Biochimica et Biophysica Acta 1821 (2012) 852–857

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

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

Review

Fatty acid transport proteins, implications in physiology and disease ☆

Melissa Kazantzis, Andreas Stahl *

Metabolic Biology, NST, UC Berkeley, Berkeley, CA 94720, USA

ARTICLE INFO

Article history:
Received 18 July 2011
Received in revised form 19 September 2011
Accepted 19 September 2011
Available online 25 September 2011

Keywords:
Fatty acid uptake protein
SLC27
Diabetes
Lipotoxicity
Hepatosteatosis
Ichthyosis

ABSTRACT

Uptake of long-chain fatty acids plays pivotal roles in metabolic homeostasis and human physiology. Uptake rates must be controlled in an organ-specific fashion to balance storage with metabolic needs during transitions between fasted and fed states. Many obesity-associated diseases, such as insulin resistance in skeletal muscle, cardiac lipotoxicity, and hepatic steatosis, are thought to be driven by the overflow of fatty acids from adipose stores and the subsequent ectopic accumulation of lipids resulting in apoptosis, ER stress, and inactivation of the insulin receptor signaling cascade. Thus, it is of critical importance to understand the components that regulate the flux of fatty acid between the different organ systems. Cellular uptake of fatty acids by key metabolic organs, including the intestine, adipose tissue, muscle, heart, and liver, has been shown to be protein mediated and various unique combinations of fatty acid transport proteins (FATPs/SLC27A1–6) are expressed by all of these tissues. Here we review our current understanding of how FATPs can contribute to normal physiology and how FATP mutations as well as hypo- and hypermorphic changes contribute to disorders ranging from cardiac lipotoxicity to hepatosteatosis and ichthyosis. Ultimately, our increasing knowledge of FATP biology has the potential to lead to the development of new diagnostic tools and treatment options for some of the most pervasive chronic human disorders. This article is part of a Special Issue entitled Triglyceride Metabolism and Disease.

1. Physiological fatty acids fluxes

Long-chain fatty acids (LCFA) comprise one of the main energy sources of the human body. They are also required for the synthesis of structural lipids such as phospholipids and sphingolipids and the covalent modification of proteins. Further, LCFAs can regulate immune responses by altering the synthesis of eicosanoids and by activating Toll-like receptors [1]. Following cellular uptake and metabolic activation, LCFA-CoAs can alter signal transduction cascades, via PKC isoforms and Ca^{2+} release [2,3], regulate important metabolic enzymes such as acetyl-CoA carboxylase and glucokinase [4,5], and ATP-sensitive K+ channels, including those linked to insulin release by pancreatic β-cells [6]. Finally, LCFAs and their acyl-CoA derivatives can bind to several transcription factors—PPARs, SREBP, ChREBP, LXR, HNF-4α and NF-κβ—and regulate the expression of numerous downstream genes [7–11].

Following release from adipocytes or lipolysis of TAG in circulating lipoproteins, LCFA are tightly bound to albumin. Though locally generated LCFA may diffuse across the plasma membrane following their concentration gradient, such passive uptake is thought to be too inefficient in the presence of physiological albumin levels to address most tissue's LCFA needs as physiological concentrations of unbound fatty acids only range around 7.5 nM [12].

Further, evidence from different tissue types has accumulated indicating the existence of protein-mediated, saturable uptake LCFA pathways, thought to contribute to the majority (~90%) of cellular LCFA acquisition [13]. Several protein groups have been implicated in cellular LCFA uptake including plasma membrane fatty acid-binding protein (FABPpm) [14,15], the scavenger receptor CD36 (fatty acid translocase) [16] and the six fatty acid transport proteins (FATP), also called solute carrier family 27A1–6 [17], which are the focus of this review.

2. Meet the family

2.1. Slc27 members

Seventeen years ago, the first member of the FATP family, FATP1, was discovered using an expression cloning strategy aimed at identifying proteins that increased the uptake of a fluorescent LCFA analog [18].

Five other FATP genes (FATP2–6) were subsequently identified in mammalian genomes based on the presence of a highly conserved 311 amino acids signature motif. Orthologs are also found in *S. cerevisiae*, *D. melanogaster* and *C. elegans*, in addition to a homologous protein with conserved LCFA transport function found in mycobacteria [19]. To indicate both species and FATP ortholog, the preferred nomenclature

☆ This article is part of a Special Issue entitled Triglyceride Metabolism and Disease.

* Corresponding author at: Dept. of Nutritional Sciences & Toxicology, 119 Morgan Hall, #3104, University of California Berkeley, Berkeley, CA 94720-3104, USA. Tel.: +1 510 642 6900; fax: +1 510 642 0535.
E-mail address: astahl@berkeley.edu (A. Stahl).

1388-1981/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbalip.2011.09.010

for FATPs comprises a two-letter prefix to designate the species (mm—*Mus musculus*; hs—*Homo sapiens*; dm—*D. melanogaster;* ce—*C. elegans*; sc—*S. cerevisiae*; mt—*Mycobacterium tuberculosis*) and a numbered suffix to indicate the isoform/family member. For example, human fatty acid transport protein member one is hsFATP1.

Cross species conservation of amino acid sequences in mammals is high with mmFATP4 and hsFATP4 exhibiting 92.2% identity [20]. Between orthologs, FATP1 and 4 show the highest (60.3%) identity [20].

FATP tissue distribution varies considerably: FATP1 is expressed in white adipose tissue (WAT), brown adipose tissue (BAT), skeletal muscle (SM) [21,22], heart and to a lesser extent in pancreas, lung, kidney and brain; FATP2 is highly expressed in kidney and liver [23]; FATP3 is found in the lung, liver, pancreas and has recently been identified in the endothelial cells of capillaries in several organs; FATP4 is broadly distributed, including heart, liver, brain, kidney, muscle, heart, skin, endothelial cells and is the predominant LCFA transporter in the small intestine [24]; FATP5 is a liver-specific protein [25], while FATP6 is found exclusively in the heart [26].

2.2. Transport mechanism/subcellular localization

The study of hypo- and hypermorphic models *in vivo* and *in vitro* have implicated FATP's in the cellular uptake of exogenous LCFA [18,21–23,27–29]. For example, stable transfection of 293 cells with FATP1 increased LCFA uptake three- to fourfold. Transient transfection of COS cells with mouse FATP1, 2 or 5, all showed increased uptake of the fluorescent 4,4-difluoro-5-methyl-4-bora-3a,4a-diaza-s-indacene-3-dodecanoic acid-labelled saturated LCFA analogue (C_1-BODIPY-C_{12}) and stable overexpression of FATP4 in 293 cells increased LCFA uptake. FATP4 is highly expressed in the small intestine and treatment of primary enterocytes with antisense FATP4 oligonucleotides inhibited [^{3}H]-oleate uptake [24] while knockout or knockdown of the liver-specific FATP5 reduced LCFA uptake in primary hepatocytes by 50% compared to control cells [25,27].

FATP structure and uptake mechanisms may be informed by the analysis of the amino acid sequence and conserved functional motives found in them. These include a 100 amino acid AMP-binding segment present at the beginning of the 300-amino acid-long FATP signature sequence (common to members of the adenylate-forming super family of enzymes that include long-chain acyl-CoA synthetases and luciferase), as well as a lipocalin motive [30] that is found in several transporters of hydrophobic proteins [31], including cytosolic fatty acid-binding proteins [32]. Based on the amino acid sequence, the presumed molecular structure of the mammalian prototypic FATP is a transmembrane molecule that crosses the plasma membrane once, with a shorter extracellular N-terminal segment and a longer cytosolic C-terminal segment containing the AMP-binding domain [33]. Thus, FATPs differ significantly from transporters of hydrophilic molecules, such as the facilitative glucose transporters of the GLUT family, which cross the plasma membrane multiple times to form a channel. Instead, it is more plausible that FATPs facilitate the transfer of hydrophobic LCFAs by forming homo- or heterodimers/oligomers [17]. Evidence for this hypothesis comes from the finding that when non-functional FATP1 mutants are co-expressed with wild-type FATP1, dominant negative inhibition of transport is seen, suggesting that dimer/oligomerization might indeed be a requirement for function [34].

In an alternative model, FATPs facilitate uptake by promptly activating incoming LCFA to their CoA-thioester and trapping them inside the cell. FATPs show 20–40% sequence identity with the long-chain acyl-CoA synthetase 1 (ACSL1) and some do display long-, very long-, or bile acid- CoA synthetase activity. LCFA-CoA synthetase activity is increased in lysates from FATP overexpressing cells and in partially purified FATP1 precipitates. Membrane extracts from COS1 cells transfected with mouse FATP4 showed elevated acyl-CoA synthetase principally towards very long-chain fatty acids (VLCFA), but also including LCFA [20]. Further, FATP5 can convert cholic acid into its CoA derivative [35,36].

Following the finding that FATP1 and ACSL1 co-immunoprecipitate in adipocytes, Richards et al. [37] showed that FATPs associate with ACSL and hypothesized that FATPs facilitates uptake while ACSL mediates the activation and trapping of the incoming LCFA by means of vectorial acylation.

Thus, while the importance of FATPs for cellular uptake is undisputed, no consensus has been reached thus far whether FATPs are bona fide transporters, enzymes with fatty and bile acid CoA synthetase activity, or dual-function proteins. To this end, one informative investigation was conducted with alanine substitutions in the yeast FATP ortholog (fat1) [38]. While some FATP mutants, particularly with substitutions within the AMP-binding motif, showed depressed fatty acid import and acyl-CoA activities, other subsets of mutants showed preferential declines in either lignoceryl-CoA synthetase or lignoceric acid transport activity indicating that the two functions can be separated and may operate independently from each other [38]. Further insight into sequences required for LCFA uptake and activation came from experiments with chimeras of mammalian FATP1 and 4 or FATP6 and 4, with preserved AMP-binding and FATP motifs, which were analyzed in terms of their ability to rescue fatty acid transport, activation, and growth of a yeast strain containing deletions of endogenous FATP (*FAT1) and ACSL (FAA1)* genes [39]. All chimeras tested were competent in arachidonate (C20:4) and lignocerate (C24:0) activation. The chimeras of the FATP1-FATP4 were proficient in fully complementing the functions of *FAT1* and *FAA1* including LCFA uptake and growth on fatty acid substrates. Interestingly, while the FATP6–FATP4 chimera I, containing the first 219 residues of FATP6 and the last 400 residues of FATP4, was competent in restoring the fatty acid transport defect and growth in plates containing oleate and cerulenin, the FATP6-FATP4 chimera II, containing the first 473 residues of FATP6 (including its ATP/AMP-binding motif and the segment upstream of FATP/VLACS) and the last 143 residues of FATP4 (containing the FATP/VLACS itself), was not. The C_1-BODIPY-C_{12} uptake tests with the chimeras detected functional transport activity in all chimeras but the FATP6-FATP4 chimera II. In conclusion, a 71–73 amino acid residue segment (residues 406–479 in FATP1), present in both FATP1 and FATP4, but not in FATP6 was hypothesized to be critical for adequate uptake activity and thus, the capacity to complement the functions of the yeast *FAT1* and *FAA1*proteins [39].

Varying claims have been made regarding the subcellular localization pattern of the various FATP orthologs. Potentially most interesting, FATP 1 has been shown to be present in dynamic pools that vary their localization in a hormone-inducible fashion. In unstimulated SM and WAT a minor fraction of the FATP1 pool resides in the plasma membrane and is mostly present as a perinuclear pool that translocates to the membrane in response to insulin, concomitant with increased LCFA influx [21]. In the same tissue the FATP4 pool is constitutively allocated to the plasma membrane and does not exhibit translocation suggesting that the two FATPs may play complementary roles where co-expressed, with FATP4 mediating constitutive LCFA uptake and FATP1 mediating the hormone-sensitive component [21]. FATP 2 is predominantly a plasma membrane transporter but a minor fraction also localizes to liver peroxisomes (Fig. 1) where it is responsible for half of the organelle's VLCFA-acyl-CoA synthetase activity [23]. FATP3 was suggested to be absent from the plasma membrane and to localize to mitochondria [40]. FATP 4 is found on the plasma membrane. In enterocytes, it is especially enriched at the apical surface of the duodenal brush-border [24]. It was also reported to be found in the endoplasmic reticulum (ER) [41]. Using immune-labeling FATP5 was predominantly localized to the basal microvilli of hepatocytes [27] but an ER localization was also proposed based on its involvement in bile acid metabolism [42] (Fig. 1).

In the heart FATP6 localizes almost exclusively to sarcolemma regions directly adjacent to small blood vessels [26].

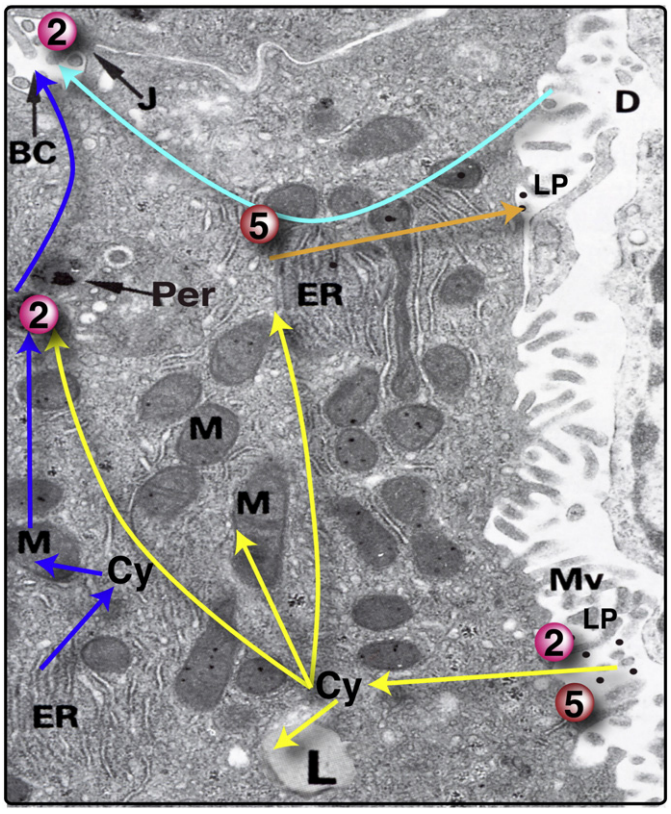

Fig. 1. Hepatic FATP2 and FATP5 are dual-function proteins. A) Hepatic FATP2 and -5 (red circles) mediate liver fatty acid uptake and activation (yellow arrows). FATP2/5 located on microvilli (Mv) in the Space of Disse (D) mediate the uptake of fatty acids. Cytoplasmic (Cy) fatty acids are directed toward TG synthesis and storage in lipid droplets (L), toward mitochondria (M) for β-oxidation, toward TG synthesis and LP assembly in the endoplasmic reticulum (ER) followed by LP secretion (orange arrow), or in the case of branched and very-long chain fatty acids toward peroxisomes (Per) potentially involving FATP2. Hepatic FATPs are also involved in bile acid synthesis (blue arrows), which is initiated in the ER, progresses through the Cy to M and Per where the bile acid precursor are activated by bile acid CoA synthetases, an activity associated with both FATP2 and -5. Bile acids are then secreted into bile canaliculi (BC). Deconjugated bile acids from the enterohepatic circulation are re-activated in the ER requiring the BACS activity of FATP5. FATP2 is also found on the microvili of the bile canaliculi, bile duct cells as well as the gallbladder.

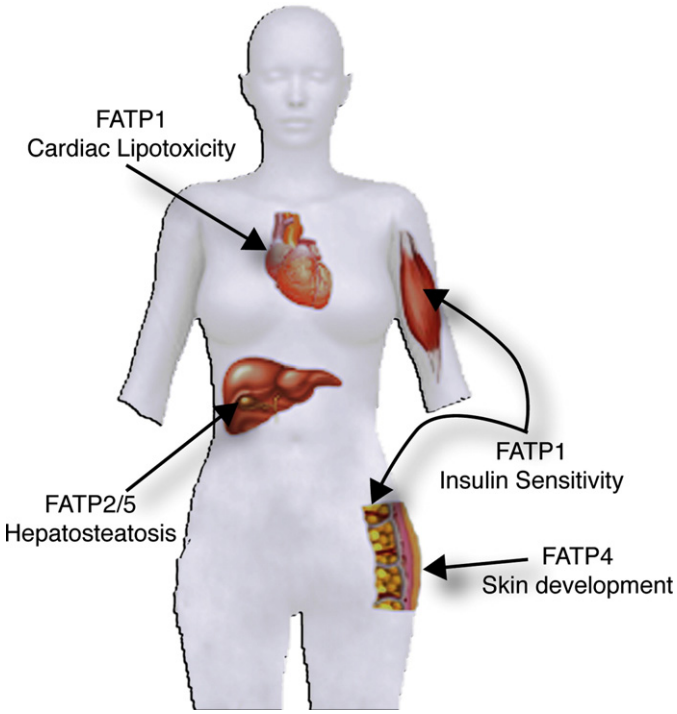

Fig. 2. FATP's role in disease based on gain and loss of function animal models and human studies. 1. Heart FATP1-TG causes lipotoxicity and affects diastolic function. 2. FATP1KO is protective against high-fat diet-induced insulin resistance by decreasing white adipose and muscle fat content. 3. Hepatic steatosis can be reversed by AAV-mediated FATP5 or FATP2 knockdown. 4. FATP4 loss alters fatty acid composition and disturbs the skin barrier function.

3. Contribution of FATPs to insulin resistance and energy expenditure

3.1. Deletion of FATP1 protects from high-fat induced insulin resistance

The study of the FATP1 null mice has been informative in elucidating the protein's role in lipid homeostasis, specifically in terms of organ lipid partitioning, hormonal regulation and cellular metabolism. Under a regular diet regimen FATP1KO animals display normal body composition and serum parameters such as insulin, fatty acids and TAG [21] but are resistant to diet-induced obesity and insulin resistance [21] as well as SM insulin desensitization following a lipid bolus injection [43]. While basal LCFA uptake of FATP1KO animals is unchanged, they fail to respond to insulin with an increase in fatty acid uptake rates that is normally observed in the fed state [21]. As a consequence, post-prandial serum LCFA are redistributed away from the SM and WAT (Fig. 2) and towards the liver, where β-oxidation rises, improving metabolic rates [21] which, in conjunction with the decreased WAT and SM lipid content (Fig. 2), has been suggested to underlie the protection from diet-induced insulin resistance [21].

3.2. FATP1 and thermogenesis

FATP1 is also expressed by BAT where it was shown to be required for cold adaptation [22]. In FATP1 null animals uptake of WAT-derived circulating LCFA was diminished resulting in smaller intracellular lipid depots. As a result of this insufficient cellular LCFA supply, FATP1KO are incapable of efficiently fueling non-shivering thermogenesis resulting in cold sensitivity [22]. In the brown adipocyte cell line HIB-1B, the expression of FATP1 parallels that of uncoupling protein 1 (UCP1). Both are poorly expressed in the pre-differentiated state and rise substantially upon differentiation. FATP1 expression increases sharply in response to isoproterenol in parallel with a rise in LCFA influx reminiscent of the effect of insulin in WAT. The isoproterenol effect was absent in RNAi-based silenced FATP1 HIB-1B clones, further confirming the requirement of FATP1 for the clearance of exogenous LCFA, especially under conditions of endocrine stimulation [22].

The reduction in non-shivering thermogenesis, and thus energy expenditure, in FATP1KO animals seems to be in apparent conflict with the observed resistance to diet-induced obesity. However, mice housed at 21 °C are not at thermoneutrality and it is possible that, similar to the UCP-1KO [44], FATP1KO mice develop compensating BAT-independent heat generating mechanisms, such as shivering, that result in unchanged metabolic rates thus masking an obesity trend.

As it was recently shown that in cold-stimulated mice BAT can account for the clearance of most post-prandial lipids and glucose [45], the impact of FATP in systemic lipemia and trygliceridemia is potentially substantial. Thus, the pattern of FATP1 subcellular localization and regulation under cold-stimulation and other conditions (thermoneutrality, fasting, and re-feeding) deserves continued investigation.

4. FATP contribution to cardiovascular disease

4.1. Cardiac lipotoxicity

The analysis of two independent heart-specific FATP1 transgenic mouse (hFATP-TG) strains [46] has shown that cardiac FATP1 levels do tightly correlate with LCFA uptake similarly to WAT, BAT and SM. These mouse lines were primarily created to address the deleterious

effects of cardiac lipid accumulation, a severe complication in diabetes, but without being confounded by additional diabetes-associated systemic alterations such as hyperinsulinemia. A four-fold increase in LCFA uptake was observed in the hFATP-TG mice and pathological analysis revealed enlargement of hearts, impaired left ventricular filling and biatrial enlargement, characteristic of diastolic dysfunction [46]. Diastolic dysfunction is frequently observed early in diabetic cardiomyopathy. Further, the electrical properties of the heart were also altered. Ambulatory electrocardiogram (ECG) monitoring detected QT prolongation, consistent with reductions observed in repolarizing, voltage-gated K^+ currents [46]. Type 1 and type 2 diabetes patients exhibit QT prolongation, which is a predictor of mortality. Though in diabetes such complications have been generically attributed to systemic metabolic perturbations, the contributions of the hyperglycemia versus the hyperlipidemia were not addressed. Thus, these findings from the hFATP-TG study support the causal role of the FATP1-dependent hyperlipidemia ("per se") in establishing diastolic dysfunction.

4.2. FATPs in endothelial cell biology

In tissues such as liver, circulating LCFA have direct access to the parenchymal cells, as the capillaries perfusing the organ contain large fenestrae allowing the passage of molecules as large as lipoproteins. However, in tissues like the adipose, the muscle and the heart, the endothelial cells are tightly bound by tight-junctions preventing the direct uptake of LCFA [47]. Thus, in most organs circulating LCFA must cross the capillary endothelial cells in order to be available to the tissue. It has been postulated that LCFA reach cardiomyocytes by crossing endothelial cells in clathrin-coated vesicles, via a pinocytotic mechanism, and subsequent release at the subendothelial capillary side to reach the interstitium [47]. There, they are re-bound to albumin and made available for uptake by fatty acid transporters on the surface of the cardiomyocytes.

Recently, FATP3 and FATP4 have been shown to be critical for the uptake of LCFA by endothelial cells. FATP3 mRNA has been detected in the endothelial fraction of heart and BAT and FATP4 mRNA has been detected in the endothelial fraction of heart, muscle and BAT [48]. Further, endothelial FATP expression may be dynamically regulated as under the stimulus of exercise or cold exposure, rising peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) levels were shown to upregulate VEGF-B expression, which in turn stimulates the expression of endothelial FATPs to increase vascular LCFA uptake and transport across the endothelial-cell layer [49]. Conversely, silencing of either FATP3 or FATP4 abolished the VEGF-B effect and VEGF-B null mice displayed increased weight and WAT fat content as their reduced FA uptake and utilization in the heart, muscle and BAT results in incremental shunting of the unconsumed FA to WAT [48].

The role of FATPs in endothelial LCFA uptake was further demonstrated in FATP3 and FATP4 overexpressing endothelial cells, where C_1-BODIPY-C_{12} uptake was shown to increase. Co-overexpression resulted in a more then additive increment in uptake, suggestive of both independent and synergystic uptake activities mediated by FATP3 and −4 [48].

Another study showed FATP1 and FATP4 are the predominant LCFA transporters in human brain microvessel endothelial cells (HBMEC) and reduction in oleate and linoleic acid transport across HBMEC monolayers is detected following loss of FATP expression [50].

5. Role of FATP4 in skin disorders

Generation of FATP4KO animals by us showed that homozygote loss of FATP4 results in embryonic lethality, potentially based on a role of the transporter in early embryonic nutrient uptake [28]. FATP4 is found in the epithelial cells of the extraembryonic endoderm, which supplies nutrients to the embryo before the chorioallantoic placenta develops [28].

Generation of an independent FATP4KO mouse strain [51] showed that, while the heterozygous mice had no apparent phenotype, the −/− newborns died just minutes after birth. They displayed severe skin alterations including tight, thick skin with no wrinkles, and a flat epidermal-dermal lining. Subsequently, they had difficulty to move and their lungs did not ventilate properly, creating respiratory distress for the mice. The increased pressure resulted in the herniation of the intestines outside the abdomen and the lack of functional skin barrier caused dehydration [51]. Further, keratinocyte-specific re-expression of FATP4 in this knockout background, via cross with involucrin promoter FATP4 transgenics, resulted in a rescue of the wrinkle-free phenotype [52].

To determine the specific contribution of epidermal FATP4 to the severe phenotype observed in the whole body knockout, the Stremmel group created a keratinocyte-specific FATP4 deficient mice [53]. This inducible conditional FATP4-deficient strain did not suffer from macroscopic alterations but displayed microscopic structural epidermal changes and disrupted skin barrier function, but no flattening of the epidermal-dermal junction or reduced number of pilo-sebaceous glands or condensed dermis [53]. The attenuated phenotype in the mice with post-developmental loss of FATP4 relative to the strain lacking FATP4 during embryogenesis, is reflective of the protein's broader tissue presence in the embryo versus the adult skin, where FATP4 is restricted to the sebaceous glands [54].

In humans, several different mutations affecting FATP4 have been described in patients with Ichthyosis prematurity syndrome (IPS). Homozygote mutations resulted in premature birth, difficulty with breathing and skin thickening (Fig. 2). In these patients skin lipids, instead of being evenly distributed along the multiple skin layers, accumulated in the stratum granulosum suggesting that the loss of FATP4 might have affected lipid distribution and homeostasis in the skin [55,56].

6. The role of FATP2 and -5 in hepatobiliary disorders

6.1. Hepatic FATPs contribute to fatty liver disease

The liver-specific FATP5 is found on microvilli in the Space of Disse in accordance with its proposed role in the uptake of LCFAs from the circulation (Fig. 1). Indeed, hepatocytes isolated from FATP5KO were demonstrated to have a 40–50% reduction in LCFA uptake capacity. As a result, hepatic fat content is decreased in FATP5KO animals particularly in the context of a high-fat diet [27]. Further, tracking the lipid distribution from ^{14}C-labeled oleate gavages revealed an altered pattern of fatty acid partitioning away from the liver and towards skeletal muscle and heart.

When the protein is knocked-down by AAV-mediated shRNA expression in WT animals fed a high-fat diet regimen, the established hepatic steatosis and hyperglycemia are ameliorated [25], highlighting the role of continued uptake of dietary lipids in the etiology of obesity-associated hepatosteatosis.

The role of FATP2 in hepatic fatty acid transport and hepatosteatosis has recently been addressed using liver-specific AAV-mediated RNA knockdown [23]. In this study, FATP2-AAV treatment of mice with diet-induced hepatosteatosis proved beneficial by lowering total hepatic TAG levels, improving liver morphology, and decreasing the number and size of intracellular fat depots. The hepatoprotective effect of loss of FATP2 function also translated into improved insulin sensitivity and glucose homeostasis [23]. Though a slight increase in skeletal and cardiac muscle lipid content was detected, FATP2-AAV-treated group had smaller fat pads and a marginal improvement in body weight [23]. Overall, while AAV-based gene therapy approaches for the treatment of hepatosteatosis seem unlikely, these current studies demonstrate a contribution of FATP2 and -5 to the etiology of hepatic steatosis and highlight potential novel treatment options.

6.2. Contribution of FATPs to bile acid homeostasis

Based on *in vitro* studies several functions for hepatic FATPs have been suggested in the bile acid biosynthesis pathway [29]. Specifically,

FATP5 as well as FATP2, had been suggested to work as a 3α, 7α, 12α-trihydroxy-5β-cholestanoic acid (TCHA) CoA ligase and mediate the activation of bile acid precursors required for the peroxisomal side-chain shortening [29] (Fig. 1). Analysis of the total bile pool in FATP5KO animals revealed no biosynthetic block in bile acid generation or cholesterol catabolism [29] indicating that FATP5 is either redundant or not involved in this pathway *in vivo*. However, qualitative liquid chromatography/mass spectroscopy analysis of FATP5KO bile acid composition revealed a significant increase in unconjugated bile acids [29], in line with a proposed function of FATP5 as a bile acid CoA ligase [29], an enzyme required for the reconjugation of deconjugated bile acids entering the liver from the enterohepatic circulation. Thus far no studies have been reported to directly address the contribution of FATP2 and -5 to biliary disorders.

7. Polymorphisms and mutations in human FATP genes

Several polymorphisms and mutations in FATP genes have been reported, highlighting the importance of these proteins for human health.

A screen of 838 individuals living in northern France for single-strand conformation polymorphism (SSCP) in the FATP1 gene revealed an A/G substitution in intron 8. The 0.60 and 0.40 frequencies for the G and A alleles, respectively were distributed in Hardy-Weinberg equilibrium [57]. This FATP1 polymorphism had a detectable impact on lipid metabolism as increased plasma TAG levels were found in the rare A/A genotype compared to G/G and G/A (particularly in women) after the groups were controlled for age and smoking, and individuals treated for metabolic diseases were excluded [57].

Further support of the association between the rare FATP1 A/A intronic allele presence and increased plasma TAG came from an independent study with a randomly selected cohort of 628 50-year old Swedish men. In this study, the A/G allele incidence in males was identical to the preceding study [58]. When analysis of the lipoprotein fractions contributing to the increased post-prandial triglyceridemia (detected during an oral-fat tolerance test—OFTT) in the A/A homozygous was carried out, increased Sf 60–400 ApoB100 to Sf 20–60 ApoB100 ratio, were detected in the A/A group 3 hours after food intake [58]. Low-density lipoprotein (LDL) particle size distribution along the genotypes was found to be A/A<G/A<G/G. Additionally, a non-significant trend towards increased post-prandial plasma chylomicrons and their remnants was as well observed in A/A individuals [58].

While initial plasma NEFA levels during OFTTs showed no differences, at later time points G/G and G/A NEFA levels dropped consistently while the A/A numbers remained higher suggesting impaired NEFA clearance from the circulation [58], which is reminiscent of the prolonged post-prandial NEFA clearance in FATP1KO animals [21].

Another screen with a cohort of 608 Swedish countrymen (50 year old males) focused on polymorphisms in the FATP4 gene [59]. A G/A polymorphism in a coding region resulting in a Gly-to-Ser mutation at position 209 (exon 3) was detected and analyzed in terms of the potential molecular alterations and binding characteristics of the FATP4 mutant and the impact to metabolic parameters, with focus on lipid metabolism and insulin resistance markers. The substitution is suggested to be located in a hydrophobic segment proposed to be exposed on the FATP4 surface and to interact with other protein partners to form heterodimeric functional units. Ser/Ser individuals were very rare, but the Gly/Ser, compared to the Gly/Gly group presented a cluster of improved systemic parameters: decreased BMI, SBP, TAG, VLDL-TAG, insulin and homeostatic model assessment (HOMA) index of insulin resistance [59].

Polymorphisms have also been detected in the FATP5 gene. A group of 716 male subjects was analyzed for a potential relationship among a FATP5 polymorphism and liver disease susceptibility [60]. A G-to-A substitution, detected in the gene promoter and the rare A allele was shown to associate with a cluster of worsened metabolic parameters: higher post-prandial TAG and insulin, lowered insulin sensitivity index and elevated ALT. A subset of individuals with histologically diagnosed nonalcoholic fatty liver disease were also susceptible to increased ALT activity when bearing the A allele, further confirming the association among liver disease and dyslipidemia with the FATP5 function [60].

8. Conclusion

Since the discovery of the FATP family of LCFA transporters the field has made significant progress in our understanding of how these proteins contribute to the development of a wide array of disorders ranging from cardiac lipotoxicity to hepatosteatosis, and ichthyosis (Fig. 2). Studies both in hyper- and hypomorphic animal model systems have lend credence to the idea that targeting FATP function in the context of overnutrition could have beneficial effects and should justify efforts for the development of pharmacological FATP inhibitors.

References

[1] A. Schaffler, J. Scholmerich, Innate immunity and adipose tissue biology, Trends Immunol. 31 (2010) 228–235.
[2] D.J. Beech, Y.M. Bahnasi, A.M. Dedman, E. Al-Shawaf, TRPC channel lipid specificity and mechanisms of lipid regulation, Cell Calcium 45 (2009) 583–588.
[3] D.B. van Rossum, R.L. Patterson, PKC and PLA2: probing the complexities of the calcium network, Cell Calcium 45 (2009) 535–545.
[4] A.B. Kohan, Y. Qing, H.A. Cyphert, P. Tso, L.M. Salati, Chylomicron remnants and nonesterified fatty acids differ in their ability to inhibit genes involved in lipogenesis in rats, J. Nutr. 141 (2011) 171–176.
[5] M. Fantino, Role of lipids in the control of food intake, Curr. Opin. Clin. Nutr. Metab. Care 14 (2011) 138–144.
[6] L. Best, E. Jarman, P.D. Brown, A dual action of saturated fatty acids on electrical activity in rat pancreatic beta-cells. Role of volume-regulated anion channel and KATP channel currents, J. Physiol. 589 (2011) 1307–1316.
[7] D.B. Jump, Fatty acid regulation of hepatic lipid metabolism, Curr. Opin. Clin. Nutr. Metab. Care 14 (2011) 115–120.
[8] P.A. Grimaldi, Metabolic and nonmetabolic regulatory functions of peroxisome proliferator-activated receptor beta, Curr. Opin. Lipidol. 21 (2010) 186–191.
[9] T. Vallim, A.M. Salter, Regulation of hepatic gene expression by saturated fatty acids, Prostaglandins Leukot. Essent. Fatty Acids 82 (2010) 211–218.
[10] M. Guan, L. Qu, W. Tan, L. Chen, C.W. Wong, Hepatocyte nuclear factor-4 alpha regulates liver triglyceride metabolism in part through secreted phospholipase A(2) GXIIB, Hepatology 53 (2011) 458–466.
[11] A. Kennedy, K. Martinez, C.C. Chuang, K. LaPoint, M. McIntosh, Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications, J. Nutr. 139 (2009) 1–4.
[12] G.V. Richieri, R.T. Ogata, A.M. Kleinfeld, Thermodynamics of fatty acid binding to fatty acid-binding proteins and fatty acid partition between water and membranes measured using the fluorescent probe ADIFAB, J. Biol. Chem. 270 (1995) 15076–15084.
[13] A. Stahl, J.G. Evans, S. Pattel, D. Hirsch, H.F. Lodish, Insulin causes fatty acid transport protein translocation and enhanced fatty acid uptake in adipocytes, Dev. Cell 2 (2002) 477–488.
[14] J.F. Glatz, J.J. Luiken, M. van Bilsen, G.J. van der Vusse, Cellular lipid binding proteins as facilitators and regulators of lipid metabolism, Mol. Cell. Biochem. 239 (2002) 3–7.
[15] H. Huang, O. Starodub, A. McIntosh, A.B. Kier, F. Schroeder, Liver fatty acid-binding protein targets fatty acids to the nucleus. Real time confocal and multiphoton fluorescence imaging in living cells, J. Biol. Chem. 277 (2002) 29139–29151.
[16] C.T. Coburn, T. Hajri, A. Ibrahimi, N.A. Abumrad, Role of CD36 in membrane transport and utilization of long-chain fatty acids by different tissues, J. Mol. Neurosci. 16 (2001) 117–121 discussion 151–117.
[17] A. Stahl, R.E. Gimeno, L.A. Tartaglia, H.F. Lodish, Fatty acid transport proteins: a current view of a growing family, Trends Endocrinol. Metab. 12 (2001) 266–273.
[18] J.E. Schaffer, H.F. Lodish, Expression cloning and characterization of a novel adipocyte long chain fatty acid transport protein, Cell 79 (1994) 427–436.
[19] D. Hirsch, A. Stahl, H.F. Lodish, A family of fatty acid transporters conserved from mycobacterium to man, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 8625–8629.
[20] T. Herrmann, F. Buchkremer, I. Gosch, A.M. Hall, D.A. Bernlohr, W. Stremmel, Mouse fatty acid transport protein 4 (FATP4): characterization of the gene and functional assessment as a very long chain acyl-CoA synthetase, Gene 270 (2001) 31–40.
[21] Q. Wu, A.M. Ortegon, B. Tsang, H. Doege, K.R. Feingold, A. Stahl, FATP1 is an insulin-sensitive fatty acid transporter involved in diet-induced obesity, Mol. Cell. Biol. 26 (2006) 3455–3467.
[22] Q. Wu, M. Kazantzis, H. Doege, A.M. Ortegon, B. Tsang, A. Falcon, A. Stahl, Fatty acid transport protein 1 is required for nonshivering thermogenesis in brown adipose tissue, Diabetes 55 (2006) 3229–3237.

[23] A. Falcon, H. Doege, A. Fluitt, B. Tsang, N. Watson, M.A. Kay, A. Stahl, FATP2 is a hepatic fatty acid transporter and peroxisomal very long-chain acyl-CoA synthetase, Am. J. Physiol. Endocrinol. Metab. 299 (2010) E384–E393.
[24] A. Stahl, D.J. Hirsch, R.E. Gimeno, S. Punreddy, P. Ge, N. Watson, S. Patel, M. Kotler, A. Raimondi, L.A. Tartaglia, H.F. Lodish, Identification of the major intestinal fatty acid transport protein, Mol. Cell 4 (1999) 299–308.
[25] H. Doege, D. Grimm, A. Falcon, B. Tsang, T.A. Storm, H. Xu, A.M. Ortegon, M. Kazantzis, M.A. Kay, A. Stahl, Silencing of hepatic fatty acid transporter protein 5 in vivo reverses diet-induced non-alcoholic fatty liver disease and improves hyperglycemia, J. Biol. Chem. 283 (2008) 22186–22192.
[26] R.E. Gimeno, A.M. Ortegon, S. Patel, S. Punreddy, P. Ge, Y. Sun, H.F. Lodish, A. Stahl, Characterization of a heart-specific fatty acid transport protein, J. Biol. Chem. 278 (2003) 16039–16044.
[27] H. Doege, R.A. Baillie, A.M. Ortegon, B. Tsang, Q. Wu, S. Punreddy, D. Hirsch, N. Watson, R.E. Gimeno, A. Stahl, Targeted deletion of FATP5 reveals multiple functions in liver metabolism: alterations in hepatic lipid homeostasis, Gastroenterology 130 (2006) 1245–1258.
[28] R.E. Gimeno, D.J. Hirsch, S. Punreddy, Y. Sun, A.M. Ortegon, H. Wu, T. Daniels, A. Stricker-Krongrad, H.F. Lodish, A. Stahl, Targeted deletion of fatty acid transport protein-4 results in early embryonic lethality, J. Biol. Chem. 278 (2003) 49512–49516.
[29] B. Hubbard, H. Doege, S. Punreddy, H. Wu, X. Huang, V.K. Kaushik, R.L. Mozell, J.J. Byrnes, A. Stricker-Krongrad, C.J. Chou, L.A. Tartaglia, H.F. Lodish, A. Stahl, R.E. Gimeno, Mice deleted for fatty acid transport protein 5 have defective bile acid conjugation and are protected from obesity, Gastroenterology 130 (2006) 1259–1269.
[30] L. Ordovas, R. Roy, P. Zaragoza, C. Rodellar, Structural and functional characterization of the bovine solute carrier family 27 member 1 (SLC27A1) gene, Cytogenet. Genome Res. 115 (2006) 115–122.
[31] J. Grzyb, D. Latowski, K. Strzalka, Lipocalins—a family portrait, J. Plant Physiol. 163 (2006) 895–915.
[32] J. Storch, L. McDermott, Structural and functional analysis of fatty acid-binding proteins, J. Lipid Res. 50 (2009) S126–S131 (Suppl).
[33] S.E. Lewis, L.L. Listenberger, D.S. Ory, J.E. Schaffer, Membrane topology of the murine fatty acid transport protein 1, J. Biol. Chem. 276 (2001) 37042–37050.
[34] M.R. Richards, L.L. Listenberger, A.A. Kelly, S.E. Lewis, D.S. Ory, J.E. Schaffer, Oligomerization of the murine fatty acid transport protein 1, J. Biol. Chem. 278 (2003) 10477–10483.
[35] S.J. Mihalik, S.J. Steinberg, Z. Pei, J. Park, G. Kim do, A.K. Heinzer, G. Dacremont, R.J. Wanders, D.A. Cuebas, K.D. Smith, P.A. Watkins, Participation of two members of the very long-chain acyl-CoA synthetase family in bile acid synthesis and recycling, J. Biol. Chem. 277 (2002) 24771–24779.
[36] S.J. Steinberg, S.J. Mihalik, D.G. Kim, D.A. Cuebas, P.A. Watkins, The human liver-specific homolog of very long-chain acyl-CoA synthetase is cholate:CoA ligase, J. Biol. Chem. 275 (2000) 15605–15608.
[37] M.R. Richards, J.D. Harp, D.S. Ory, J.E. Schaffer, Fatty acid transport protein 1 and long-chain acyl coenzyme A synthetase 1 interact in adipocytes, J. Lipid Res. 47 (2006) 665–672.
[38] Z. Zou, C.C. DiRusso, V. Ctrnacta, P.N. Black, Fatty acid transport in *Saccharomyces cerevisiae*. Directed mutagenesis of FAT1 distinguishes the biochemical activities associated with Fat1p, J. Biol. Chem. 277 (2002) 31062–31071.
[39] C.C. DiRusso, D. Darwis, T. Obermeyer, P.N. Black, Functional domains of the fatty acid transport proteins: studies using protein chimeras, Biochim. Biophys. Acta 1781 (2008) 135–143.
[40] Z. Pei, P. Fraisl, J. Berger, Z. Jia, S. Forss-Petter, P.A. Watkins, Mouse very long-chain Acyl-CoA synthetase 3/fatty acid transport protein 3 catalyzes fatty acid activation but not fatty acid transport in MA-10 cells, J. Biol. Chem. 279 (2004) 54454–54462.
[41] K. Milger, T. Herrmann, C. Becker, D. Gotthardt, J. Zickwolf, R. Ehehalt, P.A. Watkins, W. Stremmel, J. Fullekrug, Cellular uptake of fatty acids driven by the ER-localized acyl-CoA synthetase FATP4, J. Cell Sci. 119 (2006) 4678–4688.
[42] S.J. Mihalik, S.J. Steinberg, Z. Pei, J. Park, D.G. Kim, A.K. Heinzer, G. Dacremont, R.J. Wanders, D.A. Cuebas, K.D. Smith, P.A. Watkins, Participation of two members of the very long-chain acyl-CoA synthetase family in bile acid synthesis and recycling, J. Biol. Chem. 277 (2002) 24771–24779.
[43] J.K. Kim, R.E. Gimeno, T. Higashimori, H.J. Kim, H. Choi, S. Punreddy, R.L. Mozell, G. Tan, A. Stricker-Krongrad, D.J. Hirsch, J.J. Fillmore, Z.X. Liu, J. Dong, G. Cline, A. Stahl, H.F. Lodish, G.I. Shulman, Inactivation of fatty acid transport protein 1 prevents fat-induced insulin resistance in skeletal muscle, J. Clin. Invest. 113 (2004) 756–763.
[44] H.M. Feldmann, V. Golozoubova, B. Cannon, J. Nedergaard, UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality, Cell Metab. 9 (2009) 203–209.
[45] A. Bartelt, O.T. Bruns, R. Reimer, H. Hohenberg, H. Ittrich, K. Peldschus, M.G. Kaul, U.I. Tromsdorf, H. Weller, C. Waurisch, A. Eychmuller, P.L. Gordts, F. Rinninger, K. Bruegelmann, B. Freund, P. Nielsen, M. Merkel, J. Heeren, Brown adipose tissue activity controls triglyceride clearance, Nat. Med. 17 (2011) 200–205.
[46] H.C. Chiu, A. Kovacs, R.M. Blanton, X. Han, M. Courtois, C.J. Weinheimer, K.A. Yamada, S. Brunet, H. Xu, J.M. Nerbonne, M.J. Welch, N.M. Fettig, T.L. Sharp, N. Sambandam, K.M. Olson, D.S. Ory, J.E. Schaffer, Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy, Circ. Res. 96 (2005) 225–233.
[47] W. Stremmel, L. Pohl, A. Ring, T. Herrmann, A new concept of cellular uptake and intracellular trafficking of long-chain fatty acids, Lipids 36 (2001) 981–989.
[48] C.E. Hagberg, A. Falkevall, X. Wang, E. Larsson, J. Huusko, I. Nilsson, L.A. van Meeteren, E. Samen, L. Lu, M. Vanwildemeersch, J. Klar, G. Genove, K. Pietras, S. Stone-Elander, L. Claesson-Welsh, S. Yla-Herttuala, P. Lindahl, U. Eriksson, Vascular endothelial growth factor B controls endothelial fatty acid uptake, Nature 464 (2010) 917–921.
[49] D.M. Muoio, Metabolism and vascular fatty acid transport, N. Engl. J. Med. 363 (2010) 291–293.
[50] R.W. Mitchell, N.H. On, M.R. Del Bigio, D.W. Miller, G.M. Hatch, Fatty acid transport protein expression in human brain and potential role in fatty acid transport across human brain microvessel endothelial cells, J. Neurochem. 117 (2011) 735–746.
[51] T. Herrmann, F. Van Der Hoeven, H.J. Grone, A.F. Stewart, L. Langbein, I. Kaiser, G. Liebisch, I. Gosch, F. Buchkremer, W. Drobnik, G. Schmitz, W. Stremmel, Mice with targeted disruption of the fatty acid transport protein 4 (Fatp 4, Slc27a4) gene show features of lethal restrictive dermopathy, J. Cell Biol. 161 (2003) 1105–1115.
[52] C.L. Moulson, M.H. Lin, J.M. White, E.P. Newberry, N.O. Davidson, J.H. Miner, Keratinocyte-specific expression of fatty acid transport protein 4 rescues the wrinkle-free phenotype in Slc27a4/Fatp4 mutant mice, J. Biol. Chem. 282 (2007) 15912–15920.
[53] T. Herrmann, H.J. Grone, L. Langbein, I. Kaiser, I. Gosch, U. Bennemann, D. Metzger, P. Chambon, A.F. Stewart, W. Stremmel, Disturbed epidermal structure in mice with temporally controlled fatp4 deficiency, J. Invest. Dermatol. 125 (2005) 1228–1235.
[54] M. Schmuth, A.M. Ortegon, M. Mao-Qiang, P.M. Elias, K.R. Feingold, A. Stahl, Differential expression of fatty acid transport proteins in epidermis and skin appendages, J. Invest. Dermatol. 125 (2005) 1174–1181.
[55] M. Sobol, N. Dahl, J. Klar, FATP4 missense and nonsense mutations cause similar features in Ichthyosis Prematurity Syndrome, BMC Res Notes, 4 90.
[56] J. Klar, M. Schweiger, R. Zimmerman, R. Zechner, H. Li, H. Torma, A. Vahlquist, B. Bouadjar, N. Dahl, J. Fischer, Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome, Am. J. Hum. Genet. 85 (2009) 248–253.
[57] A. Meirhaeghe, G. Martin, M. Nemoto, S. Deeb, D. Cottel, J. Auwerx, P. Amouyel, N. Helbecque, Intronic polymorphism in the fatty acid transport protein 1 gene is associated with increased plasma triglyceride levels in a French population, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 1330–1334.
[58] K. Gertow, C. Skoglund-Andersson, P. Eriksson, S. Boquist, K. Orth-Gomer, K. Schenck-Gustafsson, A. Hamsten, R.M. Fisher, A common polymorphism in the fatty acid transport protein-1 gene associated with elevated post-prandial lipaemia and alterations in LDL particle size distribution, Atherosclerosis 167 (2003) 265–273.
[59] K. Gertow, K.H. Pietilainen, H. Yki-Jarvinen, J. Kaprio, A. Rissanen, P. Eriksson, A. Hamsten, R.M. Fisher, Expression of fatty-acid-handling proteins in human adipose tissue in relation to obesity and insulin resistance, Diabetologia 47 (2004) 1118–1125.
[60] A. Auinger, L. Valenti, M. Pfeuffer, U. Helwig, J. Herrmann, A.L. Fracanzani, P. Dongiovanni, S. Fargion, J. Schrezenmeir, D. Rubin, A promoter polymorphism in the liver-specific fatty acid transport protein 5 is associated with features of the metabolic syndrome and steatosis, Horm. Metab. Res. 42 (2010) 854–859.