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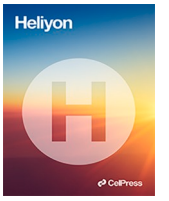

Review article

Role of ACSL5 in fatty acid metabolism

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ABSTRACT

Free fatty acids (FFAs) are essential energy sources for most body tissues. A fatty acid must be converted to fatty acyl-CoA to oxidize or be incorporated into new lipids. Acyl-CoA synthetase long-chain family member 5 (ACSL5) is localized in the endoplasmic reticulum and mitochondrial outer membrane, where it catalyzes the formation of fatty acyl-CoAs from long-chain fatty acids (C16–C20). Fatty acyl-CoAs are then used in lipid synthesis or β-oxidation mediated pathways. ACSL5 plays a pleiotropic role in lipid metabolism depending on substrate preferences, subcellular localization and tissue specificity. Here, we review the role of ACSL5 in fatty acid metabolism in multiple metabolic tissues, including the liver, small intestine, adipose tissue, and skeletal muscle. Given the increasing number of studies suggesting the role of ACSL5 in glucose and lipid metabolism, we also summarized the effects of ACSL5 on circulating lipids and insulin resistance.

1. Introduction

Free fatty acids (FFAs) are classified into long-chain fatty acids (LCFAs) (12 or more carbons), short-chain fatty acids (fewer than six carbons), and medium-chain fatty acids (6–12 carbons) based on the length of the aliphatic chain [1]. The primary source of FFAs are dietary lipids, de novo synthesized FAs, triacylglycerol (TAG) turnover, and cholesterol esters [2,3]. FFAs are essential energy sources for most body tissues and significant components for lipids synthesis, which have multiple metabolic fates, including storage as triacylglycerols (TAGs) in fat tissue, β-oxidation in mitochondria, incorporation into complex lipids, esterification to proteins [4], and synthesis of eicosanoids [5]. FFAs are also involved in intracellular signaling [6]. The initial step in producing fatty acyl-CoA in mammals is catalyzed by the acyl-CoA synthetase, in which CoA is added to fatty acid in the presence of ATP, CoA and Mg^{2+} [7,8]. The acyl-CoA synthases can be divided into very long-chain acyl-CoA synthases, long-chain acyl-CoA synthases (ACSLs), and medium and short-chain acyl-CoA synthases according to the carbon chain length of FFAs they act upon. ACSLs mainly catalyze the reaction of fatty acids with the carbon chain length of 12–20 carbons [9,10]. Five isoforms of ACSLs have been identified and annotated as members 1,

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3, 4, 5, and 6, respectively. ACSLs have distinct functions according to their unique pattern of tissue expression, subcellular localization, and preference for the substrate [8,9].

Acyl-CoA synthetase long-chain family member 5 (ACSL5) is a key member of ACSLs, widely expressed in mammalian liver, small intestine, fat, spleen, uterus, lung, and skeletal muscle [11]. ACSL5 catalyzes the formation of acyl-CoAs using long-chain fatty acids (C16–C20) as substrates in the cytoplasm [12]. These are then used to synthesize complex lipids and other products in the endoplasmic reticulum (ER) or enter mitochondria for β-oxidation [13]. The fatty acids catalyzed by ACSL5 include palmitic acid (C16:0), palmitoleic acid (C16:1), oleic acid (C18:1) and linoleic acid (C18:2) [11,12,14].

In recent years, the role of ACSL5 in fatty acid metabolism has received much attention. ACSL5 has different metabolic regulatory effects on fatty acids in different environments, which may be related to the tissue distribution and intracellular localization of ACSL5. In addition, studies have shown that ACSL5 may be involved in glucose and lipid metabolism [15,16], suggesting that it may play an essential role in metabolic disorders. Herein, we reviewed the role of ACSL5 in fatty acid metabolism and its impact on circulating lipids and insulin resistance.

2. Characterization of ACSL5

2.1. Gene localization and protein isoforms

The human ACSL5 gene, which was firstly identified in 1998 [14] maps to the q25.1-q25.2 region of chromosome 10 [11]. ACSL5 has two in-frame AUG-translational initiators generating isoforms of different lengths [10]. Human ACSL5 encodes three isoforms: the long isoform (739 amino acids, aa), the short isoform (683aa) and, less frequently, the shorter isoform (659aa). The long isoform is produced from the first AUG1, whereas the short isoform is dependent on the downstream AUG2. The rare 659aa isoform resulted from a 72 bp deletion corresponding to exon 20 and was designated ACSL5-Δ20 [10,17]. Rodents primarily produce one isoform of 683aa [10]. Current research shows that the ACSL5-Δ20 isoform might be involved in the pathogenesis of cell growth and migration [18,19].

2.2. Tissue distribution and subcellular localization

In humans, ACSL5 mRNA is expressed at high levels in the spleen, uterus, liver, and small intestine [11]. In rodents, ACSL5 protein is mainly expressed in the small intestine, liver, and brown adipose tissue [11,16,20]. The subcellular localization of ACSLs is, therefore, an essential aspect of their functions in fatty acid metabolism. Lewin et al. [13] isolated the ER and mitochondria by sucrose gradient centrifugation and percoll gradient, and they observed two bands of 73- and 74.5 kDa in the ER fraction as well as a 76 kDa band in the rat liver mitochondrial fraction by immunoblotting with an antibody against ACSL5. Subsequently, Mashek et al. [21] overexpressed Acsl5 in a rat hepatoma cell line (McArdle-RH7777) and found that FLAG-tagged ACSL5 localizes to both the ER and mitochondria by confocal microscopy. Reinartz et al. [22] showed that ACSL5 localizes to mitochondria in human hepatoma cells (HepG2) but did not provide evidence as to whether ACSL5 is found in the ER [22]. Gassler et al. [17] expressed ACSL5 long isoform and ACSL5-Δ20 in human colorectal adenocarcinoma cells (CaCO2). Both isoforms were located in the mitochondria and ER using immunofluorescence and subcellular organelle separation. ACSL5 is highly expressed in the human and rodent small intestine. In humans, ACSL5 protein is predominantly found in the villus epithelium, with little expression in the crypt epithelium. Its expression shows an increasing trend along the crypt-villus axis (CVA) of the small intestine [17,23,24]. In rodents, the jejunum is the organ where Acsl5 is most abundantly expressed, especially in C57BL/6 mice [16]. D'Aquila et al. [25] found that mouse ACSL5 protein was localized to the area on or around lipid droplets and mitochondria of intestinal enterocytes by immunofluorescence and immunoelectron microscopy. ACSL5 protein is less expressed in skeletal muscle. Rajkumar et al. [26] overexpressed human ACSL5 in mouse myoblasts (C2C12) and showed by confocal microscopy that the ACSL5 short isoform was localized to a greater extent in the mitochondria rather than the ER, where the long isoform was instead mostly expressed [26]. Furthermore, the ACSL5 short isoform was predominantly in human skeletal muscle, with ~60% of ACSL5 being localized in mitochondria of human myotubes [25]. In contrast, mouse ACSL5 was more expressed in the ER of C2C12 cells (myoblast line) than in mitochondria [26]. In Table 1, we have summarized the subcellular localization of ACSL5.

Table 1
Subcellular localization of ACSL5.

Organ or tissue	Cells	subcellular localization	Ref.
Liver	McArdle-RH7777	Mitochondria and ER	Mashek, 2006 [21]
	HepG2	Mitochondria	Reinartz, 2010 [22]
Intestines	CaCo2	Mitochondria and ER	Gassler, 2007 [17]
	Primary enterocytes of C57BL/6 mice	Mitochondria and lipid droplets	D'Aquila, 2015 [25]
Skeletal muscle	Human ACSL5 short isoform in C2C12	Mitochondria (dominantly) and ER	Rajkumar, 2018 [26]
	Human ACSL5 long isoform in C2C12	Mitochondria and ER (dominantly)	Rajkumar, 2018 [26]
	Mouse ACSL5 in C2C12	Mitochondria and ER (dominantly)	Rajkumar, 2018 [26]

McArdle-RH7777: rat hepatoma cell lines; ER: endoplasmic reticulum; HepG2: human hepatoma cell lines; CaCo2: human colorectal cell lines; C2C12: mouse muscle myoblasts.

2.3. Regulation of ACSL5

The expression of ACSL5 is regulated by factors that mediate lipogenesis or catabolism. Acsl5 is a target gene of sterol regulatory element-binding protein (SREBP)-1c, and its mRNA expression in rat liver was found to be highly induced upon carbohydrate refeeding for 8 h [27]. Consistently, fasting induced a ~50% decrease in ACSL5 mRNA levels in rat liver [14]. This is in line with previous findings from Mashek et al. [21]. However, Lewin et al. [13] found that refeeding for 24 h following 48 h of fasting did not affect the protein expression of Acsl5 in rat liver mitochondria. On the contrary, 48 h of fasting could upregulate the protein expression of Acsl5 in rat liver mitochondria [13]. The discrepancy between the two studies could be explained by the timing of fasting and refeeding. Some believe this inconsistency may be due to cross-reactivity of - antibodies against ACSL5 with an as yet unidentified ACSL isoform that has a mitochondrial localization upregulated by starvation [27]. There is also a possibility that fasting may result in reduced or unchanged total ACSL5 protein in hepatocytes but increased ACSL5 protein partitioning into mitochondria, which promotes fatty acids β-oxidation in response to changes in nutritional status. In addition, leptin treatment was shown to reduce hepatic ACSL5 mRNA levels in mice with leptin signalling pathway genetic defects (ob/ob) [28]. Other studies have also shown that peroxisome proliferator-activated receptors γ (PPAR-γ) agonist upregulated Acsl5 expression in brown fat (6-fold) and liver (1.5-fold) of rats [29]. In the intestine, it was shown that Acsl5 is regulated by hepatic nuclear factor 4 (HNF4), which activates ACSL5 in intestinal epithelial cells to maintain intestinal stem cell self-renewal [30]. In human colon cancer cells, miR-27b-3p, miR-135a-5p, miR-497-5p can inhibit the expression of ACSL5 at the transcriptional level [31]. In addition, oncogenic factor ONECUT2 can activate ACSL5 transcription [32]. However, it remains unclear whether they have such a regulatory role under normal physiological conditions. Oncostatin M (OM) can upregulate hepatic ACSL5 transcription and promote fatty acids entry into the β-oxidation pathway [33]. In addition, deletion of the rs7903146 region corresponding to the transcription factor 7 like 2 (TCF7L2) (a causal gene for type 2 diabetes) resulted in a significant downregulation of ACSL5 expression [15]. Whether some unknown targeting signal molecules also regulate ACSL5 remains to be elucidated. In Fig. 1, the regulatory factors of ACSL5 have been summarized.

3. Effects of ACSL5 on fatty acid metabolism in different tissues

3.1. ACSL5 in rodent liver

The liver plays a central role in the synthesis, catabolism, and transport of lipids. Liver FFAs derived from de novo synthesis or uptake from the circulation are catalyzed into fatty acyl-CoAs by ACSLs, which function to 1) serve as synthetic materials for the synthesis of lipids such as triglyceride (TG), phospholipid (PL), and cholesterol ester (CE) in the ER; 2) enter mitochondria for β-oxidation. It remains controversial whether ACSL5 is the major ACSL in rodents and affects cellular ACSL activity. Mashek et al. [21] overexpressed Acsl5 by adenovirus and observed a 17-fold increase in ACSL5 activity and a 2-fold increase in total ACSL activity in rat hepatocytes (McArdle-RH7777). Bu et al. [34] found only a 27% decrease in total ACSL activity in cell homogenates following knockdown of Acsl5 by small interfering RNA (siRNA) in rat primary hepatocytes. Of note, most studies performed on mice led to controversial findings. Bowman et al. [16] found that inactivation of Acsl5 in the whole body resulted in approximately 50% reduction in hepatic ACSL activity. However, Meller et al. [35] found no significant decrease in ACSL activity in homogenates of primary hepatocytes from Acsl5 knockout mice compared with wild-type littermates. The reasons for the observed differences are not clear.

It has been shown that ACSL5 is mainly localized in the ER and mitochondria [17,21,26,36]. The ER is the central organelle for

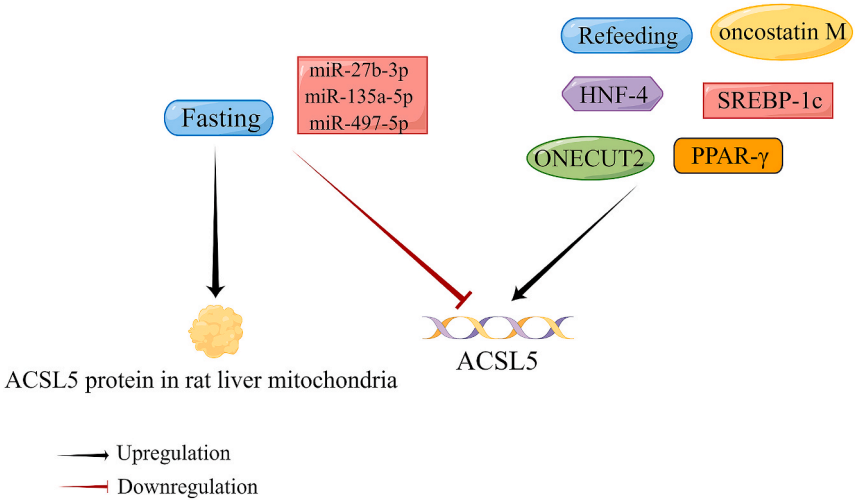

Fig. 1. A schematic for the regulation of ACSL5. HNF4: hepatic nuclear factor 4; SREBP-1c: sterol regulatory element binding protein-1c; PPAR-γ: peroxisome proliferator-activated receptor-γ. Fasting inhibits ACSL5 at the transcriptional level but upregulates protein expression of ACSL5 in rat liver mitochondrial.

lipogenesis, while mitochondria are the site of fatty acid oxidation, suggesting that ACSL5 may be involved in lipogenesis and β-oxidation. It was found that overexpression of Acsl5 increased intracellular TG content in oleic acid-treated rat hepatocytes (100 mM oleic acid) by 21% without affecting the TG content of the culture medium, suggesting that ACSL5 may promote hepatic TG synthesis but not alter its secretion [21]. Further radiolabeling studies demonstrated that overexpression of Acsl5 could promote the synthesis of TG and diacylglycerol (DAG) from 14C labelled oleic acid, but ACSL5 did not affect the synthesis of fatty acid, PL or CE, nor did it affect the synthesis of TG from 14C labelled acetic acid [21], suggesting that ACSL5 may not affect the metabolism of endogenous fatty acids. In addition, rat hepatocytes treated with Acsl5 siRNA found a 30–40% reduction in TG content (cells were also exposed to 1000 μM oleic acid), and the knockdown of Acsl5 inhibited the esterification of fatty acids to PL, DAG and CE [34]. However, Acsl5 knockdown did not affect cellular uptake of fatty acids, the metabolic rate of TG or PL, and the expression of genes involved in lipogenesis (such as SREBP-1c) [34]. Although experiments in cultured cells showed that ACSL5 might be involved in synthesizing hepatic TG, *in vivo* experiments did not corroborate such findings. Our group [37] and others also found that Acsl5 knockout did not affect hepatic TG content [16].

Furthermore, it was shown that knockdown of Acsl5 significantly promotes fatty acid β-oxidation [34]. Notably, triacsin C (an inhibitor of ACSL1, 3, and 4) treatment decreased intracellular acid-soluble metabolite (ASM) (a product of incomplete fatty acid oxidation) synthesis by ~ 21% in Ad-Acsl5-infected hepatocytes. In comparison, it reduced ASM by 66% in Ad-GFP-infected hepatocytes [21], suggesting that ACSL5 may also be involved in activating fatty acids oxidation. In general, the available evidence suggests that ACSL5 in rodent liver may predominantly direct fatty acids for lipogenesis. However, under specific conditions (such as triacsin C treatment), ACSL5 also directs fatty acids for β-oxidation. The role of ACSL5 in fatty acid metabolism in rat hepatocytes is summarized in Fig. 2.

3.2. ACSL5 in human liver

Zhou et al. [33] evaluated the effects of overexpression and knockdown of ACSL5 on TG content and fatty acid oxidation in HepG2 cells. ACSL5 overexpression increased the total ACSL activity in cell homogenates by 16.7%, resulting in 49.5% increased β-oxidation in cells treated with 14C labelled palmitic acid (200 μM) [33]. In addition, the knockdown of ACSL5 caused a significant increase in intracellular TG content [33]. In rat hepatocyte cell lines, Acsl5 overexpression increases TG synthesis, and knockdown of Acsl5 reduces cellular TG synthesis and promotes fatty acid oxidation [21,34]. In contrast, ACSL5 overexpression in HepG2 cells promotes fatty acid oxidation [33] (Fig. 3). Reinartz et al. [22] showed that exogenous long-chain fatty acids induced lipid droplet formation in HepG2 and human primary hepatocytes in a concentration- and time-dependent manner, accompanied by upregulation of ACSL5 mRNA and protein levels, suggesting that exogenous long-chain fatty acids may regulate expression of ACSL5 in human hepatocytes. Interestingly, the expression of both ACSL5 mRNA and protein in the liver of patients with steatosis is significantly increased compared to healthy individuals [22], although it is still unclear whether ACSL5 is directly involved in fatty liver disease.

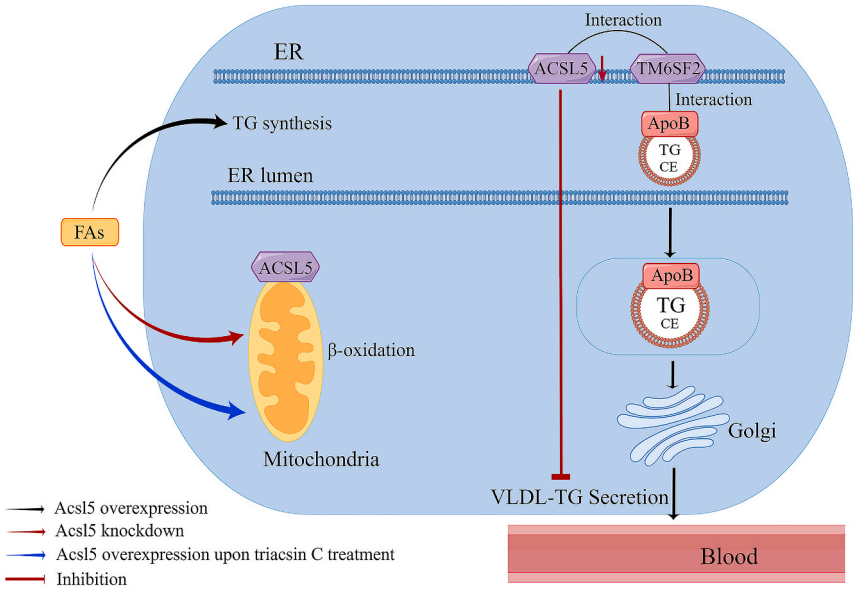

Fig. 2. Role of ACSL5 in fatty acid metabolism in rat hepatocytes and effects on circulating lipids. ER: endoplasmic reticulum; FAs: fatty acids; VLDL: very low-density lipoprotein; TG: triglyceride; CE: cholesterol ester. In rat hepatocyte cell lines, ACSL5 localizes to mitochondria and the endoplasmic reticulum. Overexpression of *Acsl5* promotes cellular TG synthesis, while both knockdown of *Acsl5* as well as overexpression of *Acsl5* upon triacsin C treatment channel fatty acids into mitochondria for β-oxidation. In the *Acsl5* whole-body knockout mice model, *Acsl5* knockout inhibits hepatic VLDL-TG secretion into the blood. In addition, ACSL5 interacts with TM6SF2, suggesting that ACSL5 may be closely related to the metabolism of VLDL.

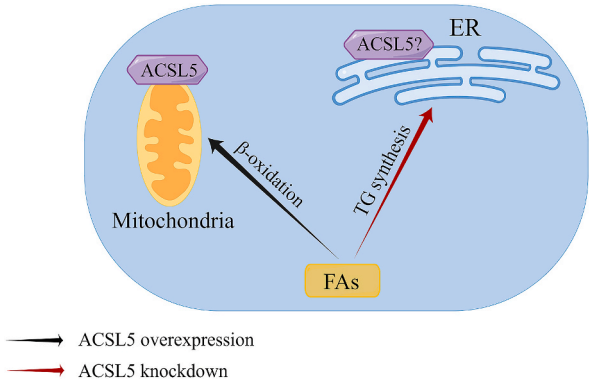

Fig. 3. Role of ACSL5 in fatty acid metabolism in HepG2 cells. ER: endoplasmic reticulum; FAs: fatty acids. In human hepatoma cell lines (HepG2), ACSL5 was found to localize to mitochondria, and whether it localizes in the endoplasmic reticulum is unknown. ACSL5 overexpression promotes fatty acid oxidation, and ACSL5 knockdown significantly increased cellular TG content.

Al-Thihli et al. [36] reported a family with six affected family members characterized by recurrent vomiting and diarrhoea. Whole-exome sequencing showed a homozygous mutation in ACSL5 (NM_203379.1:c.1358C > A p. T453K) segregating with the disease. The activity of ACSL5 (T453K) mutant protein was significantly lower than that of wild-type ACSL5, suggesting that ACSL5 T453K may result in loss of ACSL5 activity [36]. In addition, 5 out of the six affected members had fatty liver [36]; however, whether ACSL5 (T453K) is associated with the development of fatty liver remains unclear. Overall, unlike rodents, ACSL5 is mainly involved in fatty acid β-oxidation in human hepatocytes. Inhibition or loss of function of *ACSL5* may lead to hepatic TG accumulation.

3.3. Role of other ACSL isoforms with similar functions to ACSL5 in hepatic fatty acid metabolism

3.3.1. ACSL1

ACSL1 is one of the major ACSL expressed in the liver [38]. Like ACSL5, ACSL1 also localizes to mitochondria and the ER [13,39], which determines its similar function to ACSL5 in hepatic fatty acid metabolism, i.e., lipogenesis and fatty acid oxidation. *In vivo* studies showed that *Acsl1* overexpression led to a 2-fold increase in hepatic TG content in mice [40]. *In vitro*, liver-specific knockout of *Acsl1* reduces TAG synthesis in mouse primary hepatocytes [38]. But different from ACSL5, *Acsl1* overexpression in rat hepatocytes increased the incorporation of 14C labelled oleate into DAG and PL, but not TAG [41]. In addition, overexpression of *Acsl1* increases the incorporation of endogenous fatty acids into TAG, DAG and PL, suggesting that ACSL1 can activate both exogenous and endogenous fatty acids for lipid synthesis (ACSL5 can only activates exogenous fatty acids) [41]. Recent studies have shown that Tank-Binding Kinase 1 (TBK1) is induced under fasting conditions and mediates the localization of ACSL1 in liver mitochondria, thus directing fatty acids for oxidation. Conversely, under obese conditions, TBK1 translocates ACSL1 to the ER, favouring lipid synthesis [42]. Given that ACSL5 also functions both in directing fatty acids for lipid synthesis and β-oxidation in rodent liver, it remains to be shown whether the localization of ACSL5 in the liver ER and mitochondria is also regulated by unknown protein rheostats.

3.3.2. ACSL3

ACSL3 is mainly located in ER and lipid droplets [43]. When additional exogenous fatty acids were added, ACSL3 was rapidly translocated from the ER into nascent lipid droplets, suggesting its important role in lipogenesis [44]. Like ACSL5, ACSL3 is also regulated by OM [33]. Activation of OM upregulates the mRNA levels of ACSL3/5. Knockdown of *ACSL3/5* resulted in a significant increase in intracellular TG content in HepG2 cells. However, unlike ACSL5, overexpression of *ACSL3* in HepG2 cells resulted in a 37% reduction in intracellular TG content, whereas only a trend toward reduced intracellular TG content was observed with overexpression of *ACSL5* [33].

3.3.3. ACSL4

Chen et al. [45] found *in vitro* that knock-down of *ACSL4* in Human hepatoma cells (Huh7 and SMMC-7721) reduced the levels of intracellular TG and cholesterol, suggesting that ACSL4 promotes lipid accumulation in Human hepatoma cells. Furthermore, the authors found that ACSL4 enhances the expression of lipogenic enzymes by upregulating SREBP1 [45]. In animal experiments, Duan et al. [46] showed that liver-specific *Acsl4* knockout in mice ameliorated high-fat diet induced hepatic steatosis. In mechanism, knockdown of *ACSL4* in HepG2 cells enhanced mitochondrial respiration by promoting fatty acid oxidation. These findings suggest that unlike ACSL5, ACSL4 may direct fatty acids for lipogenesis in both rodent and human hepatic fatty acid metabolism.

3.4. ACSL5 in the small intestine

Dietary TGs are hydrolyzed into glycerol and free fatty acids. When absorbed by small intestinal mucosal cells, free long-chain fatty acids are catalyzed into fatty acyl-CoA by ACSLs. Subsequently, fatty acyl-CoA is incorporated into TGs, and packaged into

chylomicrons (CM) for delivery to the circulation [47,48]. When fatty acids are in excess, the newly synthesized TGs may be incorporated into enterocyte lipid droplets [25].

The 80% reduction in total ACSL activity in the jejunal mucosa of Acsl5 knockout mice suggests that ACSL5 is the predominant ACSL isoform in mouse jejunum [16]. To investigate the ACSL5 function in the intestine, mice were injected with tyloxapol and gavaged with an olive oil bolus after a 4-h fast. The rate of triglyceride appearance in serum was significantly delayed in Acsl5−/− mice compared to control mice [16]. Similarly, O'Brien et al. [49] described a group of Australian Kelpie dogs characterized by intestinal lipid malabsorption due to the complete absence of ACSL5 and partial loss of ZDHHC6. These findings suggested that ACSL5 may be essential in intestinal fat absorption. However, in another study exploring the effects of Acsl5 knockout on intestinal fatty acid absorption, mice were gavaged with 50 μl olive oil, supplemented with ^{3}H labelled oleic acid, and radiotracer levels were measured in plasma 90 min after gavage [35]. No difference in the accumulation of plasma radiotracer between Acsl5 knockout mice and wild-type was observed, suggesting that Acsl5 knockout did not affect intestinal fatty acid absorption [35]. It is possible that gavage with 50 μl olive oil only forms fewer lipid droplets, and thus the effects of Acsl5 knockout on plasma triglycerides are diminished. Sheng et al. [50] evaluated the effects of intestinal microbiota on lipid absorption by generating germ-free and antibiotic-treated zebrafish models. A significant reduction in ACSL5 mRNA expression was shown in the intestine of antibiotic-treated zebrafish compared to the control zebrafish group [50]. In addition, the authors found that the lipid droplets of small intestinal epithelium were significantly reduced in the antibiotic-treated zebrafish group compared with the control group by oil red O staining. This finding suggests an important role for ACSL5 in TG synthesis in enterocytes. In addition, ACSL5 expression may be regulated by intestinal microbiota.

3.5. ACSL5 in adipose tissue

ACSL5 is mainly expressed in precursor adipose tissue and brown adipose tissue (BAT) and to a lesser extent in white adipose tissue (WAT) [20]. The differentiation of precursor adipocytes into mature adipocytes is accompanied by intracellular TG accumulation [51]. Oikawa et al. [14] found by northern blot that ACSL5 mRNA expression remained unchanged during the differentiation of 3T3-L1 mouse precursor adipocytes. In contrast, ACSL1 mRNA expression was consistently induced during differentiation. This result suggests that ACSL5 may not be involved in TG synthesis during differentiation of preadipocytes or that ACSL5 is not the major ACSL isoform involved in fatty acid metabolism in preadipocytes. However, Yu et al. [52] showed that ACSL5 overexpression induced TG synthesis in bovine preadipocytes, suggesting that ACSL5 in preadipocytes may direct fatty acids for lipid synthesis. Given the species specificity of ACSL5, the conflict in the results of the two studies may be attributed to species differences. Notably, the authors found that silencing of ACSL5 resulted in only a trend toward decreased cellular TG [52]. Possible explanations are compensatory effects of other ACSL isoforms or that ACSL5 is not the predominant ACSL isoform in bovine preadipocytes. Unfortunately, the authors did not examine the expression of each ACSL isoform in bovine preadipocytes.

WAT is an essential mammal tissue, mainly storing excess fatty acids as TG in cytosolic lipid droplets. Bowman et al. [16] observed a significant decrease in the mass of subcutaneous and gonadal adipose tissue (WAT) in Acsl5 knockout mice and an increase in the expression of fatty acid oxidation genes such as uncoupling protein-1 (UCP1) in WAT, along with increased hepatic and serum fibroblast growth factor 21 (FGF-21) levels, while serum free fatty acid levels were normal. Studies on FGF-21 transgenic mice have shown that the increase of FGF-21 levels is related to the increase of WAT lipolysis and the conversion of WAT to beige adipose tissue [53–55], which suggests that the decrease of WAT mass may be attributed to the increase of WAT lipolysis caused by the upregulation of FGF-21. Given the importance of ACSL5 for intestinal fatty acid absorption, increasing WAT lipolysis may make up for decreasing intestinal fatty acid absorption, resulting in normal serum-free fatty acid levels. These findings suggest that the inactivation of ACSL5 contributes to reduced WAT and increased WAT to beige adipose tissue conversion and may have clinicals implications for treating obesity.

BAT primarily functions in thermogenesis utilizing fatty acid oxidation in mitochondria. As the primary fuel for BAT thermogenesis, long-chain fatty acids mainly come from WAT lipolysis or CM hydrolysis in the circulation after a meal [56]. Indeed, there is also substantial de novo lipogenesis in BAT, and the expression of lipogenesis genes in BAT is regulated by ambient temperature [57]. Genes mediating both lipogenesis and fatty acid oxidation are upregulated when in cold conditions [56,57]. It is reported that Acsl5 is highly expressed in BAT and is the main ACSL isoform in mitochondria [58]. Way et al. [29] found that PPAR-γ agonists upregulated the expression of genes mediating lipogenesis and fatty acid oxidation in rat BAT, with an approximately 6-fold increase in ACSL5 mRNA. As glucose-lowering drugs to improve insulin resistance, PPAR-γ agonists have essential effects on glycolipid metabolism in BAT, such as promoting TG synthesis within BAT in rats [59].

Moreover, Forner et al. [58] isolated mitochondria from cold-stimulated mouse BAT and found that cold exposure caused a 3–5 folds increase in ACSL5 protein expression in BAT mitochondria. These findings suggest that ACSL5 may play an essential role in BAT fatty acid metabolism. In Acsl5$^{-/-}$ mice established by Bowman et al. [16], the authors found that modest elevation of type 2 deiodinase (Dio2) mRNA in mouse BAT of Acsl5$^{-/-}$ when compared with control mice. Adaptive thermogenic regulation of BAT is subject to the sympathetic nerve. Dio2 can activate thyroid hormone by converting the prohormone thyroxine (T4) to bioactive 3,3′, 5-triiodothyronine (T3). Although there is no change in the UCP1 transcription level in BAT of Acsl5−/− mice [16], the increased activity of D2 may accelerate T4 to T3 conversion, which leads to increased BAT responsiveness to epinephrine, allowing BAT to generate heat [60].

3.6. Role of other ACSL isoforms with similar functions to ACSL5 in adipocyte fatty acid metabolism

3.6.1. ACSL1

Ellis et al. [61] generated *Acsl1* adipose-specific knockout mice. These mice showed increased fat mass and unaffected TAG synthesis in adipocytes. Further, *Acsl1* knockout leads to impaired fatty acid oxidation in white adipocytes. These findings suggest that ACSL1 directs fatty acid for β-oxidation in adipose tissue of mice. Different from rodents, Joseph et al. [62] found that the mRNA and protein levels of ACSL1 continued to increase during the differentiation of human adipocytes, accompanied by an increase in intracellular TG content. In addition, knockdown of *ACSL1* in adipocytes resulted in a significant reduction in cellular TG content.

3.6.2. ACSL4

Unlike ACSL5, previous studies have shown that the substrate preference of ACSL4 is arachidonic acid (AA) and eicosapentanoic acid [63]. ACSL4 activates AA within cells and directs its incorporation into PL and TAG [64,65]. The adipocyte-specific *Acsl4* knockout mouse generated by Killion et al. [66] were protected against high fat diet-induced obesity. They found *Acsl4* knockout resulted in reduced fat weight and liver TAG accumulation. Furthermore, glucose tolerance test and insulin tolerance test showed that insulin sensitivity was improved in *Acsl4* adipocyte-specific knockout mice. Moreover, the authors found that *Acsl4* knockout reduced the production of the lipid peroxidation product 4-hydroxynonenal (4-HNE) in adipocytes, which can impair adipocyte metabolism. Taken together, these findings suggest that expression of ACSL4 contributes to obesity induced adipocyte dysfunction. Notably, in addition to ACSL4, high fat diet upregulated ACSL1/3/5 mRNA levels in mouse adipocytes. Interestingly, knockdown of *Acsl4* counteracted this effect (excluding ACSL1) [66]. This seems to imply that expression of ACSL3 and ACSL5 may also contribute to obesity associated adipocyte dysfunction, including insulin resistance. This is supported by the metabolic improvement effect of *Acsl5* whole-body knockout mice established by Bowman et al. [16].

3.7. ACSL5 in skeletal muscle

Skeletal muscle is one of the essential tissues that utilizes lipids. ACSLs activate free long-chain FAs entering skeletal muscle to produce long-chain fatty acyl-COAs as substrates for the synthesis of TG or β-oxidation. Current research shows that at rest, extracellular fatty acids are first incorporated into intramuscular triacylglycerol (mTG) before oxidation in mitochondria, and mTG derived fatty acids are the primary source of mitochondrial fatty acid oxidation [67,68]. However, plasma-free fatty acids may also enter mitochondria directly for β-oxidation during exercise [69].

Human ACSL5 rs2419621 (C > T) T allele carriers were reported to experience more rapid weight loss after controlled diet and lifestyle interventions compared with control individuals [70]. Adamo et al. [70] performed skeletal muscle biopsy on mutant homozygous individuals and found that the expression of ACSL5 mRNA increased by 2.2-fold. Further, Rajkumar et al. [26] found a 1.85-fold increase in ACSL5 short isoform protein levels in skeletal muscle from carriers of the T allele by Western-blot. Considering that ACSL5 predominantly localizes to mitochondria in human skeletal muscle cells, the researchers examined the levels of fatty acid oxidation in skeletal muscle from carriers of the T allele. *In-vitro* studies demonstrated a 1.46-fold increase in complete fatty acid oxidation level in skeletal muscle carriers of the T allele [26]. Consistent with this result, Kwak et al. [71] showed that overexpression of ACSL5 in human skeletal muscle cells significantly increased oxidation of ^{14}C palmitic acid. These results suggest that ACSL5 directs fatty acids for β-oxidation in human skeletal muscle.

Skeletal muscle lipid metabolism is regulated to some extent by diet and exercise. Stierwalt et al. [72] explored the effects of diet and exercise on ACSLs in mouse skeletal muscle and found that neither a high-fat diet nor exercise training affected ACSL5 protein levels in mouse gastrocnemius muscle. Consistent with these findings, ACSL5 mRNA is the lowest expressed ACSL isoform in rat skeletal muscle, and diet did not affect its expression [20].

4. Effects of ACSL5 on circulating lipids

To investigate the impact of ACSL5 on lipid metabolism, Acsl5 knockout mice were generated. Bowman et al. [16] obtained Acsl5 whole-body knockout mice (Acsl5−/−) by systematically mating Acsl5 loxP/loxP mice with transgenic mice expressing a CMV Cre. On chow diet, Acsl5−/− mice showed a significant ~50% decrease in fasting plasma TG compared to Acsl5 loxP/loxP mice (155.9 ± 18.5 vs 65.4 ± 3.9 mg/dl). The level of TG in plasma mainly derives from very-low-density lipoprotein (VLDL)-TG secreted by the liver and CM-TG secreted by the intestine. In circulation, TG in VLDL and CM can be hydrolyzed by lipoprotein lipase (LPL) into glycerol and free fatty acids, which can be taken up by oxygen-consuming tissues, liver, or adipose tissue. By injecting non-ionic surface activator Triton WR-1399 into mice to inhibit the activity of LPL, the clearance of VLDL and CM in plasma can be prevented. Mice were injected with Triton WR-1399 (500 mg/kg), followed by 200 ml olive oil gavage administration, and then TG content in plasma was analyzed. Compared with Acsl5 loxP/loxP mice, the accumulation of TG in the plasma of Acsl5−/− mice was significantly reduced, suggesting that ACSL5 is important for intestinal lipid absorption. However, in this experiment, the increase of TG in plasma corresponds to the content of VLDL-TG secreted by the liver and CM-TG absorbed by the intestine. Therefore, it is hard to say that the difference in plasma TG results from the difference in the amount of VLDL-TG secreted by the liver or CM-TG. Acsl5 whole-body knockout mice were also established by our group, and a similar phenotype was found [37]. We injected Triton WR-1399 (500 mg/kg) via the tail vein after starving the mice for 4 h and subsequently detected TG content in plasma, corresponding to the amount of secreted hepatic VLDL-TG [37]. We found that the secretion of VLDL-TG in the liver of Acsl5−/− mice decreased significantly when compared with wild-type mice [37], suggesting that ACSL5 may be involved in forming VLDL. We also found that ACSL5 interacts with transmembrane six

superfamily member 2 (TM6SF2) [73]. TM6SF2 is involved in the lipidation of VLDL, which also suggests that ACSL5 may be closely related to the metabolism of VLDL. The effects of ACSL5 on circulating lipids are summarized in Fig. 2. Plasma cholesterol and TG levels in Acsl5$^{-/-}$ mice established by Meller et al. [35] were not significantly different from wild-type. The reasons for the different lipid alterations observed in Acsl5$^{-/-}$ mice established by different groups remain unclear. One possible explanation is the difference in genetic background. *Acsl5*$^{-/-}$ mice derived from Bowman et al. [16] were of pure C57BL/6J background, whereas those generated by Meller et al. [35] were of mixed C57BL/6 × 129s background.

5. Relationship between ACSL5 and insulin resistance

Insulin resistance is the culprit in the pathogenesis of type 2 diabetes (T2D), which mainly occurs in the liver, adipose, and muscle tissues. The mechanism of insulin resistance is closely related to free fatty acids, ER stress, and mitochondrial dysfunction [74–76]. ACSL5 is an essential factor guiding lipogenesis or fatty acid oxidation, which also has profound effects on insulin resistance [15,16,71].

The liver regulates insulin sensitivity by regulating carbohydrate and lipid metabolism. Hepatic insulin resistance is manifested by the impaired ability of insulin to suppress endogenous glucose production and reduce hepatic glycogen synthesis along with increased lipid synthesis [74,77]. Studies in rodents have shown that Acsl5 knockdown in rat hepatocytes results in a significant decrease in intracellular TG synthesis [34]. Acsl5−/− mice showed reduced fasting glucose, increased insulin sensitivity, and a significant increase in hepatic and circulating FGF-21 [16]. These findings suggest that inhibition of Acsl5 improves insulin resistance in rodents. Studies in rats and primates have shown that FGF-21 improves glucose tolerance and increases insulin sensitivity [53,78,79]. In the liver, FGF-21 may improve insulin resistance by inhibiting lipogenesis and increasing hepatic fatty acid oxidation [80]. Therefore, the mechanism of inhibiting Acsl5 to improve insulin resistance may be associated with elevated FGF-21.

In addition, the effect of ACSL5 on insulin sensitivity may be related to hepatic ceramide production. Studies have shown that increased hepatic and adipose tissue C16 ceramide synthesis is closely associated with obesity and insulin resistance [81]. Ceramide impairs the insulin signalling pathway by inhibiting lipolysis, leading to decreased tissue glucose uptake and the development of insulin resistance [82,83]. Ceramide synthesis mainly includes palmitoyl CoA and serine involved in de novo synthesis and the sphingomyelin hydrolysis pathway. Therefore, reducing palmitoyl CoA, which is required for hepatic C16 ceramide synthesis, would be beneficial to mitigating the deleterious effects of ceramide and could be a means of treating obesity. Considering that ACSL5 serves as a raw material for fatty acyl-CoA synthesis, it is reasonable to speculate that inhibition of ACSL5 may lead to a decrease in ceramide synthesis and subsequently improve insulin resistance, which may be one of the mechanisms underlying the enhanced insulin sensitivity in Acsl5−/−mice established by Bowman et al. However, unexpectedly, Senkal et al. [84] found that knockdown of *ACSL1/5* in HCT116 cell lines resulted in ceramide accumulation via the de novo pathway of ceramide synthase. Conversely, *ACSL5* overexpression exhibited lower levels of ceramide. Further, *in vivo* experiments revealed that ceramide is converted to acylceramide in liver lipid droplets by the ACSL5-ceramide synthase complex under pathological conditions of fatty liver. The authors suggested that the interaction of ACSL5 and ceramide synthase in liver lipid droplets may be beneficial due to its removal of ceramide from the cell membrane, thereby exerting metabolic benefits such as improved insulin resistance [84]. This seems to suggest that in conditions of metabolic syndrome such as fatty liver, inhibition of ACSL5 in hepatocytes would impair its metabolic benefits. Therefore, the effects of liver-specific *Acsl5* knockout or overexpression on insulin sensitivity under physiological and pathological conditions such as fatty liver warrant further study.

Conventional wisdom held that increased TG content in skeletal muscle is associated with obesity and insulin resistance while increasing the levels of FA oxidation in skeletal muscle would be beneficial for increasing insulin sensitivity [85,86]. Because ACSL5 predominantly increases fatty acid oxidative in human skeletal muscle [26,71], ACSL5 expression appears to contribute to improving skeletal muscle insulin resistance. However, Kwak et al. [71] overexpression of ACSL5 in human skeletal muscle cells increased mitochondrial superoxide production and manganese superoxide dismutase (MnSOD) protein expression, suggesting that ACSL5 overexpression in human skeletal muscle increases mitochondrial oxidative stress. In addition, the authors found significantly reduced protein levels of AKT and AKT substrate of 160 kDa (AS160) in human skeletal myotubes overexpressing ACSL5 [71]. These findings demonstrate that ACSL5 overexpression in human skeletal muscle impairs insulin signaling. Interestingly, although increasing ACSL5 expression in human skeletal muscle contributes to reducing weight and body fat content [69,70,87], it also leads to developing skeletal muscle insulin resistance.

Studies have shown that the T allele of rs7903146 in TCF7L2 is strongly associated with the pathogenesis of T2D [15]. The authors generated a base deletion in this region by gene editing in HCT116 cells and found that ACSL5 expression was significantly reduced. This suggests that ACSL5 expression might be involved in the pathogenesis of T2D and further speculates that inhibition of ACSL5 may be beneficial for improving insulin resistance.

6. Conclusions

ACSL5 plays a vital role in lipid metabolism by producing long-chain fatty acids for lipogenesis and β-oxidation. The fate of long-chain fatty acids is linked to the distribution and localization of ACSL5 and its isoforms. ACSL5 may predominantly channel fatty acids for lipogenesis in small intestine and liver in murine models; however, in human skeletal muscle it is employed for β-oxidation of fatty acids. Detailed understanding of the subcellular distribution and localization patterns of ACSL5 and its isoforms in different species and tissues may help shed more light in its function. Knockout of Acsl5 results in decreased circulating TG levels without causing hepatic TG deposition in mice suggesting that ACSL5 may serve as a potential novel target for lipid-lowering. However, the differential effects

of ACSL5 on fatty acid metabolism *in-vitro* and in pre-clinical models suggest that future studies should focus more on the role and mechanism of ACSL5 in hepatic lipid metabolism and circulating lipids in humans. In addition, inhibition of ACSL5 was associated with improved insulin resistance, suggesting that ACSL5 may serve as a therapeutic target for metabolic disease.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no competing interests.

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