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Long-chain acyl-CoA synthetases and fatty acid channeling

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Abstract

Thirteen homologous proteins comprise the long-chain acyl-CoA synthetase (ACSL), fatty acid transport protein (FATP), and bubblegum (ACSBG) subfamilies that activate long-chain and very-long-chain fatty acids to form acyl-CoAs. Gain- and loss-of-function studies show marked differences in the ability of these enzymes to channel fatty acids into different pathways of complex lipid synthesis. Further, the ability of the ACSLs and FATPs to enhance cellular FA uptake does not always require these proteins to be present on the plasma membrane; instead, FA uptake can be increased by enhancing its conversion to acyl-CoA and its metabolism in downstream pathways. Since altered fatty acid metabolism is a hallmark of numerous metabolic diseases and pathological conditions, the ACSL, FATP and ACSBG isoforms are likely to play important roles in disease etiology.

A family of acyl-CoA synthetases activates intracellular long-chain fatty acids

Before a fatty acid (FA) from an exogenous or endogenous source can enter any metabolic pathway with the exception of eicosanoid metabolism, it must first be activated to form an acyl-CoA. This activation step is catalyzed by acyl-CoA synthetase (ACS) via a two-step reaction: 1) the formation of an intermediate fatty acyl-AMP with the release of pyrophosphate, and 2) the formation of a fatty acyl-CoA with the release of AMP.

The ACS family is comprised of at least 25 members [1]. Although overlap exists, ACS family members are broadly classified by their substrate specificities for FAs of varying chain length. This review will focus on the three subfamilies of ACS enzymes that activate long-chain and/or very-long-chain saturated and unsaturated FAs, long-chain ACSs (ACSL), very-long-chain ACSs (FATP), and bubblegum (ACSBG) isoforms [2].

The ACSL, FATP and ACSBG families include multiple isoforms, each encoded by a separate gene (Tables 1, 2). Additionally, splice variants of ACSL isoforms have been identified in both humans and rodents [3]. ACS enzymes share significant amino acid sequence similarity, particularly in two highly conserved regions, a putative ATP-AMP signature motif for ATP binding and a motif for FA binding [4]. Despite these similarities, purified ACSL and FATP isoforms and their splice variants show distinct enzyme kinetics, differences in sensitivity to inhibitors (Table 1,2) and differences in their substrate preferences. For example, ACSL4 has

a marked preference for C20:4 [5], whereas ACSL1 prefers saturated and monounsaturated FA that are 16–18 carbons in length [6]. Very-long-chain ACS isoforms, also designated as FATP (FA transport proteins), generally prefer 16–18 carbon FA but can also activate FA as long as 26 carbons [7,8]. It should be noted that FAs may not only be the sole substrate for some isoforms. For example, FATP5 preferentially activates bile acids and FATP2 activates both long-chain FA and 3 α , 7 α , 12 α -trihydroxy-5 β -cholestanoate [9]. The ACSBG isoforms prefer long-chain FA [10,11].

The intracellular locations of the ACSL and FATP isoforms differ depending upon the cell type (Table 1). Not only can several ACSL isoforms be present in different subcellular locations within a single cell, but a single ACSL isoform may vary in its subcellular location. For example, ACSL1 has been reported to be located on the plasma membrane [12] and in GLUT4 vesicles [13] in adipocytes, and on the ER in hepatocytes [14] and mitochondria in epithelial cells [15]. Cell-specific differences in location could arise by differential splicing or protein-protein interactions, both of which may contribute to tissue-specific functions. Such functions include facilitating FA uptake into cells, channeling FAs towards specific synthetic and degradative pathways, and regulating the use of FAs and acyl-CoAs as ligands for transcription factors and as modifiers of cellular physiology.

Role of acyl-CoA synthetases in modulating FA uptake

The FATP family was discovered in 1994 when Schaffer and Lodish searched for adipocyte proteins that would increase cellular uptake of the fluorescent FA analog Bodipy-C12 [16]. They cloned two proteins—one was the previously cloned ACSL1 [6], and they named the other FATP (subsequently FATP1). An additional 5 FATP isoforms have since been cloned, and considerable discussion has taken place regarding whether the FATP family members transport FA directly or, instead, indirectly facilitate FA transport.

Both *in vitro* and *in vivo* studies in a variety of cell types and tissues have shown that manipulating the expression of FATP1 affects FA uptake [17–19]. Interestingly, insulin causes FATP1 and FATP4 to translocate from the ER to the plasma membrane, a process that could enable insulin to enhance FA uptake [20]. The location of FATP5 on the basal plasma membrane of hepatocytes [21] and FATP6 on the plasma membrane of monkey cardiac myocytes [22] suggest that a plasma membrane location is required to mediate FA uptake, since hepatocytes from mice lacking FATP5 have 50% lower rates of FA uptake and overexpressing FATP6 in HEK293 cells enhances FA uptake [21,22].

However, in some instances FA uptake appears to depend more on inherent ACS activity than on a plasma membrane location, and some members of the FATP and ACSL families increase FA uptake despite their location on internal cell membranes. For example, overexpressing ACSL and FATP isoforms increases FA uptake despite the fact that ACSL1 [15,23], ACSL4 [24], ACSL5 [25], and FATP4 [15] are located only on intracellular organelles in the cells examined. (FATP4 is present on the apical side of enterocytes but it was not located to a specific membrane [26]). Like the ACSL family members, most FATP isoforms have either been directly or indirectly shown to possess ACS activity. Purified FATP1 and FATP4 activate a wide range of FAs and show no preference for very-long-chain FAs [7,27]. Additionally, when overexpressed in a genetically modified yeast strain with low ACS activity, all FATPs with the exception of FATP5 are able to increase ACS activity using different long-chain and very-long-chain substrates [28]. The same study shows that rates of FA uptake and ACS activity are often dissociated. Yet, others show that ACS activity is required for FATP-mediated FA uptake, so that when FATP1 contains a mutation that abolishes ACS activity, overexpression severely suppresses FA uptake [29]. Similarly, overexpressing normal FATP4 enhances FA uptake in COS cells, but overexpressing a FATP4 mutant that lacks ACS activity abolishes

these effects [15]. Clearly, the role of ACS activity of ACSL and FATP isoforms in facilitating FA transport needs further evaluation.

Because FAs must first be converted to acyl-CoAs before they enter most metabolic pathways, their activation by ACSLs and FATPs traps them within the cell as acyl-CoAs, and thereby diminishes intracellular FA pools so that less FA is available for efflux [30]. Thus, intracellular acyl-CoA metabolism may enhance FA influx regardless of the location of the ACSL or FATP protein.

Role of acyl-CoA synthetases in FA channeling

The existence of 13 ACSL, FATP and ACSBG isoforms that all activate long-chain FA has suggested that each has an independent role in channeling FA within cells. Unique roles for ACS isoforms were first identified in studies of *Saccharomyces cerevisiae* mutants that lacked the ACS isoforms Faa1 and Faa4, and were unable to use exogenously provided fatty acids [31]. Similarly, complementation studies of ACS-deficient *E. coli* showed that each of the 5 rat ACSL isoforms differs in its ability to channel FA into specific pathways like phospholipid synthesis and β -oxidation [32]. The ACSL and FATP isoforms also differ in their ability to complement FA uptake and activation in mutated yeast strains that lack ACS activity [28,33].

In cultured mammalian cells, gain-of-function and loss-of-function studies also strongly suggest that the different ACSL isoforms channel FA into specific metabolic pathways, consistent with differences in their subcellular locations and substrate preferences. In rat hepatocytes and human fibroblasts, for example, triacsin C, a competitive inhibitor of ACSL1, ACSL3, and ACSL4 [34,35], preferentially decreases [^{14}C]oleic acid incorporation into TAG relative to other glycerolipids and oxidation products [36,37]. These indirect studies suggested that ACSLs direct the metabolic fate of FAs, but did not identify unique roles for individual ACSL isoforms.

Overexpression studies in mammalian cells have shown the effects of specific ACSL isoforms more directly. Adenovirus-mediated overexpression of ACSL5, which doubles total ACS activity in McArdle-RH7777 rat hepatoma cells, partitions oleic acid almost exclusively into intracellular TAG without increasing the amount of TAG secreted into the medium [25]. Because overexpressing ACSL5 does not increase the incorporation of [^{14}C]acetic acid into any lipid class, it appears that ACSL5 uses only exogenous FA and does not activate FA synthesized *de novo* within the cell. Overexpressing ACSL1 in NIH-3T3 fibroblasts or PC12 neurons, also increases oleic acid incorporation into TAG [38,39], and in ACSL1 heart-specific transgenic mice, heart TAG content increases approximately 12-fold and the choline glycerophospholipid content increases 50% [17], again suggesting an anabolic role for ACSL, although ACS activity itself was not measured in these hearts. In contrast to its role in TAG synthesis, overexpressing ACSL1 in rat primary hepatocytes resulted in a 3.7-fold increase in ACS activity but did not enhance incorporation of oleic acid into TAG [14]; instead, ACSL1 increased oleate incorporation into phospholipid and diacylglycerol while decreasing incorporation into cholesterol esters. Pulse-chase experiments further revealed that overexpressed ACSL1 decreased the turnover of intracellular TAG and phospholipids, possibly through altering the reacylation of lysophospholipids. Unlike ACSL5, overexpressed ACSL1 increases the incorporation of *de novo* synthesized FA into glycerolipids [14]. In somewhat contrasting experiments in HepG2 cells, adenovirus-mediated overexpression of ACSL1 resulted in a 20-fold increase in ACS activity, increases in cell acyl-CoA content, and enhanced oleic acid partitioning into cellular TAG [40]. However in this study, the lack of carnitine in the medium may have limited CPT-1 activity and FA β -oxidation, while the marked increase in ACS activity may have overwhelmed other pathways. Adenoviral-mediated overexpression of ACSL1 in rodent liver *in vivo* also increased hepatic TAG, but did not affect FA clearance

from the blood; cholesterol and phospholipid metabolism were not measured [40]. Taken as a whole, these overexpression studies suggest that, not only do ACSL1 and ACSL5 channel FA towards different lipid pathways, but that the direction of channeling may vary in different cell types. A caveat to this interpretation is that in several of the studies cited above, overexpression was ascertained only by changes in mRNA without measuring ACS activity directly. A very large increase in activity could potentially give results that are not relevant to the physiological function.

Similar to these ACSL overexpression studies, altering the expression of FATP isoforms also affects FA channeling. For example, overexpressing FATP1 in HEK293 cells alters partitioning of both exogenously added oleic acid and FA synthesized *de novo* from acetate into cellular lipids and increases cellular TAG content while decreasing cholesterol and sphingomyelin content [41]. In skeletal muscle, adenovirus-mediated overexpression of FATP1 increases the partitioning of oleate or palmitate into TAG and away from β -oxidation [18], and overexpression in mouse heart increases FA uptake and TAG content and causes a lipotoxic cardiomyopathy [42]. Conversely, in muscle from FATP1 null mice fed a high fat diet, the content of TAG, DAG and acyl-CoA is lower than in wildtype controls (Table 3) [19]. Knockdown of FATP1 in 3T3-L1 adipocytes reduces FA uptake without changes in lipolysis, but knockdown of FATP4 does the reverse; it does not affect FA influx, but instead, increases basal lipolysis [43]. In isolated enterocytes, antisense knockdown of FATP4 diminishes the uptake of oleate 50% [26]. Like the ACSL isoforms, these differences in FA metabolism suggest the possibility that interactions with downstream enzymes may mediate the fates of acyl-CoAs synthesized by FATP1 and FATP4. To date, however, no studies have examined such potential interactions. The ACSBG isoforms have not been studied with respect to FA uptake into cells.

The different substrate preferences of the individual ACSL and FATP isoforms suggest that altering the activity of a single isoform might change the FA composition of intracellular glycerolipids. For example, ACSL6 preferentially activates very-long-chain polyunsaturated FAs, and when ACSL6 is overexpressed in PC12 neurons, it enhances the uptake and metabolism of docosahexaenoic acid relative to oleic acid [44]. In the several mouse models that lack FATP4 (Table 3), mice are variably characterized by altered epidermal FA composition accompanied by a neonatally lethal restrictive dermopathy [45], altered skin development, impaired hair growth and abnormal lipid metabolism [46], and early embryonic lethality [47]. The decreased amount of very-long-chain FAs in tissues from FATP4 knockouts supports data from ACS activity assays showing that FATP4 prefers very-long-chain FAs over long chain FAs [45]. Supporting this interpretation are data from fibroblasts from FATP4 null mice in which the rate of 24:0 degradation and incorporation into phospholipids, TAG and cholesterol esters were diminished [1]. In contrast, compared to wild type controls, livers from FATP5 null mice contain 60% less TAG, a greater decrease in saturated and polyunsaturated FAs in TAG relative to monounsaturated FA, and 37% lower unesterified FA [21]. Although no studies have tested whether the different ACSL and FATP isoforms alter the FA composition of phospholipids in specific cellular organelles, the FA preferences of these enzymes suggest that they could mediate the composition of distinct lipid pools.

Differential regulation of acyl-CoA synthetases

Specific functional roles for individual ACSL isoforms are suggested by their tissue-specific responses to nutritional changes and to unique transcriptional regulation. For example, when rats are fasted for 48 h, hepatic *Acs11* and *Acs14* mRNA abundance increases, but *Acs13* and *Acs15* mRNA abundance decreases [48]. When rats are refed a high sucrose diet, the reverse occurs: hepatic *Acs11* and *Acs14* mRNA decreases, and *Acs15* mRNA abundance increases [48]. These responses may reflect regulation by different transcription factors. PPAR α , which

is upregulated in liver during fasting, increases *Acs11* gene expression via a PPRE in the *Acs11* promoter [49]. In contrast, the increase of hepatic ACSL5 mRNA by refeeding is consistent with its upregulation by insulin via SREBP-1c [50]. Insulin also up-regulates *Acs16* in heart [51]. Although the controls are, as yet, unknown, ACSLs are regulated differently in different tissues. Thus, the fasting-induced changes in hepatic *Acs13* and *Acs15* mRNA levels are not observed in adipose tissue or gastrocnemius muscle [48]. High-fat feeding greatly increases *Acs11* mRNA in rat liver [6], but has no effect on *Acs11* mRNA in rat heart [51]. Treatment of rats with PPAR γ agonists has no effect on *Acs11* mRNA in heart, but decreases it in liver, and increases it 7-fold in epididymal and omental adipose tissue and 3-fold in skeletal muscle [52]. These examples of tissue-specific regulation suggest that the ACSL isoforms each contribute activated FAs that have different metabolic fates in each tissue.

In addition to transcriptional regulation with changes in mRNA abundance, the protein amounts of individual ACSL isoforms, and total ACS activities are discordant under fasting and refeeding condition and during development [48,53], suggesting that each isoform may be regulated translationally or by post-translational modifications. The disconnect between mRNA, protein and activity should be considered and further characterized in future studies. Indirect evidence also suggests that ACS activity is regulated acutely. For example, in rat adipocytes, norepinephrine and glucagon simultaneously decrease ACS activity and increase lipolysis, whereas insulin rapidly reverses the norepinephrine effect and restores ACS activity to control levels within 5 minutes [54]. The similar dose-response curves for ACS inactivation and lipolysis stimulation [54], suggest that ACSL and hormone-sensitive lipase may be regulated concomitantly in adipocytes. Since ACSL1 is the most abundant ACSL isoform in adipocytes, and insulin does not alter the content of ACSL1 protein [55], the acute regulation by insulin must occur via another mechanism. Perhaps during fasting, glucagon acutely inhibits adipocyte ACSL1 by phosphorylation. Inactivating ACSL1 would prevent re-esterification of newly hydrolyzed FA and would enhance the release of FA into the circulation. Rodent and human ACSL1 contain two highly conserved serine residues that are predicted sites for protein kinase A and Tyr-85 is phosphorylated in ACSL1 from rat liver [56].

Again arguing for independent regulation, ACSL isoforms are not only expressed in a tissue-specific manner, but they are also expressed differently during development. During 3T3-L1 adipocyte differentiation, *Acs11* mRNA abundance increases ~160-fold while other isoforms remain unchanged [23], suggesting that ACSL1 is the major isoform responsible for TAG synthesis in adipocytes. In contrast, during the differentiation of PC12 neuronal cells, *Acs11* and *Acs13* mRNA content remains unchanged whereas that of *Acs14*, 5, and 6 increases significantly [23]. Further, in mouse heart, *Acs11* mRNA increases 4-fold postnatally, while *Acs13* mRNA decreases and other ACSL isoforms do not change. These data suggest that ACSL1 is the main isoform responsible for the 14-fold increase in ACS activity as the heart adapts to the use of FA as its primary source of energy in the postnatal period [53]. In summary, the unique developmental patterns of the ACSL isoforms suggest that they play different tissue-specific roles during different stages of life.

Except for FATP1, the regulation of the FATP isoforms has been less well studied. *Fatp1* mRNA increases 5- to 7-fold when 3T3-L1 cells differentiate into mature adipocytes [20]. In mouse adipose tissue, fasting increases *Fatp1* mRNA, suggesting a role that would be unrelated to FA uptake or TAG synthesis [57]. Characterization of the FATP1 null mouse also suggests that FATP1 is critical for acute insulin-stimulated uptake of exogenous FA [58].

FAs and acyl-CoAs affect multiple cellular process that influence the etiology of metabolic diseases

ACSL and FATP isoforms regulate the intracellular content of long-chain FA and acyl-CoA, both of which are important intracellular signaling molecules. Long-chain acyl-CoAs have the potential to alter multiple cellular processes including signal transduction via PKC isoforms and Ca^{2+} release, enzymes involved in lipid and energy metabolism like acetyl-CoA carboxylase and glucokinase [59], and ATP-sensitive K^+ channels, including those that control insulin release from pancreatic β -cells [60]. FAs and acyl-CoAs regulate numerous transcription factors including the PPAR family, SREBP, ChREBP, LXR, HNF-4 α and NF- $\kappa\beta$ [61].

Additionally, alterations in specific ACSL and FATP isoforms influence the concentration and content of numerous intracellular lipids, many of which are intimately involved in disease development. For example, apoptosis increases after pancreatic islets are incubated with FAs, and is preceded by an 82% rise in ceramide; both apoptosis and the rise in ceramide can be blocked by triacsin C, an inhibitor of ACSL isoforms 1, 3, and 4 [62]. On the other hand, palmitate may induce apoptosis independent of ceramide production [63], perhaps related to its inhibition of cardiolipin synthesis [64,65]. Palmitate-mediated apoptosis requires metabolism, as evidenced by the finding that in β -cells, triacsin C blocked apoptosis as well as the palmitate-mediated decrease in the anti-apoptosis factor Bcl-2, indicating that changes in Bcl-2 requires acyl-CoAs or their metabolites [66]. Transgenic mice with overexpressed ACSL1 in heart have increased TAG content in cardiac myocytes, cardiac hypertrophy, severe left-ventricular dysfunction, and apoptosis of cardiac myocytes [17]. These studies exemplify the importance role of the ACSL and FATP-isoforms in regulating fatty acid metabolism and the subsequent metabolic changes that may lead to or prevent a host of metabolic diseases.

Acyl-CoA synthetases in pathological conditions

Increases or decreases in ACSL isoforms under pathological conditions suggest that each is playing an independent role that cannot be compensated for by alterations in other isoforms. For the most part, however, the effects of these alterations on tissue lipids or fatty acid composition have not been investigated. ACSLs have been associated with various forms of cancer, including acute myelogenous leukemia (ACSL6) [67], colorectal adenocarcinomas (ACSL5) [68,69] and colon adenocarcinomas (ACSL4) [70]. It has been suggested that upregulation of ACSL4, which has a marked preference for arachidonate [5], promotes carcinogenesis by blocking the apoptosis that free arachidonate would otherwise induce [71]. ACS specific activity and *Acs11* mRNA abundance are upregulated in liver and adipose tissues in genetic obese models such as Zucker fatty rat (*fa/fa*) and *ob/ob* mice [72,73]. Although the causality between the change of ACSL isoforms and specific diseases has not been established, these observations indicate that ACSL isoforms are linked to metabolic changes or FA demand under several pathological conditions. For example, in patients with inflammatory bowel disease, the increase of *Acs11* and *Acs14* mRNA in the terminal ileum and colon might provide acyl-CoAs for the synthesis of phospholipids; these can serve as precursors for inflammatory mediators or support membrane integrity of the affected intestine [74].

Despite the presence of other ACSL isoforms in brain, human ACSL4 is associated with depression [75] and mutations in the human *Acs14* gene that decrease 20:4-CoA synthetase activity cause a form of X-linked mental retardation [76–78]. The effect of these mutations suggests that ACSL4 is critical for normal brain function, perhaps related to its preference for long-chain polyunsaturated FAs [35], which are enriched in brain phospholipids.

Conclusion

The differences in tissue expression, cellular location, enzyme kinetics and substrate preferences suggest that individual ACSL, FATP, and ACSBG isoforms play unique roles in FA channeling and lipid metabolism. In addition to controlling the metabolic fate of FAs, the ACSL and FATP isoforms also regulate intracellular pools of FAs and acyl-CoAs, both of which have broad effects on cellular metabolism ranging from altering gene expression to allosterically regulating enzymes. Despite the importance of the ACS family in FA trafficking and the intimate role of lipid metabolism in disease etiology, mechanisms linking the two have been largely neglected.

Future perspectives

Although recent advances have provided insight into the physiological role of ACSLs, FATPs, and ACSBGs, much work remains to elucidate their roles in FA channeling and the development of disease. We anticipate that future studies will show that individual isoforms of these enzymes differ in function depending on tissue-specific expression, expression of splice variants, subcellular location, translational or post-translational modifications, and expression of other proteins that interact with a given isoform. Because it is widely accepted that the composition of FAs largely dictates their regulatory effects within the cell, identifying the ACSL, FATP, and ACSBG isoforms that mediate specific effects of different FAs should provide valuable insights. Additionally, identifying isoforms that influence the formation of distinct pools of other intracellular lipids like DAG and ceramide may identify novel pharmaceutical targets for diseases characterized by altered lipid metabolism and lipotoxicity.

Executive summary

Acyl-CoA synthetases in FA activation

- ACSL, FATP, and ACSBG activate long-chain and very-long-chain FA by a two-step reaction
- ACSL, FATP, and ACSBG families include multiple isoforms that have distinct enzyme kinetics, different but overlapping FA preferences, and unique subcellular locations

The role of acyl-CoA synthetases in FA uptake

- ACSL and FATP isoforms are major regulators of both FA transport and metabolism
- ACSL and FATP isoforms located on intracellular membranes increase FA uptake, suggesting that ACS activity and downstream metabolism enhance FA uptake and that location on the plasma membrane is not required.
- ACSL and FATP appear to enhance FA uptake by activating FAs, a process that traps FAs as acyl-CoAs within the cell and prevents efflux.
- Little is known about the specific role of the ACSBG isoforms.

The role of acyl-CoA synthetases in FA channeling

- In rat hepatoma cells, ACSL5 increases FA uptake and partitions it to TAG
- ACSL1 appears to be involved in TAG accumulation in adipose tissue, but, in liver, it contributes to the synthesis of phospholipid and cholesterol. Thus, the functions of individual isoforms may be tissue-specific

- Similar to ACSL1, most studies support a role for FATP1 in TAG synthesis in adipose tissue
- FATP4 is essential for normal skin development and its presence is required for neonatal survival.

Differential regulation of acyl-CoA synthetases

- ACSL isoforms display tissue-specific response to nutritional changes. Potential mechanisms include transcriptional, translational and post-translational regulations
- ACSL isoforms have different developmental patterns, suggesting specific roles during adipocyte and heart development
- FATP1 expression responds to cell differentiation and nutritional changes

Acyl-CoA synthetases in pathological conditions

- Alterations in ACSL and FATP isoforms influence the content of intracellular lipids
- ACSL isoforms may be involved in certain cancers and in disorders like obesity, diabetes and inflammatory bowel disease
- Mutations in the human *Acs14* gene cause a form of X-linked mental retardation

Unanswered questions

- What are the roles of splice variants of ACSL4 and ACSL6?
- Is ACSL1 inhibited in adipocytes during lipolysis to prevent reesterification and promote FA efflux?
- How are FATPs regulated acutely, transcriptionally, and during development?
- Is channeling mediated by protein-protein interactions?
- What is the role of ACSBG in FA metabolism?

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Fig. 1.

Pathways initiated by ACSL, FATP, and ACSBG isoforms. In addition to initiating the synthesis of triacylglycerol (TAG) and all the glycerophospholipids, acyl-CoAs are required for the synthesis of cholesterol esters, ceramide and sphingolipids, for fatty acid (FA) degradation pathways and for FA modification pathways of elongation and desaturation. Intermediates in the glycerolipid synthetic pathway, lysophosphatidic acid (LPA), phosphatidic acid (PA), and diacylglycerol (DAG) are intracellular signals. Both FA and acyl-CoAs are also intracellular signals and regulators of cellular physiology as well as purported ligands for PPAR and HNF4 α transcription factors. G-3-P, glycerol-3-phosphate; PI, phosphatidylinositol; PG, phosphatidylglycerol; CL, cardiolipin; PE, phosphatidylethanolamine; PC, phosphatidylcholine; PS, phosphatidylserine.

Table 1

Long-chain acyl-CoA synthetases

Isoforms	Tissue expression with highest mRNA abundance	Intracellular locations ¹	Inhibitors	Accession Numbers (Human) ²
ACSL1 ³	Liver, adipose tissue, heart [6, 48]	ER, nuclear fraction, plasma membrane (3T3-L1 adipocytes) [12]; GLUT4 vesicle (rat adipocytes) [13]; mitochondria (PitK2 epithelial cells) [15]; ER, MAM, cytosol (rat liver) [79]; lipid droplet fraction (3T3-L1 adipocytes) [80]	Triacsin C [35,81]	NP_001986
ACSL3	Brain, gonads [48,82]	Lipid droplet fraction (3T3-L1 adipocytes [80]; HuH7 cells [83]; CHO cells [84]; epithelial A431 cells [85]; HepG2 cells [86]	Triacsin C [35]	NP_004448 NP_976251.1
ACSL4	Adrenal gland, liver [5,48]	MAM, peroxisomes (rat liver) [79]; lipid droplet (3T3-L1 adipocytes [80]; HuH7 cells [83], CHO cells [84], HepG2 hepatoma cells [86]	Triacsin C, rosiglitazone, troglitazone, pioglitazone, N-ethylmaleimide [35,81]	NP_004449 NP_075266
ACSL5	Small intestine, liver, brown adipose tissue [48,87]	ER, mitochondria (rat liver) [25,79]; ER, mitochondria (McArdle-RH 7777 hepatoma cells) [25]; lipid droplets (rat liver) [88]	—	NP_057318 NP_976313 NP_976314
ACSL6	Brain, gonads [48,89]	—	—	NP_056071 BAA74860

¹ ER, endoplasmic reticulum; MAM, mitochondrial-associated membrane

² Multiple numbers indicate splice variants

³ See [3] for other aliases

Table 2

Fatty acid transport proteins/Very-long-chain acyl-CoA synthetases/ACSBG

Isoforms	Tissue expression in highest mRNA abundance	Intracellular locations	Inhibitors	Accession Numbers (Human)
FATP1 ¹ (Sic27a1)	Heart, WAT, skeletal muscle [21]	Plasma membrane (3T3-L1 adipocytes) [12,16], mouse adipocytes [20]; plasma membrane, Golgi (human primary muscle cells) [18]	---	NP_940982
FATP2 ² (Sic27a2)	Kidney cortex, liver [90]	Microsomes, peroxisomes (mouse hepatocytes) [90]	—	NP_003636
FATP3 (Sic27a3)	Broad distribution, highest in lung, adrenal, gonads [91]	Mitochondria, MAM (MA-10 Leydig cells, mouse Neuro2a cells) [91] ER (overexpressed in COS-7) [91]	—	NP_077306
FATP4 (Sic27a4)	Small intestine [92]; brain, liver, kidney [93]	Apical plasma membrane (mouse enterocyte) [26]; plasma membrane (mouse adipocytes) [20]; ER (multiple cell lines) [15]; mitochondria, nuclei, MAM, peroxisomes (skin fibroblasts) [1]	n-dodecyl-D-maltopyranoside, triacsin C (C16:0 esterification), troglitazone (C16:0 esterification) 4-aryl-dihydropyrimidinones [8,27,94]	NP_005085
FATP5 (Sic27a5)	Liver (exclusively) [21,95]	Basal plasma membrane (mouse hepatocytes) [21]	—	NP_036386
FATP6 (Sic27a6)	Heart (exclusively) [22]	Sarcolemma (monkey cardiomyocytes) [22]	—	NP_054750
ACSBG1	Brain, adrenal, gonads, spleen [2,10,96–98]	Cytoplasm (COS-1 cells, [2], mouse Leydig tumor cells; mitochondria (Neuro2a cells, mouse brain) [10]; microsomes (COS7 cells) [98]	—	NP_055977
ACSBG2	Testis [11,99]	Cytoplasm (COS-1 cells, mouse TM4 Sertoli cells) [99]; microsomes (mouse testis) [99]; mitochondria, microsomes (COS-7 cells) [11]	—	NP_112186

¹ FATP has been termed ACSVL and VLCS² FATP2 has been termed VLCS and VLACS³ FATP5 has been termed ACSB, BACS, VLCS-H2 and VLCSR

ACSL and FATP knockout mice

Table 3

Isoforms	Mouse phenotype	FA uptake and labeling studies	Lipid abnormalities	Ref.
ACSL4	Female heterozygote: decreased fertility, enlarged uteri with cysts		Uterus: 50% increases in PGE ₂ , 6-keto PGF _{1α} , PGF _{2α}	[100]
FATP1	Normal phenotype; protection from high fat-induced insulin resistance; no diet-induced obesity; smaller adipocytes;	Skeletal muscle: no change in FA uptake; Adipocytes; decreased insulin-stimulated FA uptake	Muscle: no increase in TAG, acyl-CoA on high fat diet; Liver: contains more TAG with both chow and high fat feeding	[19,58]
FATP2	Normal phenotype and histology		Decreased peroxisomal acyl-CoA synthetase activity with 24:0; decreased β-oxidation of 24:0; no accumulation of very-long-chain FA	[101]
FATP4	Lethal restrictive dermopathy; smallmouth and nose, low set ears, flexion contractures		Squamous epithelium: absent lipid droplets	[46]
FATP4	embryonic lethality at 9.5 d of gestation	Heterozygote enterocytes: 40% reduced FA uptake; no difference in diet fat absorption	—	[47]
FATP4	Lethal restrictive dermopathy with hyperkeratosis, flexion contractures, facial dysmorphia	Decreased 24:0 activation	Liver, brain, lung, intestine: no changes in lipids; Liver: 15–30% decreases in molar content of PC, PE, cholesterol esters; 81% increase in ceramides with increased 16–24 carbon FA and decreased C26:0 and C26:0-OH FA	[8,45]
FATP5	No weight gain on high fat diet because of decreased intake and increased energy expenditure	Hepatocytes: 40% decrease in uptake of C12-Bodipy; Intestine: normal diet FA uptake	Liver: 60% less TAG with relatively less saturated and polyunsaturated FA; 37% less free FA; 60% increase in PS content; no change in FA composition of phospholipids; increased fatty acid synthase mRNA; impaired VLDL secretion and ketogenesis (probably due to decreased liver TAG; decreased bile acid conjugation	[21,102]

FA, fatty acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; TAG, triacylglycerol