetone phosphate.

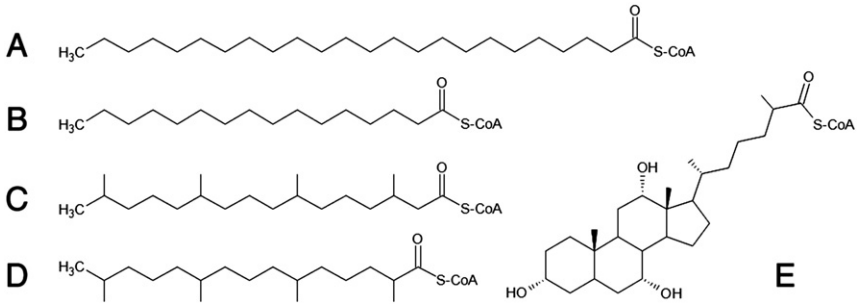

Fig. 4. Structures of peroxisomally relevant acyl-CoAs. Shown are the CoA derivatives of: A, the VLCFA, lignoceric acid (C24:0); B, the long-chain FA, palmitic acid (C16:0); C, the β-methyl branched-chain FA phytanic acid (3,7,11,15-tetramethyl hexadecanoic acid); D, the α-methyl branched-chain FA pristanic acid (2,6,10,14-tetramethyl pentadecanoic acid; and E, the bile acid precursor trihydroxycholestanoic acid.

the second and third reactions. Because of the 2-methyl group, a three carbon compound, propionyl-CoA, is released. Concomitantly, a shortened branched-chain acyl-CoA, 4,8,12-trimethyltridecanoyl-CoA, is produced, which undergoes further rounds of β-oxidation (Fig. 3). Similar to pristanic acid, the side chains of bile acid precursors di- and trihydroxycholestanoic acids must be activated to their CoA derivatives before chain shortening by three carbons via the same peroxisomal β-oxidation pathway (Fig. 3). Not surprisingly, elevated levels of bile acid precursors are found in the same disorders in which pristanic acid accumulates [14].

R- and *S*- stereoisomers of branched-chain compounds such as phytanic acid, pristanic acid, and bile acid precursors exist in nature due to the presence of asymmetric carbon centers. While the phytanic acid α-oxidation pathway is not stereospecific, yielding both (2*S*,6*R*,10*R*)- and (2*R*,6*R*,10*R*)-isomers of pristanic acid, the branched-chain β-oxidation pathway is stereospecific, only degrading substrates in the *S*-conformation [24]. Similarly, the bile acid precursors di- and trihydroxycholestanoic acids exist as 25*R*- and 25*S*-stereoisomers. Peroxisomal α-methyl-acyl-CoA racemase (AMACR) interconverts the CoA derivatives of *R*- and *S*-enantiomers, thus functioning as an auxiliary β-oxidation enzyme.

2.4. Plasmalogen synthesis

Ether phospholipid, or plasmalogen, synthesis is impaired in rhizomelic chondrodysplasia punctata and disorders of peroxisome biogenesis. Several steps in plasmalogen synthesis require activated FAs (Fig. 3). The first step unique to this pathway is catalyzed by peroxisomal glyceronephosphate acyltransferase; in this reaction an intraperoxisomal fatty acyl-CoA is esterified to the *sn1* position of dihydroxyacetone phosphate [25]. In the next biosynthetic step, the peroxisomal enzyme alkylglycerone phosphate synthase catalyzes the replacement of the fatty acyl group at *sn1* with a 16- or 18-carbon fatty alcohol. Fatty alcohols are produced by fatty acyl-CoA reductases located on the cytoplasmic face of the peroxisome membrane [26]; as the enzyme name indicates, this process requires an activated FA substrate.

3. Peroxisomal ACSs

Historically, the identification of peroxisome-specific ACS activity was hampered by several factors. Until the importance of mammalian peroxisomes in lipid metabolism was recognized in the 1980s, most scientists investigating ACSs focused their attention on mitochondria and the endoplasmic reticulum (microsomes). Inspection of many of the early methods used to isolate mitochondria and microsomes suggests that preparations were likely contaminated with peroxisomes. Even when peroxisomal lipid metabolism began to receive recognition in the scientific literature, procedures for isolation of relatively pure peroxisomes were slow to develop. Despite studies suggesting the existence of very long-chain ACS activity in 1971 [5], it was not until 1985 - shortly after peroxisomal VLCFA β-oxidation was discovered — that an enzyme with very long-chain chain ACS (lignoceroyl-CoA ligase) activity was first reported in the literature [27,28]. Furthermore, much pioneering work on ACS activity associated with peroxisomes was carried out using methods of classical biochemistry, prior to the "molecular biology/cloning" and "genomic" eras.

The amino acid sequences of many, but not all, peroxisomal proteins contain either of two peroxisome targeting signals, PTS1 or PTS2 [29]. Unfortunately, few ACSs contain a *bona fide* or even a potential PTS1 and, to the best of our knowledge, none contain a PTS2. Thus, our ability to predict in advance which ACSs are peroxisomal is limited.

3.1. Yeasts and fungi

One of the earliest references to a peroxisomal ACS is from Mishina et al., who reported that one of the two fatty acid activating enzymes in the yeast *Candida lipolytica* was found in mitochondria and microsomes, whereas the other enzyme localized to "microbodies", or peroxisomes [30]. The existence of a peroxisomal ACS was a significant finding, as FA β-oxidation occurs solely in this organelle in yeast. Gordon and coworkers identified 4 long-chain ACS genes (*FAA1–4*) in *Saccharomyces cerevisiae*, but reported that none of them was exclusively responsible for targeting exogenous FAs to peroxisomes for β-oxidation [31]; importantly, they also found that yeast could still grow using FAs as sole carbon source even after deletion of all four *FAA* genes, suggesting the existence of at least one additional ACS in this organism. Gene deletion studies suggest that Faa1p and/or Faa4p provide activated FA for peroxisomal β-oxidation [32], but specific localization studies were not carried out. Although initially thought to be a long-chain ACS, Faa2p was subsequently determined to be an intraperoxisomal medium-chain ACS that localizes to the inner leaf of the peroxisomal membrane [33–35]. It is thought that medium-chain FAs enter yeast peroxisomes by diffusion (flip–flop) and are then activated in the organelle matrix. This is similar to the process by which medium-chain FAs enter mammalian mitochondria, which does not require the regulated carnitine-dependent mechanism used for transport of long-chain acyl-CoAs into the mitochondrial matrix. It is also possible that medium-chain FAs can enter peroxisomes via the pore-forming protein, Pxmp2, or its homologs [36].

Kalish et al. found very long-chain ACS activity associated with peroxisomes in the yeast *Pichia pastoris* [37]. Subsequently, the orthologous enzyme was identified in *S. cerevisiae* and determined to be the product of the FAT1 gene [38,39]. Studies of gene deletion mutants revealed that the ACS activity of Fat1p was associated with microsomes as well as peroxisomes. Mechanistic studies by Black, DiRusso, and colleagues demonstrated that Fat1p and Faa1p (and to a lesser extent Faa4p) constitute a tightly regulated system for the import, activation, and peroxisomal β-oxidation of long- and very

long-chain FAs [40,41]. *S. cerevisiae* also contains a gene, FAT2, encoding a protein predicted to be a peroxisomal ACS [9,42]. Fat2p contains the two highly conserved motifs characteristic of all ACSs (Fig. 2) [6], as well as the cannonical peroxisome targeting signal 1 (PTS1), the tripeptide −SKL, at its carboxy terminus. However, the substrate specificity and metabolic function of Fat2p remain unknown.

Peroxisomal ACSs have also been found in some fungi. A survey of the *Aspergillus nidulans* genome identified six likely ACSs, one of which was peroxisomal [43]. This enzyme, FaaB, was found to be the major ACS for degradation of long-chain FAs. FaaB was required for growth of *A. nidulans* on FAs as carbon source, and its gene was induced when this fungus was grown in the presence of FAs. The two final reactions in the synthesis of penicillin by *Penicillium chrysogenum* are also peroxisomal [44,45]. The ACS phenylacetyl-CoA ligase supplies the activated substrate for acyl-CoA:6-amino penicillanic acid acyltransferase; the product of the latter reaction is penicillin G.

3.2. Plants

Plants require ACS activity for the formation of phospholipids, triacylglycerol, jasmonate, and for the oxidation of fatty acids. In 2002, nine long-chain ACSs were identified in *A. thaliana* [46]. Two of these long-chain ACSs, LACS6 and LACS7, were shown to be located in the peroxisome, where a majority of β-oxidation takes place during plant seedling development [47]. The knockout of either *A. thaliana* peroxisomal ACS alone did not robustly alter plant viability; however, the knockout of both peroxisomal ACSs caused defective seed lipid mobilization [48]. The identification of plant LACS at the interface between lipid bodies and peroxisomes suggested that lipids are mobilized from lipid bodies, activated by peroxisomal ACSs, and then degraded by β-oxidation [49]. Thus, plant peroxisomal ACS activity, and subsequent β-oxidation, is required for normal seed germination.

Jasmonic acid is potent plant signaling molecule that plays roles in regulating plant defense mechanisms, metabolism, and development. Jasmonate is synthesized from linolenic acid (C18:3ω3) through a process that occurs in three cellular compartments: plastids, peroxisomes, and cytosol. In 2005 and 2006, several 4-coumarate:CoA ligase-like *Arabidopsis* peroxisomal proteins were found to have ACS activity towards jasmonate precursors as well as long-chain FAs [50–52]. These data suggest that formation of jasmonic acid requires the ligase activity provided by peroxisomal ACS enzymes; however the specific ACS required for this activity has not been identified.

3.3. Invertebrate ACSs

Firefly luciferase is a peroxisomal enzyme whose two-step reaction mechanism resembles that of ACSs (illustrated in the Introduction). In the first ATP-requiring step, the substrate, luciferin, is adenylated with the release of PPi. The second step is the oxygen-dependent conversion of the adenylated substrate to oxyluciferin with release of AMP and the production of light. Oba and colleagues demonstrated that luciferases from the North American firefly (*Photinus pyralis*) and the Japanese firefly (*Luciola cruciata*) also had long-chain ACS activity, suggesting that they were bifunctional enzymes [53]. In *D. melanogaster*, the firefly luciferase ortholog, CG6178, has ACS activity but not luciferase activity [54]. An expansive, but not comprehensive, phylogenic analysis of the acyl-CoA synthetases across species suggests that CG6178 forms a clade with unknown fungi ACS genes and plant 4-coumarate:CoA ligase (4CL), and these genes are phylogenetically distinct from ACSL genes in mammals and yeast [54]. Of the ACS genes phylogenetically analyzed, the luciferases, plant 4CLs, several fungi ACSs, and CG6178 contain a PTS1, whereas none of the vertebrate ACSL genes contain this targeting motif, suggesting that the peroxisomal-specific nature of these ACSs has been lost in the vertebrate lineage. *D. melanogaster* also expresses a homolog of human ACSL4, dAcsl, early in embryonic development [55]. Mutations in dAcsl cause defects in embryonic segmentation, although the mechanism by which dAcsl affects this process remains unclear. In *C. elegans*, the ACSL homolog Y65B4BL.5 and the ACSVL homolog F28D1.9 do not lead to growth defects when knocked down using RNA interference [56]. Thus, specific ACSL isoform activities appear to be critical for fly development, but are not for worm development. Furthermore, the PTS1 found in invertebrate ACSs are not conserved in vertebrates suggesting distinct evolutionary differences in the roles of ACSL enzymes.

3.4. Mammals: long-chain acyl-CoA synthetases (ACSL)

Activation of palmitic acid (C16:0) in peroxisome-enriched fractions of rat liver was reported by Shindo and Hashimoto at about the same time as the discovery of ACS in *Candida* peroxisomes [57]. This finding was soon confirmed in purified peroxisomes by other laboratories [58,59]. ACS activity remained associated with peroxisomal membranes when organelles were disrupted, indicating that it was not a matrix enzyme [59]. Most of this palmitoyl-CoA synthetase activity was destroyed when intact peroxisomes were treated with the proteinase Pronase, suggesting that it was topographically orientated facing the cytoplasm [59]. Measurement of ACS activity in liver subcellular fractions showed that approximately 16% of liver long-chain ACS activity occurs in peroxisomes [60]. Peroxisomal long-chain ACSs are also thought to catalyze the activation of the branched-chain FAs phytanate and pristanate [23,61–63].

3.4.1. Which ACSL isoform is peroxisomal?

None of the five mammalian ACSL isoforms contain either PTS1 or PTS2. To determine which ACSL isoform is expressed in the peroxisome, Lewin et al. examined protein abundance of ACSL1, ACSL4, and ACSL5 in liver subcellular fractions using isoform specific antibodies [64]. Peroxisomal fractions were identified by high peroxisomal-specific catalase activity. These peroxisomal fractions were clear of microsomal and mitochondrial contamination as evidenced by the lack of esterase and glutamate dehydrogenase activity. ACSL4 was highly abundant in the peroxisomal fraction. This protein was also detected in the mitochondria-associated membrane fraction, but its abundance was nearly 10-fold higher in the peroxisomal fraction. Troglitazone, an inhibitor of ACSL4 but not of the other ACSL isoforms [65,66], decreased total ACSL activity by ~30% in the peroxisomal rich fractions, suggesting that other ACS enzymes (likely very long-chain ACSs) contribute up to 70% of the remaining ACS activity. These data suggest that ACSL4 is highly expressed in liver peroxisomes.

Purified peroxisomal fractions have been analyzed by mass spectrometry to identify the peroxisomal proteome. In 2003, proteomic analysis of rat liver peroxisomes, isolated by subcellular fractionation followed by immunoprecipitation of organelles using an antibody to the 70-kDa peroxisomal membrane protein (ABCD3), identified "long-chain acyl-CoA synthetase 2" (now called ACSL1) as a peroxisomal membrane protein [67]. This was confirmed in a 2006 proteomic analysis of rat liver peroxisomal membrane fractions isolated by fractionation followed by incubation at high pH to release inner peroxisomal proteins [68]. Islinger et al. investigated the hepatic peroxisomal proteome of rats treated with the peroxisome proliferator, clofibrate, and also identified ACSL1 as a peroxisomal protein [69]. In 2010, proteomic analysis of rat liver heavy peroxisome fraction was compared to light peroxisomal fraction isolated by fractionation [70]. These authors identified ACSL1 in the mitochondria, peroxisome, and the ER while ACSL5 was found in the ER. The lack of identification of ACSL4 and ACSL3 in any of the fractions, suggests that either common fractionation methods lead to loss of substantial proteins or that the mass spectrometry methods employed do not allow for complete identification of all ACSL proteins. Overall the proteomic approach strongly suggests that ACSL1 is a peroxisomal protein in the liver.

An inherent problem with fractionation methods is the contamination of peroxisomal fractions with ER proteins; thus it is difficult to conclusively determine whether a protein identified by proteomics from a peroxisomal fraction is truly peroxisomal and not ER contamination. Furthermore, because ACSL4 is a membrane-associated protein but not a transmembrane protein, and because it was not identified in any cell fraction from any of the above mentioned studies, it is possible that ACSL4 is removed from the fraction by the methods used. Despite the identification of ACSL1 in the peroxisome by proteomics , there are no studies that identify ACSL1 as a peroxisomal protein using non-proteomic approaches, nor are there reports that elude to ACSL1 playing a functional role in the peroxisome.

3.4.2. ACSL4 effects on metabolism

Because ACSL4 is the only ACSL isoform to be identified at the peroxisome using specific antibodies, it is likely that ACSL4 serves a specialized role at the peroxisome. *R*ecombinant ACSL4 has a high preference for long-chain polyunsaturated FAs, mainly arachidonic acid (C20:4ω6) (AA) and eicosapentaenoic acid (C20:5ω3). The high abundance of ACSL4 in steroidogenic tissues and its preference for AA and eicosapentaenoic acid, the precursors for prostaglandin and leukotriene synthesis, suggests that ACSL4 plays a role in regulating the availability of these fatty acids for the synthesis of eicosanoids [71]. Because eicosanoid synthesis begins with a free fatty acid, not an acyl-CoA, ACSL4 activity would be predicted to reduce the flux of fatty acids towards eicosanoid synthesis. Indeed the overexpression of ACSL4 in human smooth muscle cells leads to reduced prostaglandin E_2 (PGE_2) secretion [72]. Likewise, the inhibition of ACSL4 with rosiglitazone or triacsin C increased PGE_2 release from smooth muscle cells [72]. These data suggest that ACSL4 plays a role in regulating prostaglandin synthesis. While inhibition of ACSL4 with thiazolidinediones increases eicosanoid synthesis in smooth muscle cells, the knockdown of ACSL4 in Leydig cells of the testis decreases progesterone synthesis [73]. Similarly, the knockdown of ACSL4 in cancer cells decreases the production of 5-, 12-, and 15-hydroxyeicosatetraenoic acids and PGE_2 [74]. The high expression of ACSL4 seen in some cancers is linked to increased invasiveness. Thus, the increased invasiveness of tumors that highly express ACSL4 is potentially mediated by increased steroid and eicosanoid production [75]. Alternatively, the increased ACSL4 expression may be a mechanism of cancer cells to decrease apoptosis that is triggered by free arachidonate levels [76]. Whether ACSL4s activity on AA occurs at the peroxisome or the mitochondria-associated membrane has not been investigated, thus any potential link between peroxisomal ACSL4 and prostaglandin synthesis remains unclear. Very little research has been conducted to determine the peroxisomal-specific ACSL isoform and the function of ACSLs at the peroxisome. We conclude that further investigation into the role of ACSL at the peroxisome is warranted.

3.5. Mammals: very long-chain acyl-CoA synthetases (ACSVL)

The discovery that peroxisomal β-oxidation of VLCFA was impaired in peroxisome biogenesis disorders and in X-linked adrenoleukodystrophy prompted several laboratories to search for a peroxisomal ACS that could activate VLCFA substrates. Using methods of classical biochemistry, Hashimoto and colleagues succeeded in purifying such an enzyme from rat liver peroxisomes in 1996 [77]. These investigators then used genetic methods to clone cDNA encoding the protein [78]. The amino acid sequence of this enzyme, which our laboratory subsequently designated ACSVL1 because it was the first *bona fide* very long-chain ACS reported [79], was similar to, but distinct from, that of ACSL isoforms known at that time. The sequence was, however, more similar to that of "fatty acid transport protein" (now FATP1, or SLC27A1) (see Table 1) [80]. ACSVL1 (FATP2; SLC27A2) is found in both peroxisomes and microsomes [19,78]. The C-terminus of the human, rat, and mouse protein ends in the tripeptide -LKL; although this is not a recognized variant of PTS1, its similarity to the consensus sequence –SKL suggests that it may be partially functional. ACSVL1 is primarily expressed in liver and kidney, with little expression in brain [19]. In peroxisomes, the role of this enzyme is presumed to be the activation of VLCFA for β-oxidation. Studies done using skin fibroblasts from patients with peroxisome biogenesis disorders and X-linked adrenoleukodystrophy suggested that for VLCFA to be β-oxidized in peroxisomes, activation had to occur in peroxisomes, not microsomes. Although its abundance in microsomes is significantly higher than in peroxisomes, ACSVL1's function in the endoplasmic reticulum is not known.

Overexpression of ACSVL1 in COS-1 cells suggests that this enzyme can activate long-chain FAs (e.g. palmitic acid; C16:0), VLCFAs (e.g. lignoceric acid; C24:0), and branched-chain FAs phytanic acid and pristanic acid [19]. The topographic orientation of ACSVL1 in the peroxisomal membrane has not completely been resolved [15–19]. Investigations into the function of the peroxisomal membrane protein ABCD1, which is defective in X-linked adrenoleukodystrophy, suggests that VLCFA are activated extraperoxisomally via ACSVL1 (or another ACS) oriented facing the cytoplasm, after which the CoA derivatives are transported into the organelle by ABCD1 [81]. On the other hand, orientation of the enzyme facing the matrix is appealing with respect to branched-chain FA metabolism. When phytanic acid is degraded by the peroxisomal α-oxidation pathway, the product, pristanal, is then oxidized to pristanic acid. If the ACSVL1 active site faces the peroxisomal matrix, pristanic acid could then be activated intraperoxisomally to its CoA derivative and then further degradation via peroxisomal β-oxidation in a metabolically efficient manner (Fig. 3). Whether phytanic acid is activated primarily by ACSVL1, or by another ACS (e.g. ACSL1 or ACSL4) oriented in the peroxisomal membrane facing the cytoplasm [23,61], remains unresolved.

The bile acid precursor, trihydroxycholestanoic acid, was also a substrate for ACSVL1 when the enzyme was expressed in COS-1 cells [82]. Trihydroxycholestanoyl-CoA undergoes one cycle of peroxisomal β-oxidation, yielding the CoA derivative of the primary bile acid, cholate (Fig. 3). Intraperoxisomal choloyl-CoA then reacts with glycine or taurine to form the conjugated bile acids glycocholate and taurocholate, respectively [83]. However, it is unclear whether it is the peroxisomal ACSVL1 or the microsomal ACSVL1 that activates bile acid precursors.

An ACSVL1 knockout mouse was generated by Heinzer et al. [84]. Although this mouse had no obvious phenotypic abnormalities, the rate of hepatic and renal VLCFA β-oxidation was reduced. Despite decreased VLCFA degradation in these tissues, plasma levels of VLCFA were not elevated in the ACSVL1 knockout mouse.

There is evidence that another member of the ACSVL family, FATP4 (SLC27A4; suggested name ACSVL5 [85]), partially localizes to peroxisomes. FATP4 localized to the endoplasmic reticulum when heterologously expressed in several cell lines, including HeLa and COS [86]. While the endogenous enzyme was found in endoplasmic reticulum, it was detected in peroxisomes, mitochondria, and mitochondria-associated membranes as well [87]. The C-terminus of human, rat, and mouse FATP4 ends in the tripeptide −EKL. Like the situation with ACSVL1, this sequence is not recognized as a PTS1 variant but may be partially functional. FATP4 was found to be the primary VLCFA-activating enzyme in skin fibroblasts and, unlike ACSVL1, was also found in brain, adipose tissue, skeletal muscle, heart, and intestine [87]. Fibroblasts grown from the skin of FATP4-null mice had a >50% reduction in the rate of VLCFA β-oxidation, suggesting that FATP4 may be the primary ACSVL in tissues not expressing ACSVL1. In HeLa cells heterologously expressing FATP4, the protein was oriented in the endoplasmic reticulum with its N-terminus toward the lumen [86]; the topographic orientation of endogenous FATP4 in peroxisomes or other organelles has not been studied. A role for this enzyme in peroxisomal metabolic processes other than VLCFA β-oxidation has not been evaluated.

4. Peroxisomal ACSs and human disease

Although ACSs are clearly indispensible for several peroxisomal metabolic pathways, there have been no direct correlations between peroxisomal deficiency of a specific ACS and human disease. In the mid to late 1980s, it was hypothesized that deficiency of "the peroxisomal very long-chain ACS" was the biochemical defect in X-linked adrenoleukodystrophy [88–92]. This was proven incorrect when the defective gene in this disease, ABCD1, was identified in 1993 by positional cloning [93]. Nonetheless, results of yeast two-hybrid and surface plasmon resonance experiments suggest that ABCD1 and ACSVL1 physically interact in peroxisomes [94]. Studies by Yamada et al. with ABCD1-deficient mice also indicated that ABCD1 was required for proper localization and functioning of ACSVL1 [95,96]. However, Smith and colleagues separately produced ABCD1 knockout mice and reported no effects on either expression or localization of ACSVL1 [84].

Deficiency of FATP4 causes a restrictive dermopathy in mice [97,98]. Because the lungs cannot expand normally, newborn pups rarely survive for more than a day. Mutations in FATP4 have been found in humans with the autosomal recessive disorder, ichthyosis prematurity syndrome [99]. Individuals with this disease are born prematurely and have neonatal asphyxia. Throughout life, they have nonscaly ichthyosis with atopic manifestations. Decreased very long-chain ACS activity and reduced incorporation of VLCFA into cellular lipids was observed in skin fibroblasts from a patient with ichthyosis prematurity syndrome [99]. Because this enzyme is found in multiple cellular compartments, it is unclear if either peroxisomal FATP4, or metabolism of FATP4-derived VLCFA-CoA in peroxisomes, contributes to the clinical manifestations of this disease.

Several laboratories have reported changes in peroxisomal ACSs that have potential relevance to diabetes and/or insulin resistance. Singh and coworkers measured ACS activity in peroxisomes and mitochondria isolated from livers of diabetic rats. They found that in peroxisomes, activation of the long-chain FA palmitate was increased 2.6-fold, while in mitochondria there was a 2.1-fold increase; peroxisomal VLCFA-CoA synthesis measured with lignoceric acid was increased 2.6-fold [100]. Durgan et al. studied the transcriptional regulation of ACSL isoforms in mouse heart and found that neither diabetes experimentally induced with Streptozotocin nor a high-fat diet induced expression of ACSL4 [101]. However, in humans with nonalcoholic fatty liver and insulin resistance, hepatic ACSL4 mRNA was significantly increased [102]. In a study of 600 Swedish men, a single nucleotide polymorphism in ACSL4 (rs7887981) was associated with statistically significant elevations in fasting serum insulin and triglyceride concentrations [103]. It was mentioned previously that thiazolidinedione insulin-sensitizing drugs such as troglitazone, rosiglitazone, and pioglitazone used in the treatment of diabetes specifically inhibited ACSL4 activity [66,104]. Thiazolidinediones are also PPARγ ligands, but the effects of these drugs on ACSL4 may be independent of PPARγ [66]. Whether or not inhibition of ACSL4 is responsible for the anti-diabetic properties of thiazolidinediones will require further investigation.

Hepatic steatosis is a complication of estrogen deficiency in tamoxifen-treated breast cancer patients; this has been studied in a mouse model in which the gene encoding aromatase, an essential enzyme of estrogen biosynthesis, has been knocked out [105]. In this mouse, ACSVL1 mRNA was decreased, along with peroxisomal VLCFA β-oxidation activity [105]. Treatment of aromatase-deficient mice with either the PPARα agonist, bezafibrate, or a novel statin, pitavastatin, restored ACSVL1 mRNA levels along with mRNA for several enzymes of peroxisomal β-oxidation [106,107].

5. Peroxisome proliferators, xenobiotics, and peroxisomal ACSs

Many xenobiotic compounds containing an aliphatic carboxylic acid function can serve as substrates for ACSs located in peroxisomes and other subcellular compartments. Once activated, these compounds can be incorporated into complex lipids and/or be degraded. Some of these compounds (e.g. clofibrate, nafenopin, and related fibric acid derivatives) have also been identified as peroxisome proliferators in rodents and function as ligands for PPARs, primarily PPARα. Other xenobiotics thought to be activated by peroxisomal long-chain ACS include 2-arylpropionates (e.g. ibuprofen, naproxen, and related non-steroidal anti-inflammatory drugs) and herbicides (e.g. silvex and 2,4,5-trichlorophenoxyacetate). These topics have been comprehensively reviewed by Knights [12].

PPARα activation by xenobiotics (or perhaps their CoA derivatives) induces the expression of peroxisomal long-chain ACS activity. Lewin et al. reported a 40% increase in ACSL4 mRNA abundance in livers of rats treated with the synthetic PPARα agonist GW9578 [64]. Peroxisomal very long-chain ACS activity was induced 4-fold in rats treated with the PPARα ligand ciprofibrate [108].

Peroxisomal β-oxidation is thought to be an important route for degradation of some xenobiotics, such as ω-phenyl FAs; Yamada and coworkers found that peroxisomal β-oxidation of a 12-carbon ω-phenyl FA required activation by an ACS found in peroxisomes [109]. The CoA thioester of the anti-epileptic drug valproic acid was reported to be metabolized by β-oxidation in peroxisomes, suggesting the participation of a peroxisomal ACS [110]; however, more recent work suggests that valproate is also degraded in mitochondria [111].

Xenobiotics are not exclusively activated by peroxisomal ACSs, however. Sulfur- and sulfoxy-substituted FA analogues (e.g. tetradecylthioacetic acid) [112], oxa-FAs (e.g. 3,6,9-trioxadecanoic acid) [113], ciprofibrate [114], and fenoprofen [115] were activated by ACSs in mitochondria and/or microsomes as well as in peroxisomes.

6. Concluding remarks

It has firmly been established that several peroxisomal metabolic pathways require the participation of one or more ACSs. These include the β-oxidation of VLCFA, the α- and β-oxidation of branched-chain FAs and the synthesis of plasmalogens. Most, if not all, of the ACSs present in the genomes of humans, mice, and many other species have been identified. Despite this progress over many decades of research, rigorous assignment of a specific ACS to a specific pathway has not yet been achieved. The activation and oxidation of branched-chain FA, VLCFA, and xenobiotics at the peroxisome suggest an important role for peroxisomal ACSs in cellular metabolism. The existence of multiple ACS enzymes associated with peroxisomes suggests that each isoform has a specific function in peroxisomal metabolism. Alternatively, peroxisomal ACSs may have overlapping responsibilities because these enzymes play critical roles in cellular metabolism. Clarification of these complex issues will require further investigation.

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