Pflugers Arch - Eur J Physiol (2004) 447:722–727
DOI 10.1007/s00424-003-1106-z

Andreas Stahl

A current review of fatty acid transport proteins (SLC27)

Received: 18 December 2002 / Revised: 31 March 2003 / Accepted: 28 April 2003 / Published online: 11 July 2003

Abstract Long-chain fatty acids (LCFAs) are not only important metabolites but contribute to many cellular functions including activation of protein kinase C (PKC) isoforms and nuclear transcription factors such as peroxisome proliferator-activated receptors (PPAPs). To assert their diverse effects LCFAs have first to traverse the plasma membrane, a process that can occur either through diffusion or be mediated by proteins. Considerable evidence has accumulated to show that in addition to a diffusional component, the intestine, heart, adipose tissue, and the liver express a saturable and specific LCFA transport system. Identifying the postulated fatty acid transporters is of considerable importance, since both increased and decreased fatty acid uptake have been implicated in diseases such as type-2 diabetes and acute liver failure. Fatty acid transport proteins (FATPs/solute carrier family 27) are integral transmembrane proteins that enhance the uptake of long-chain and very long chain fatty acids into cells. In humans FATPs comprise a family of six highly homologous proteins, hsFATP1–6, which are found in all fatty acid-utilizing tissues of the body. This review will focus on a brief discussion of FATP expression patterns, regulation, structure, and mechanism of transport.

Keywords Fatty acid transport proteins · FATP · Solute carrier family 27 · Fatty acid uptake · Metabolism

Introduction

Uptake of unesterified long-chain fatty acids (LCFAs) into mammalian cells occurs through both a passive flip-flop as well as a saturable, protein-mediated mechanism. At physiological serum to albumin ratios the concentration of unbound fatty acids is low (7.5 nM) [31], and over 90% of the LCFA uptake into tissues such as adipocytes occurs via the saturable pathway [45]. Besides adipose tissue, other organs such as the intestine [16, 40], the liver [41], and the heart [35, 42] express a saturable and specific LCFA transport system [1]. Several membrane proteins that increase the uptake of LCFAs when overexpressed in cultured mammalian cells have been identified. The most prominent and best characterized of these are fatty acid translocase (FAT)/CD36 [6], long-chain fatty acyl-coenzyme A (CoA) synthetases (LACS) [5, 33], and fatty acid transport proteins (FATPs). This review will focus on FATPs, the solute carrier family 27.

Based on the presence of a FATP signature sequence, a 311-amino acid sequence highly conserved among FATP family members [9, 17] (Fig. 3A), six FATP genes have been identified in human and mouse genomes (FATP1–6) [2, 3, 11, 17, 32, 33, 36, 39, 46]. The phylogenetic relationship among the six human and murine family members is shown as an unrooted tree in Fig. 1. In addition to mammals, FATPs have been found in invertebrate genomes such as *Drosophila melanogaster* (three FATPs) and *Caenorhabditis elegans* (two FATPs). *Saccharomyces cerevisiae* expresses one FATP family member [17]. Interestingly, mycobacteria also express a protein highly homologous to mammalian FATPs [17]. To distinguish between the different species and FATP family members each FATP has a designated two-letter prefix indicating the species (mm, *Mus musculus*; hs, *Homo sapiens*; mt, *Mycobacterium tuberculosis*; dm, *D. melanogaster*; ce, *C. elegans*; sc, *S. cerevisiae*; etc.) and a number based on homology to the six human FATPs (or a roman letter for non-mammalian species).

The FATP family

mmFATP1 was the first family member identified [33] and is thus far the best studied. hsFATP1 is a 71-kDa transmembrane protein and is the major FATP in adipose tissue [33]. It is also found in heart and skeletal muscle [4,

A. Stahl (✉)
Research Institute, Palo Alto Medical Foundation,
Ames Bldg., 795 El Camino Real, Palo Alto, CA 94301, USA
e-mail: AStahl@Stanford.edu
Tel.: +1-650-6143293
Fax: +1-650-3299114

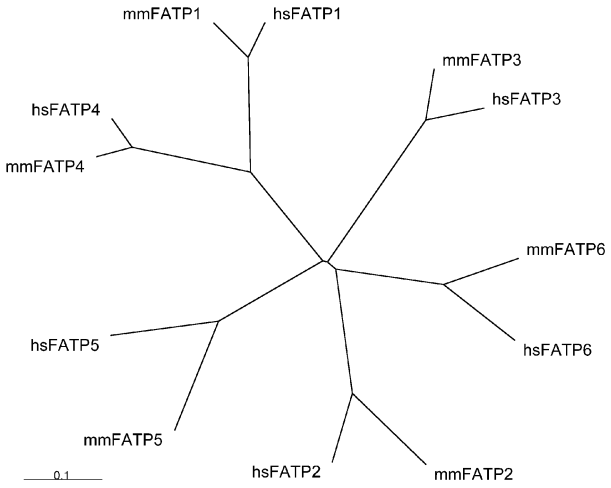

Fig. 1 Alignment of human fatty acid transport proteins (*FATPs*). Full-length protein sequences of all six human and murine FATPs were aligned using the Clustal algorithm. Based on the alignment, an unrooted phylogenetic tree was generated using TreeViewPPC. The *bar* indicates the number of substitutions per residue with 0.1 corresponding to a distance of 10 substitutions per 100 residues (*mm* Mus musculus, *hs* Homo sapiens)

17, 33]. FATP1 is an insulin-sensitive LCFA transporter. In adipocytes, insulin induces translocation of mmFATP1 from an intracellular perinuclear compartment, where it co-localizes with the insulin-sensitive glucose transporter, Glut4, to the plasma membrane [38] (Fig. 2A). Insulin-induced FATP1 translocation coincides with increased LCFA uptake [38], suggesting that hormonal regulation of FATP activity may play an important role in energy homeostasis. Interestingly, a study of 1144 French subjects showed that an A/G polymorphism in intron 8 of the FATP1 gene is associated with increased plasma triglyceride levels [26]. FATP2 is found almost exclusively in liver and kidney cortex [17]. Not much is currently known about FATP3. FATP3 shows a broader expression pattern with notably high mRNA and protein levels in the lung [17, 37]. This is of potential importance, since the pneumocytes in the adult lung rely on the acquisition of LCFAs to generate the dipalmitoylphosphatidylcholine and other phospholipids that constitute the pulmonary surfactant, a phospholipid-protein complex that prevents the collapse of the alveoli by reducing surface tension at the air-liquid interface [18]. FATP4 is the only FATP expressed in the small intestine, and is localized to the apical brush border of the epithelial cells (Fig. 2B), where it is responsible for absorption of dietary lipids. Studies with FATP4-over-expressing cell lines and with isolated enterocytes have demonstrated that FATP4 is both necessary and sufficient for efficient uptake of long-chain and very long chain fatty acids [36]. FATP4 and FATP1 are also the predominant FATPs in the brain [11]. FATP5 expression is exquisitely liver specific and transient over-expression mediates uptake of LCFAs [17]. FATP6 is expressed principally in the heart where it is the predominant FATP family member [15, 46]. Immunofluorescence microscopy of FATP6 in primate and murine hearts has revealed that the protein is exclusively located on the sarcolemma where it is restricted to areas of the plasma membrane juxtaposed to small blood vessels and colocalizes with CD36 [15] (Fig. 2C). The chromosomal location of all six human FATP genes is summarized in Table 1.

FATP structure and substrates

Hydropathy analysis of FATP sequences suggests multiple membrane-spanning domains. Based on the primary amino acid sequence, models with one to four transmembrane domains have been proposed [21, 32]. The exact number of transmembrane domains, however, is difficult to predict due to the hydrophobic nature of a protein that interacts strongly with fatty acids. More detailed analysis of the membrane topology of FATP1 has demonstrated that the protein has at least one transmembrane and

Table 1 SLC27—the fatty acid transport protein (FATP) family

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/ coupling ions	Tissue distribution and cellular/ subcellular expression	Link to disease	Human gene locus	Sequence accession ID	Splice variants and their specific features
SLC27A1	FATP1		Long-chain fatty acids	Unknown	Adipose tissue, muscle, brain, heart	Unknown	19p13.1		Unknown
SLC27A2	FATP2	VLACS	Long-chain fatty acids	Unknown	Kidney cortex, liver	Unknown	15q21.2	NM_003041	Unknown
SLC27A3	FATP3		Long-chain fatty acids	Unknown	Lung, multiple organs	Unknown	1q21.1	NM_024330	Unknown
SLC27A4	FATP4		Long-chain fatty acids	Unknown	Intestine, brain, adipose tissue, muscle	Unknown	9q34	NM_005094	Unknown
SLC27A5	FATP5	VLCS-H2	Long-chain fatty acids	Unknown	Liver	Unknown	19q13.4	NM_012254	Unknown
SLC27A6	FATP6	VLCS-H1	Long-chain fatty acids	Unknown	Heart	Unknown	5q23		Unknown

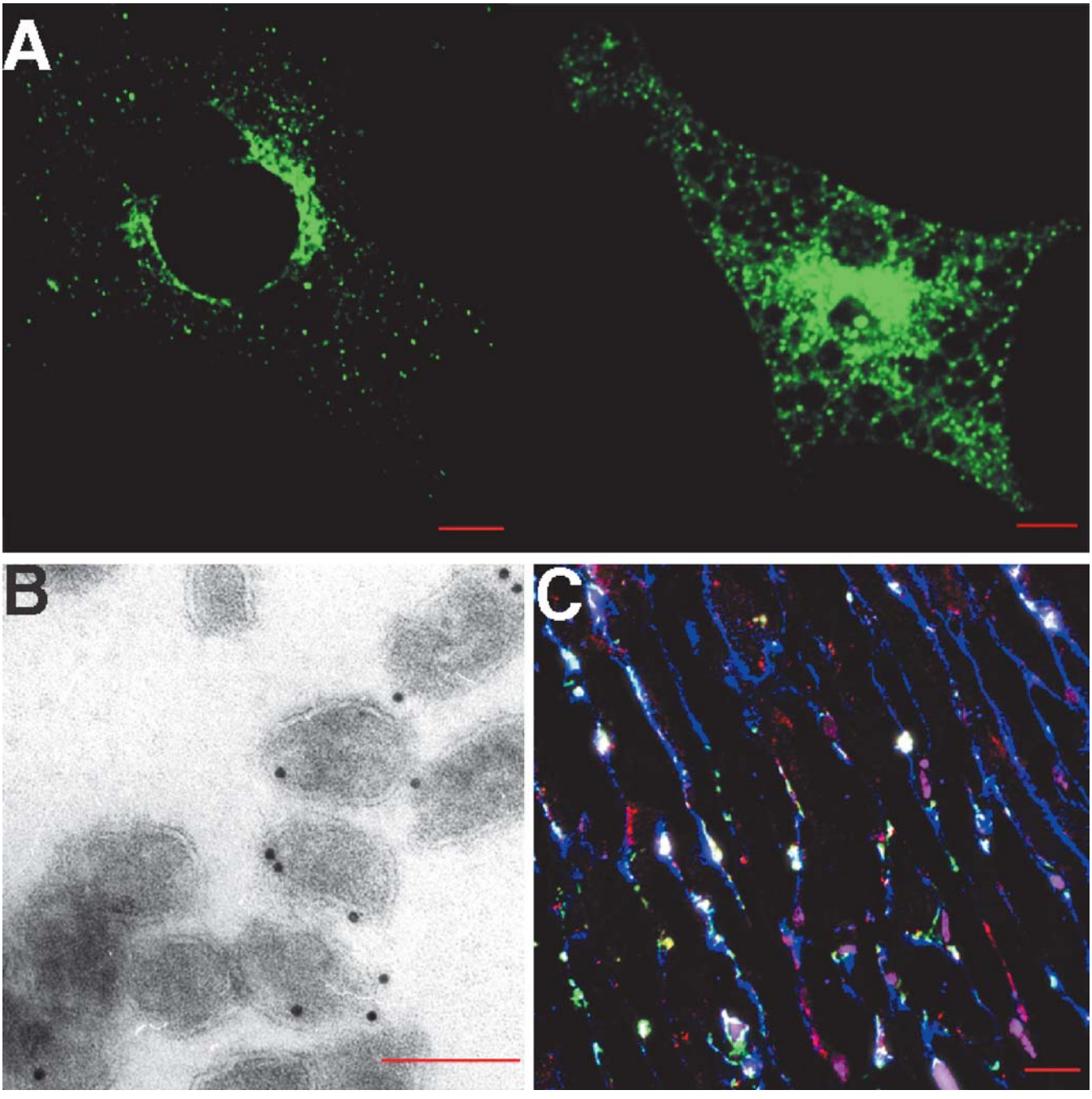

Fig. 2A–C FATP subcellular localization. **A** Serum-starved (*left*) adipocytes or cells treated for 1 h with 50 ng/ml insulin (*right*) were stained with antibodies for FATP1. A single *z*-section of a confocal image stack is shown [38]. **B** Localization of FATP4 by immuno-electron microscopy in cryo sections of murine ileum [36]. **C** Confocal fluorescent microscopy image of a thin section of mouse heart stained for FATP6 (*red*), CD36 (*green*), caveolin3 (*blue*), and DNA (*pink*). Color channels were scanned separately and digitally superimposed. Colocalization of FATP6, CD36, and caveolin3 is apparent in the *white areas* [15]

multiple membrane-associated domains [21] (Fig. 3A). Using epitope tags, the same group has shown that the amino terminus is located on the extracellular side, while the carboxy terminus faces the cytosol [21]. Based on overall sequence similarity [37] (Fig. 3B), it is likely that these basic observations will hold true for other FATP family members as well.

Recent studies using epitope-tagged versions of mm-FATP1 and protein fragments have revealed that FATP1 forms homo-dimeric, and possibly higher-order, complexes, most likely through interactions in the cytoplasmic loop between amino acids 191 and 475 [30] (Fig. 3A). It will be of great interest to determine whether other FATP family members also form homo-, and possibly, hetero-dimers.

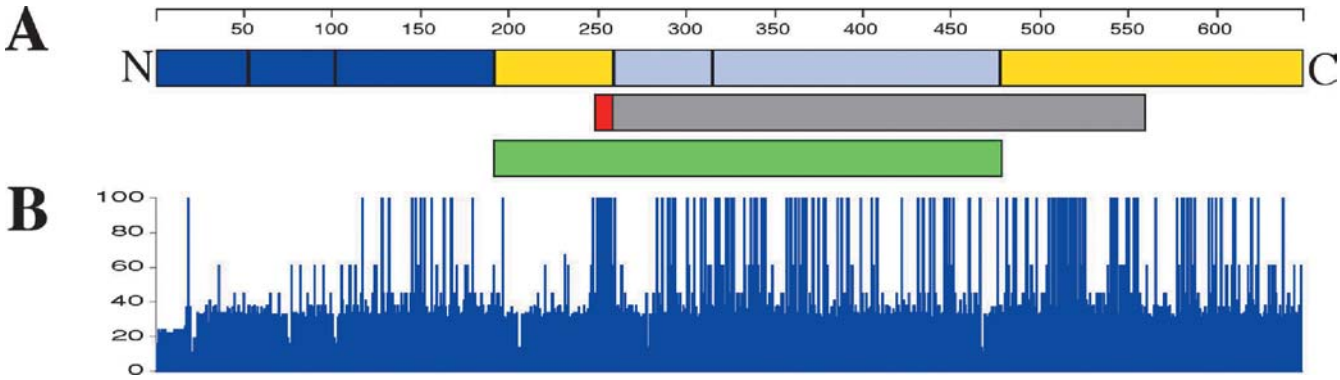

Fig. 3A, B Structure of FATP1. **A** Structural domains of FATP1. The N-terminus (*N*) is facing the outside of the cell while the C-terminus (*C*) is located in the cytoplasm. Protein fragments of amino acids 1–51, 52–100, and 101–190 (*blue*) contain signals for integral membrane association, while protein regions from residues 258–313 and 314–475 (*light blue*) mediate peripheral membrane association [21]. Additional domains indicated are, FATP signature sequence (*gray*) with AMP binding domain (*red*) [17] and a fragment containing the dimerization motif (*green*) [30]. **B** Percentage similarity of FATP1 residues aligned with FATP2–6

The most commonly used substrate in FATP-based uptake assays has been the fluorescent fatty acid analogue C1-Bodipy-C12, which mimics a LCFA. It was used for the expression cloning of FATP1 [33] as well as for the characterization of subsequent family members [17, 33, 36]. More detailed substrate studies based on ^{14}C-labeled fatty acids have been presented for FATP1 [33, 38] and -4 [36]. Uptake of fatty acids shorter than 10 carbon atoms, such as butyric and octanoic acids, is unaffected by FATP expression, while uptake of common long-chain fatty acids, such as palmitate and oleate, is robustly enhanced [33, 36]. Further substrate studies, based on the ability of unlabeled compounds to compete at a 20-fold molar excess with the uptake of C1-Bodipy-C12, have shown that saturated and unsaturated long- and very long chain fatty acids are transported by FATP4. In contrast, fatty acid esters as well as lipid-soluble vitamins do not compete [36].

Regulation of expression

Nutrients, hormones and cytokines reportedly regulate FATP expression. Rats fed a high-fat diet showed increase FATP expression in the heart but not the liver [29]. Several reports have shown positive regulation of mouse FATP by ligands that activate either peroxisome proliferator-activated receptor-γ (PPAR-γ), PPAR-α, or PPAR-γ/retinoid X receptor (RXR) heterodimers in hepatoma cell lines, the liver, and the intestine [24, 25, 28]. Further, a PPAR binding site has been identified in the murine FATP1 promoter [13]. Since fatty acids and their derivatives, such as prostaglandins, are ligands for PPARs [12], it is possible that a positive feedback loop regulates expression of FATPs, allowing cells to import LCFAs as long as they are present in the circulation. Surprisingly, the adipogenic hormone insulin reportedly increases LACS expression in adipocytes [19] but down-regulates FATP1 expression in the same cells [23]. However, no change of FATP1 protein levels in adipocytes are observed after an over-night insulin treatment [38]. Rather, insulin mediates rapid translocation of FATP1 from an intracellular compartment to the plasma membrane resulting in increased LCFA transport activity [38]. Tumor necrosis factor-α (TNF-α) is a negative regulator of FATP expression and down-regulates FATP mRNA in liver [27] and FATP1 and -4 proteins in adipocytes [38]. Interestingly, the adipocyte-secreted hormone-like protein adiponectin/adipocyte complement-related 30-kDa protein (ACRP30) has been linked to increased FATP1 expression in skeletal muscle but not in adipose tissue or liver [22].

Mechanism of transport

The mechanisms and requirements for LCFA uptake by FATPs are poorly understood. FATPs do not show any obvious similarities to other transporter families, and, thus far, the evidence for them being bona fide transporters is based predominantly on the observations that they are integral membrane proteins present on the plasma membrane of tissues involved in LCFA metabolism, and that LCFA uptake correlates directly with levels of FATP expression.

An AMP-binding sequence is found in all known FATPs at the beginning of the 300-amino acid-long FATP signature sequence [17] (Fig. 3A). The AMP-binding motive in FATP1 mediates ATP binding and is required for LCFA transport, since mutations within this motif abolish transport activity [43, 44]. Oligomerization also seems to be required for transport function, since co-expression of non-functional FATP1 mutants with wild-type FATP1 result in dominant negative inhibition of transport [30].

Based on the finding that both long-chain and very long chain acyl-CoA synthetase activities are increased in lysates from FATP over-expressing cells [39] and in partially purified FATP1 precipitates [7], it has been suggested that FATP mediated LCFA uptake is directly

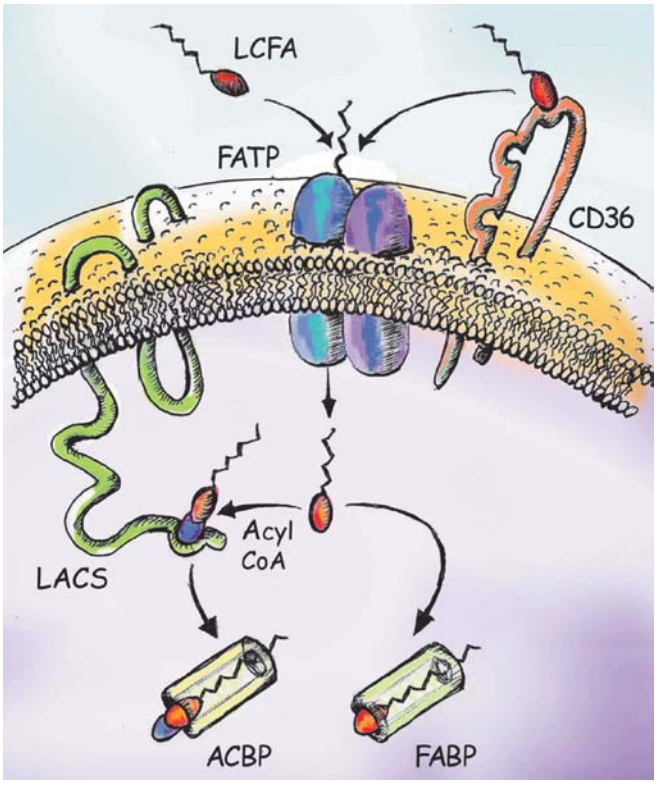

Fig. 4 A model for cellular fatty acid uptake. Extracellular long-chain fatty acids (*LCFAs*) might directly bind to FATP complexes (*blue*) and be transported into cells. Alternatively, LCFAs could bind first to CD36 (*yellow*), which hands on the LCFAs to FATP dimers. Intracellular LCFAs are coupled to coenzyme A (*CoA*) by long-chain fatty acyl-CoA synthetase (*LACS*, *green*), preventing their efflux, while fatty acid binding proteins (*FABPs*) act as a cytoplasmic buffer for incorporated LCFAs (*ACBP* acyl-CoA binding protein)

coupled to CoA activation of fatty acids [7]. However, recent studies of the yeast FATP gene (*Fat1*) have demonstrated that specific mutations in this gene can distinguish fatty acid import from acyl-CoA synthetase activity [47], indicating that the protein has dual independent functions. In bacteria, fatty acid uptake and activation to acyl-CoA are closely coupled and mediated by two independent genes, *FadL* and *FadD*, respectively [8]. It seems likely that a similarly linked system is found in eukaryotic cells to prevent the efflux of LCFA after uptake. Whether LCFAs are activated directly by FATPs or through closely associated acyl-CoA ligases remains to be determined. It is likely that in vivo, several proteins interact with FATPs to facilitate efficient uptake of fatty acids. In the heart, FATP6 colocalizes with CD36 [15], and other FATPs may interact in different organs with this protein as well. Besides FATPs, two other groups of proteins implicated in LCFA uptake, LACS and fatty acid binding proteins (FABP), have tissue specific isoforms [34] and could form organ specific complexes with FATPs. In accordance with this hypothesis, LACS are membrane-bound proteins and co-localize with FATP1 on the adipocyte plasma membrane [14]. Taking these possible interactions into account, we suggest the following model for LCFA uptake (Fig. 4). In addition to a usually small, diffusional component, LCFAs are either transported directly by FATP complexes across the plasma membrane or, alternatively, are first accumulated on the plasma membrane by binding to CD36, which subsequently hands the fatty acids on to FATPs. The latter scenario could be more important under conditions of low fatty acid-to-albumin ratios, where CD36 has been shown to be more effective in facilitating LCFA transport [10]. Following uptake, LCFAs would be activated rapidly by LACS to prevent efflux. Further, binding of intracellular LCFAs and acyl-CoA to FABPs and acyl-CoA binding proteins would facilitate the unloading of transporters and synthetases and act as an intracellular fatty acid buffer [20]. Clearly, much work remains to be done to determine the molecular mechanisms of FATP mediated fatty acid transport and the role of these proteins for energy homeostasis.

Acknowledgements I thank Dr. Allen D. Cooper and Mrs. Kathe O'Hearn for critical reading of this manuscript and valuable suggestions. This work was supported by a training and feasibility grant from the Digestive Disease Center, Stanford University and by a Beginning Grant-in-Aid from the American Heart Association (0265311Y).

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