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Holger Doege and Andreas Stahl


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Protein-Mediated Fatty Acid Uptake: Novel Insights from In Vivo Models

Long-chain fatty acids are both important metabolites as well as signaling molecules. Fatty acid transport proteins are key mediators of cellular fatty acid uptake and recent transgenic and knockout animal models have provided new insights into their contribution to energy homeostasis and to pathological processes, including obesity and insulin desensitization.

Transport of Fatty Acids

Long-chain fatty acids (LCFAs) are vital components of our diet and contribute to a plethora of processes including metabolic energy generation and storage, plasma membrane synthesis, and protein anchoring. In addition, LCFAs have hormone-like properties since they can profoundly affect gene expression via nuclear receptors such as HNF4 and the PPAR family (reviewed in Ref. 45), trigger insulin release through activation of the G-protein-coupled receptor (GPCR) GPR40 by β-cells (89), affect the innate immune response by modulating toll-like receptor (TLR) signaling in a number of cell types (reviewed in Ref. 53), and suppress food intake by inhibiting the release of neuropeptide Y (NPY) and Agouti-related protein (AgRP) in a subpopulation of hypothalamic neurons (reviewed in Refs. 51, 78). Because of the physiological significance of LCFAs, chronic imbalances in lipid fluxes and metabolism often cause a variety of (metabolic) abnormalities and pathologies, including hyperlipidemia, obesity, Type 2 diabetes mellitus, nonalcoholic fatty liver disease, heart disease, and cancer (16, 37, 50, 54, 56, 57, 64, 73).

Although in some tissues and cell types LCFAs can signal through GPCRs or TLRs (53, 89), they typically have to first cross the plasma membrane to elicit their effects. In general, the uptake of fatty acids from the circulation into cells includes the sequence of 1) localized generation of free fatty acids through hydrolysis of triglyceride (TG)-rich lipoproteins by lipases inside the endothelial lumen and binding of fatty acids to albumin, 2) fatty acid dissociation from albumin followed by binding to plasma membrane proteins or integration into the lipid bilayer, 3) their transport across the plasma membranes, and 4) their intracellular association with fatty acid binding and acyl-CoA binding proteins (FABPs and ACBPs, respectively) (1, 33, 91), as illustrated in FIGURE 1A. The mechanism by which fatty acids cross the plasma membrane has been debated for several years. Because fatty acids are predominantly lipophilic, it was initially proposed that they traverse the lipid bilayer by diffusion (passive flip-flop) without the involvement of protein mediators (35, 68). However, many organs and cell types display a rapid, saturable, substrate-specific, and hormonally regulated LCFA uptake mechanism indicative of protein-mediated processes (8, 10, 83). Although the occurrence of both LCFA uptake processes are now widely accepted, during the past years considerable data have demonstrated that protein-mediated transport accounts for the majority of fatty acid uptake by tissues with high LCFA metabolism and storage such as skeletal muscle (99), adipose tissue (75), liver (22, 24, 26, 82, 93, 95), and heart (81, 94). Particularly, at physiological concentrations and serum-to-albumin ratios, the concentration of unbound fatty acids is low (7.5 nM) and >90% of LCFA uptake occurs via the protein-mediated pathway (71). The crucial role of proteins for efficient LCFA uptake has been underscored by a number of knockout (KO) model systems with impaired or enhanced fatty acid transport, as we will discuss later in more detail.

Several candidate proteins have been proposed to be involved in the uptake process of LCFAs including fatty acid translocase (FAT/CD36) (17), FABPs (32, 41), long-chain fatty acyl-CoA synthetases (ACSL) (15), ACBP (49), and fatty acid transport proteins (FATPs) (83). These proteins differ widely in their expression pattern in the body as well as in their subcellular localization. Moreover, lipid rafts may also be important for fatty acid influx and efflux (23, 67). Although the above-mentioned proteins can drive the initial uptake of LCFAs, additional factors such as the rate of mitochondrial LCFA uptake, β-oxidation, or reesterification can also become rate limiting, leading to a saturation of cellular fatty acid binding and transport components and decreased uptake of exogenous LCFAs. Although many of the above-mentioned proteins and processes are important for LCFA uptake and metabolism, recent in vivo studies have particularly highlighted the contribution of FATPs to lipid metabolism and fatty acid-associated disorders; thus we will focus the remainder of this review on this interesting family of proteins.

FATPs

The family of FATPs (gene name: solute carrier family 27, Slc27) is comprised of six related members in humans and mice (FATP1 to FATP6) that differ widely in their tissue expression patterns (FIGURE 2B). Similar FATP genes are found in many other species including prokaryotes, but not in E. coli, and conservation of
FATP-mediated LCFA transport has been shown for such diverse organisms as humans (40), *C. elegans* (40), yeast (20), and mycobacterium (40). The phylogenetic relationship among FATPs of several species is shown in **Figure 2A**. The first discovered FATP, now named FATP1, was identified in an expressing cloning screen for proteins that enhance the accumulation of a fluorescently labeled fatty acid analog in fibroblasts (75). FATP1 has at least one transmembrane domain with the N-terminus facing the outside of the cell and an intracellular C-terminus (52, 74). Based on overall sequence similarity (83, 85), it is likely that these basic characteristics will hold true for other FATP family members as well. At least FATP1, and possibly other FATPs, form homodimers, and dimerization is required for transport function (70). Follow-up studies on FATP1 as well as on the later identified FATPs 2, 4, and 5 demonstrated that these proteins can also catalyze the formation of CoA.

**Figure 1.** Free fatty acid uptake and action in mammalian cells

A: serum free fatty acids (FFA) are generated from lipoproteins by the action of endothelial lipoprotein lipase (LpL). At physiological conditions, the majority of FFAs is bound to albumin, whereas the concentration of unbound FFAs in this equilibrium is low. Plasma membrane traversing of FFAs into the cell under these conditions occurs mainly by a protein-mediated mechanism either by interaction of the FFAs directly with FATP complexes or by a preceding binding to cell-surface proteins, such as CD36, which subsequently hands the FFAs on to the FATPs. On the cytosolic site, FFAs are quickly activated and coupled to coenzyme A (CoA) by the catalysis of long-chain fatty acyl-CoA synthetases (ACSLs) or the by FATPs itself. Fatty acid binding proteins (FABPs) or acyl-CoA binding proteins (ACBPs) facilitate an intracellular unloading of the transporters and the synthetases and can also function as an intracellular fatty acid buffer. In the cell, FFAs can act at different subcellular localizations and have functions in energy generation and storage, membrane synthesis, protein modification, and activation of nuclear transcription factors. In addition to acting intracellularly, unbound FFAs can also signal extracellularly, e.g., by stimulating the G-protein-coupled receptor GPR40 in β-cells to induce insulin secretion or by activating toll-like receptors (TLRs) to initiate the innate immune response. Furthermore, FFAs can act in the brain, e.g., by controlling the release of Agouti-related protein (AgRP) and neuropeptide Y (NPY) in the hypothalamus.
FATPs do not show any obvious similarities to other transporter families, and the predicted single-transmembrane domain is unusual for a transport protein [in comparison, the members of the GLUT family of glucose transporters consist of 12 transmembrane domains (63)], although it is unknown whether transport proteins for amphipathic molecules, like fatty acids, necessarily would require the same type of structure, i.e., a water-filled pore, as transport proteins for hydrophilic substrates (e.g., the GLUT proteins for glucose). These properties caused some doubt as to whether FATPs are proteins that mediate the traversing of fatty acids across membranes or rather are proteins that facilitate LCFA uptake by intracellular LCFA esterification. In particular, as illustrated in Figure 1B, it is still an ongoing debate whether FATPs 1) are solely transmembrane transport proteins mediating LCFA uptake, possibly in close association with other proteins like ACSLs (69), 2) are themselves membrane-bound long-chain and very-long-chain acyl-CoA synthetases that trap LCFAs inside the cell following fatty acid diffusion across the plasma membrane, 3) combine the transport with acyl-CoA synthetase activity for optimal uptake, or, alternatively, 4) are multifunctional proteins that mediate LCFA uptake independently of their esterification activities. Studies by the Schaffer group have supported the first view by demonstrating that FATP1 in adipocytes forms heterodimers with ACSL1 (69) and suggest that both proteins are needed for uptake. This model would thus be analogous to the well-studied fatty acid uptake system in E. coli consisting of a transport protein, FadL, and an acyl-CoA synthetase, Fad (19, 21). Proponents of the second model, however, have pointed out that purified FATPs possess very-long-chain acyl CoA synthetase activity (18). The third model is supported by elegant experiments in yeast, where different murine FATP1 mutants were used to reconstitute transport and ACSL activity in yeast strains lacking the endogenous FAT, Fat1p. These studies identified mutants that only supported either transport or esterification activity, albeit at reduced levels (21). Last, it is possible that at least in some cases the enzymatic activity of FATPs is not coupled with uptake. This notion is particularly supported by the observation that the substrate specificities for uptake and esterification are not identical (21, 66).

Further studies of FATP structure and function are needed to delineate the exact transport mechanism. However, it is clear that the presence of FATPs enhances LCFA uptake and that loss of FATP function results in often dramatic phenotypes, as we will explore in the next part of this review.

Animal Models of FATP Function

Although initial progress in FATP research mainly came from in vitro loss-of-function [e.g., in yeast (8)] or gain-of-function studies [e.g., transfectants in cultured mammalian cells (40)], recent reports of FATP transgenic and KO mouse model systems have highlighted the significance of this protein family for the maintenance of a normal lipid homeostasis in mammalian organisms. They also reveal the lack of compensation on loss of a particular FATP by other FATP family members leading to a variety of physiological abnormalities ranging from altered feeding behavior (42) to embryonic lethality (31).

**FATP1**

FATP1 is the major FATP family member expressed in adipose tissue. FATP1 protein is also found in skeletal muscle and, to a lesser extent, in heart (Figure 2B). Using an α-myosin heavy chain (MHC-α) gene promoter, heart-specific overexpression of FATP1 was achieved in a transgenic mouse model (14, 15). The observed eightfold overexpression of FATP1 protein in heart muscle compared with wild-type mice resulted in early cardiomyocyte LCFA accumulation and increased cardiac lipid metabolism, and subsequently caused lipotoxic cardiomyopathy. Although FATP1 overexpression in vitro had previously demonstrated the ability of the molecule to increase LCFA uptake (75), this transgenic mouse model provided the first evidence that FATPs enhance LCFA import in vivo. In this study, it was also demonstrated that dysregulation of FATP expression can perturb lipid homeostasis even in the absence of other compounding metabolic alterations, e.g., high-fat feeding, and cause pathologies reminiscent of those observed in diabetic patients (15).

One prominent hypothesis to explain the link between obesity and insulin desensitization is that excessive uptake of dietary fatty acids by skeletal muscle and subsequent accumulation of intramuscular diglycerides and TGs lead to alterations in the insulin-signaling cascade and ultimately to Type 2 diabetes (9, 79). Thus one would predict that reducing LCFA uptake by muscle would rescue insulin signaling from high-fat-induced suppression. Indeed, using FATP1 KO mice created by the Lodish group, Kim and colleagues (48) found in hyperinsulinemic-hyperglycemic clamp studies that FATP1 KO mice were protected from the insulin-desensitizing effects of lipid injections or short-term high-fat feeding (48). In accordance with the proposed function of FATP1 as a rate-limiting fatty acid transporter, loss of FATP1 function reduced muscle TG content and prevented a reduction of insulin receptor substrate-1 tyrosine phosphorylation and PI3-kinase association (48).

Interestingly, in vitro studies in cultured adipocytes showed that insulin induces translocation of FATP1 from an intracellular perinuclear compartment to the plasma membrane, coinciding with increased LCFA uptake (84). Following up on these initial observations, our laboratory (99) could demonstrate that FATP1 translocation is not restricted to adipocytes but is also...
found in skeletal muscle (FIGURE 3). Importantly, loss of FATP1 protein abolished insulin-induced LCFA uptake in adipocytes and skeletal muscle isolated from FATP1 KO mice, whereas basal LCFA uptake was unaffected (99), demonstrating the absolute requirement of FATP1 for insulin-induced fatty acid uptake. These novel findings suggest the existence of an analogous system for LCFA regulation as was discovered almost two decades ago for glucose (7, 13, 27, 43, 46). Here, basal uptake is mediated by one transporter (GLUT1) and inducible uptake by a second family member (GLUT4) (3, 63). Correspondingly, we propose a model in which insulin counteracts the postprandial rise in dietary lipids by increasing the FATP1 concentration on the plasma membrane of adipocytes and muscle, whereas the basal LCFA uptake is mediated by other proteins including FATP4 and CD36 (17). Since little is known regarding the underlying cell biology of this translocation process, it will be interesting to study the potential overlap of the GLUT4 and FATP1 transport systems in the future.

Another key finding of the report by Wu et al. (99) was that FATP1 KO mice are completely resistant to diet-induced obesity, insulin desensitization, and
other parameters of the metabolic syndrome (76). However, lack of FATP1 altered fatty acid uptake and TG metabolism in adipocytes and skeletal muscle; thus it remains unclear whether the protective effect was mediated by fat, muscle, or both tissues.

Interestingly, FATP1 deletion led to a redistribution of postprandial fatty acid uptake (FIGURE 4) and TG deposition in vivo (99). TG accumulation and dietary lipid deposition in skeletal muscle and adipose tissue was reduced, whereas uptake by the liver, which is primarily mediated by FATP2 and 5, was increased. A similar FATP isoform-dependent redistribution of lipids was observed for the recently generated liver-specific FATP5 KO mouse model (22), as discussed below.

Last, it should be mentioned that results of Wu et al. (99) also demonstrated for the first time that members of the FATP family are predominantly involved in the uptake, but not in the export, of LCFAs (99). Since fluxes of fatty acids across the adipocyte membrane are both inward and outward, dependent on the metabolic status of the animal, the identity of a hypothetical fatty acid exporter remains unknown.

**FATP2**

FATP2 is predominantly expressed in liver and kidney (83, 96). A FATP2 KO mouse model has been recently described (36) with a particular emphasis on phenotypes reassembling X-linked adrenoleukodystrophy. However, no link between FATP2 function and this neurodegenerative endocrine disorder was found (36). Although FATP2 KO mice exhibit a decreased peroxisomal very-long-chain acyl-CoA synthetase activity and decreased peroxisomal VLCA β-oxidation in liver and kidney, no VLCFA accumulation in either of these organs was observed (36). The consequences of FATP2 loss for hepatic and renal LCFA uptake remained unexplored.

**FATP4**

FATP4 is the only FATP family member in the small intestine where it is localized to the apical brush border of epithelial cells (86). Since FATP4 is implicated in the absorption of dietary lipids, it is of particular interest as a potential anti-obesity target. FATP4 is also expressed in other tissues other than the small intestine, including adipose tissue, brain, liver, skin, and heart (FIGURE 2B). To date, four studies on FATP4 deletions in mice have been published, demonstrating an important role of FATP4 in fatty acid metabolism. Moulson et al. (62) described a mouse strain containing a spontaneous mutation that abrogates FATP4 expression by the insertion of a retrotransposon, which introduces a premature stop codon into exon 3 of the FATP4 gene. Hermann et al. (39) generated a FATP4 KO mouse through homologous recombination, removing exon 3 and introducing a new splice acceptor site into intron 2. Both groups reported a similar phenotype for FATP4 homozygote deletion; an early neonatal lethality due to symptoms strikingly similar to restrictive dermopathy, a rare human genetic disorder (98). Neonate mice exhibited thickened, tight skin and a disrupted epidermal barrier as well as facial deformations and breathing difficulties. No effects on LCFA uptake have been examined in these two studies. However, follow-up analyses on the sec-

**FIGURE 3. Insulin-induced translocation of FATP1 in skeletal muscle**

Three-dimensional surface projections of caveolin 3 (blue), FATP1 (red), and CD36 (green; only in A) of soleus muscle. A: superimposition of all three channels of a top-view projection from 20-μm sections of hindlimb muscle from fasted insulin-injected (A1) or mock-injected (A2) C57BL/6 mice. B: inside-out projections from muscle of insulin-injected C57BL/6 mice in low (B1—B3) or high (B4) resolution, showing vesicle docking with the sarcolemma. B1: caveolin 3 staining, which was used as plasma membrane marker. B3: FATP1 staining. B2 and B4: the overlap of both signals. Nuclei were stained with DAPI and are depicted in turquoise in all images. Grid cell dimensions are 40 × 40 × 40 μm.
two different phenotypes of the FATP4 KO mice are unknown but could include expression of truncated FATP4 proteins or alternative splicing and translational read-through in the models targeting exon 3.

These FATP4 loss-of-function studies demonstrate the importance of this protein for early development as well as its important role in skin lipid metabolism. The formation of an epidermal barrier in the form of extracellular lipid-enriched lamellar membranes in the stratum corneum requires the uptake of fatty acids from extracutaneous sites, and, not surprisingly, several FATPs including FATP1, 3, 4, and 6 are expressed by keratinocytes and other cell types within the epidermis (77). Recently, a report describing an epidermal-specific conditional FATP4 KO mouse was pub-

**FIGURE 4.** Impaired postprandial serum lipid clearance and redistribution of lipid fluxes in FATP KO mouse models

Distribution of radioactivity in organs of FATP1 KO (A) and FATP5 KO (B) mice compared with wild-type animals after an intragastric administration of an olive oil bolus containing 14C-oleic acid tracer. Left figures in each panel show a time course of plasma radioactivity in wild-type and KO animals, which is directly proportional to the serum FFA concentration.
lished (38). Results of this study show that mice with epidermal-specific FATP4 deletion developed a hyperproliferative hyperkeratosis with a disturbed epidermal barrier, suggesting that epidermal FATP4 is essential for the maintenance of normal skin structure and function (38).

**FATP5**

FATP5 is expressed solely in the liver (4, 40). Confocal immunofluorescent microscopy with isolated primary hepatocytes demonstrated that FATP5 is localized to the plasma membrane of these cells (22), which was confirmed by immunoelectron microscopy of liver sections, showing a predominant localization of FATP5 proteins to basal microvilli in the space of Disse (22). Although in vitro experiments demonstrated that FATP5 exhibits fatty acid transport activity (22, 40), it has also been reported to increase both fatty acid very-long-chain acyl-CoA synthetase and bile acid-CoA synthetase activities (61, 87, 88).

FATP5 KO mice have recently been generated and characterized in two studies focusing on the role of FATP5 in both hepatic lipid metabolism (22) and bile metabolism (42). The first of these studies showed that LCFA uptake in primary hepatocytes isolated from FATP5 KO mice is reduced by 50% (22). This is the first in vivo evidence that cell surface proteins such as FATPs contribute substantially to hepatic LCFA uptake. As in the FATP1 KO mice, no compensatory upregulation of other FATP family members was found in the livers of FATP5 KO mice. Detailed analysis of the hepatic lipidome of FATP5 KO mice revealed significant quantitative and qualitative alterations. Hepatic lipid content in the KO mice was significantly reduced despite an increased fatty acid de novo biosynthesis in the KO mice compared with wild-type animals. However, no significant effects on the distribution of acyl chain lengths in different lipid classes was observed, arguing that the very-long-chain acyl-CoA synthetase activities of FATP5 play only a minor role in vivo. As was observed for FATP1 KO mice, postabsorptive lipid clearance was severely delayed in the FATP5 KO mice (FIGURE 4). Absorption of dietary lipids in FATP5 KO mice shifted away from the liver toward tissues whose uptake is dominated by other FATPs, such as heart (FATP6), fat, and skeletal muscle (both FATP1 and 4). Similarly to FATP1 KO mice, homozygote deletion of FATP5 resulted in resistance to high-fat-diet-induced weight gain and insulin resistance (42). In contrast to the FATP1 KO model, however, FATP5 KO mice displayed both decreased caloric intake and increased energy expenditure. How changes in hepatic lipid metabolism lead to altered feeding behavior is currently under intense investigation. One explanation for the altered food intake could be alterations in bile acid metabolism (97). Since FATP5 has bile-CoA ligase activity, Hubbard et al. (42) analyzed bile composition in the FATP5 KO mouse model by mass spec-tometry. They found that, although the total bile pool was unchanged, a distinct shift from conjugated to unconjugated bile acids occurred as a result of FATP5 deletion. The remaining conjugated bile acids were exclusively derived from de novo synthesis, implying an important role of FATP5 in the reconjugation of bile acids during the enterohepatic recirculation. In summary, the FATP5 KO mouse model shows an interesting, multifaceted phenotype, suggesting multiple independent functions for FATP5 in vivo supporting the mode of uptake depicted in model 4 in FIGURE 1B.

**FATP Polymorphisms in Human Populations**

Studies on human subjects have also established genetic links between FATP genes, i.e., FATP1 and FATP4, and metabolic alterations.

Genetic polymorphisms in the FATP1 gene have been linked primarily to dyslipidemia. Meirhaeghe et al. (59) identified in a study on 1,144 French subjects three single-nucleotide polymorphisms in introns 8 and 9 of the human FATP1 gene and investigated one of these (an A/G exchange at position +48 in intron 8) in more detail. Results of this work revealed the first direct link between a FATP gene polymorphism, albeit a noncoding one, and alterations in human lipid homeostasis. In an allelic dose-dependent manner, fasting plasma TG concentrations were increased in the presence of the rare allele. Interestingly, this link was gender specific and only observed in women. No association was observed with other anthropometric parameters, including body weight, body mass index (BMI), or plasma insulin and plasma glucose levels. A separate study (30) with 856 Swedish men and women analyzed the same A/G polymorphism in intron 8. In contrast to the previous findings from Meirhaeghe et al. (59), this study (30) found no association of fasting plasma TG levels with the intronic FATP1 polymorphism. However, in oral fat tolerance tests, male A/A allele carriers showed increased postprandial TG concentrations and smaller LDL particles compared with the G/G and A/G allele groups. The transcriptional activity was reduced in the A allele compared with the G allele as assessed in vitro by reporter gene transfection analyses for the region containing the intron 8 polymorphism. Taken together, these two studies suggest an association between the described intronic polymorphism (particularly the A allele) in the human FATP1 gene and changes in TG metabolism. A third study with 1,195 French subjects was conducted to assess the association between the metabolic syndrome, a complex disease characterized by impaired glucose regulation, insulin resistance, increased arterial pressure, dislipidemia and central obesity, and certain polymorphisms in human genes involved in lipid transport, including the described A/G polymorphism in intron 8 of the FATP1 gene (58). In contrast to
the first two studies, no significant associations were found. The reason for this discrepancy is not clear; however, the metabolic syndrome is a heterogeneous cluster of metabolic disorders, which may explain the lack of a significant association.

The expression levels of human FATP1 mRNA in skeletal muscle and subcutaneous abdominal adipose tissue was also investigated in independent studies in regard to differences between normal and obese or diabetic states (5). Three groups of male and female subjects were investigated: healthy lean, non-diabetic obese, and Type 2 diabetic subjects. Binnert et al. (5) found that FATP1 mRNA levels were reduced in skeletal muscle of obese nondiabetic and Type 2 diabetic women. An acute insulin infusion reduced FATP1 mRNA levels in skeletal muscle from lean women but not in any of the other female or male groups. No studies of FATP1 mRNA expression in females were undertaken in adipose tissues. In contrast, in male individuals, FATP1 mRNA muscle and fat is expressed at similar levels among the three groups investigated. The data gained from this study suggest again a role of FATP1 in the maintenance of a normal lipid homeostasis as well as gender-specific effect.

FATP4 is the second FATP family member that has been associated with pathophysiological states in humans. Bower et al. (11) investigated groups of African-American and Caucasian women, describing that an increase of FATP4 mRNA and protein levels in adipocytes of obese subjects correlates with a higher LCFA uptake rate into this cell type. A separate investigation by Gertow and colleagues (29) was designed to distinguish between influences of genetic and non-genetic parameters on FATP4 gene expression in subcutaneous adipose tissue. The study, performed with 17 pairs of monozygotic twins with intra-pair differences in BMI, obesity, and insulin resistance (one lean and one heavy sibling in each twin group) demonstrated that FATP4 mRNA expression was increased in the acquired obesity, independent of the genetic factor. This would suggest a strong influence of environmental factors on FATP4 expression. A third study (28) analyzed a polymorphism in exon 3, which leads to an amino acid exchange in FATP4 protein (G209S), with respect to the insulin resistance syndrome. This investigation demonstrated that carriers of this allele had lower values for certain metabolic parameters including BMI, TG, insulin levels, and systolic blood pressure compared with common G/G allele homozygotes. A three-dimensional modeling of FATP4 protein based on structural and functional similarities with adenylate-forming enzymes by Gertow et al. (28) suggested a potentially important function of this glycine residue in protein–protein interaction.

Since altered lipid metabolism and fatty acid uptake may underlie many genetic and acquired human disorders including acute liver failure (65, 72), mental retardation (12, 25, 36, 60), restrictive dermopathy (98), cardiovascular diseases (2, 47, 55, 92), and cancer (44, 80, 90), as well as obesity and diabetes (as described above), further elucidation of expression changes and alterations in human FATPs should provide useful risk markers as well as novel treatment options.

**Outlook**

With the recent characterizations of FATP KO and transgenic mouse strains, as well as data gained from human subjects, our knowledge of how FATP-mediated LCFA uptake process contributes to lipid homeostasis in vivo has greatly increased. Although the exact LCFA transport mechanism and the underlying questions of FATP structure and function remain controversial topics, the discussed animal models have clearly demonstrated that FATPs are important determinants of lipid distribution among different organs and can dynamically change LCFA uptake in response to altered nutrient availability. Thus FATP transgenic and KO animals are important research tools due to their ability to redirect lipid fluxes in an organ-specific fashion, which will allow us to test the contribution of LCFA uptake and TG accumulation to the development of diseases such as obesity, insulin resistance, Type 2 diabetes, or nonalcoholic fatty liver disease (NAFLD or NASH). Last, the development of FATP-specific inhibitors or modulators of FATP function may also lead to the development of novel insulin-sensitizing compounds.

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