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Characterization of a Heart-specific Fatty Acid Transport Protein*

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Fatty acids are a major source of energy for cardiac myocytes. Changes in fatty acid metabolism have been implicated as causal in diabetes and cardiac disease. The mechanism by which long chain fatty acids (LCFAs) enter cardiac myocytes is not well understood but appears to occur predominantly by protein-mediated transport. Here we report the cloning, expression pattern, and subcellular localization of a novel member of the fatty acid transport protein (FATP) family termed FATP6. FATP6 is principally expressed in the heart where it is the predominant FATP family member. Similar to other FATPs, transient and stable transfection of FATP6 into 293 cells enhanced uptake of LCFAs. FATP6 mRNA was localized to cardiac myocytes by *in situ* hybridization. Immunofluorescence microscopy of FATP6 in monkey and murine hearts revealed that the protein is exclusively located on the sarcolemma. FATP6 was restricted in its distribution to areas of the plasma membrane juxtaposed with small blood vessels. In these membrane domains FATP6 also colocalizes with another molecule involved in LCFA uptake, CD36. These findings suggest that FATP6 is involved in heart LCFA uptake, in which it may play a role in the pathogenesis of lipid-related cardiac disorders.

Under normal conditions 60–70% of the oxidative metabolism of the heart comes from the β-oxidation of fatty acids (1). Extraction of fatty acids complexed to albumin by the heart is very efficient, with as much as 70% of the LCFAs[1] from the blood entering the myocytes during a single transition through the cardiac capillary system (2). Albumin-bound fatty acids are generated in the heart from triglycerides contained in lipoprotein particles by the action of lipases. Lipoprotein lipase is bound to the luminal face of endothelial cells after secretion from the parenchymal cells of the heart (3). Unlike hepatocytes, which have direct contact with the blood, fatty acids in the heart must first traverse the endothelial cell barrier. It is unclear how the LCFAs in the blood are transported across the endothelial cells, but it is unlikely that the entire LCFA-albumin complex leaves the circulation, because albumin does not diffuse through the clefts between cardiac vascular endothelial cells in significant amounts (4). Once in the interstitial fluid between endothelial cells and myocytes, fatty acids are again bound to albumin and rapidly taken up by the muscle cells. Although it was originally believed that uptake of LCFAs into cardiac myocytes is purely mediated by diffusion across the sarcolemma (4, 5), later work has shown that transport is predominantly protein-mediated (6–9). A fatty acid transport protein (FATP) was identified by expression cloning from a murine adipocyte cDNA library as a protein that facilitates the uptake of LCFAs when overexpressed in adipocytes (9). This protein, later renamed FATP1 (10), is induced during adipocyte differentiation *in vitro* and is expressed in fat tissue and in the brain, heart, kidneys, and skeletal muscle but not the liver. Subsequently, we reported the discovery of a large family of FATPs characterized by the presence of an FATP signature sequence of 311 amino acids that is highly conserved among FATP family members (10, 11). FATP expression patterns include proteins exclusively or predominantly expressed in the liver, kidneys, small intestine, or in white adipose tissue (WAT). All FATPs are integral membrane proteins (12, 13), and detailed subcellular localization studies have been reported for FATP1 and FATP4. The intestinal FATP, FATP4, is localized to the apical side of enterocytes and mediates the uptake of dietary fatty acids (14). FATP1 is present in the heart but is also strongly expressed in adipose tissue where its subcellular localization can change on insulin stimulation from an intracellular perinuclear compartment to the plasma membrane (15). The mechanisms and requirements for LCFA uptake through FATPs are poorly understood. Acyl-CoA synthetase activity has been demonstrated for several FATPs (16, 17), and it has been suggested that this activity is required for transport. This notion has been challenged, however, by the recent observation that catalytic and transport activities of the yeast FATP homologue, FAT1, can occur independently (18).

In addition to FATPs, two other proteins have been implicated in myocardial LCFA uptake: the cytoplasmic heart-specific fatty acid-binding protein and CD36. The strongest support for the role of these proteins comes from data demonstrating that in both heart-specific fatty acid-binding protein (6) and CD36 (19) null mice cardiac fatty acid uptake and use is substantially reduced.

Here we show that a novel member of the FATP family, FATP6, is a functional fatty acid transporter with a heart-specific expression pattern. Further, FATP6 localizes to the sarcolemma of cardiac myocytes juxtaposed with blood vessels where it colocalizes with CD36. This fact suggests that a novel mechanism may exist for the uptake of LCFAs into cardiac myocytes using FATP6, thus potentially implicating the molecule in a broad range of physiological and pathological cardiac functions.

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[1] The abbreviations used are: LCFA, long chain fatty acid; FATP, fatty acid transport protein; hsFATP, *Homo sapiens* FATP; mmFATP, *Mus musculus* FATP; GST, glutathione *S*-transferase; WAT, white adipose tissue.

EXPERIMENTAL PROCEDURES

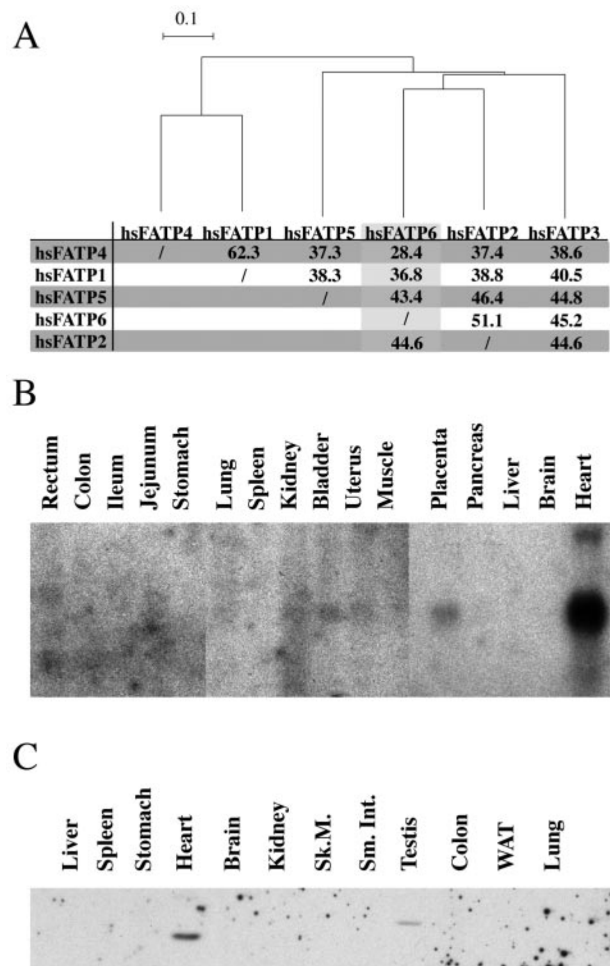
Fatty Acid Uptake Assays—Clones encoding human FATP6 were identified by a search of public data bases for sequences similar to murine FATP1–5 coding regions using the BLASTX algorithm (20). A DNA fragment containing the entire hsFATP6 coding sequence was inserted into the mammalian expression vectors pMet7 or pIRES-neo (Clontech) for transient and stable transfections, respectively. Transient transfection assays were performed as described previously (10). For stable transfections, cells that had taken up the DNA were selected with 1 mg/ml G418 (Invitrogen). BODIPY-fatty acid uptake assays using a fluorescence-activated cell sorter and ^{14}C-labeled fatty acid uptake assays were performed as described previously (10, 14).

In Situ Hybridization—Human heart samples were obtained from the University of Pittsburgh Medical Center. *In situ* hybridizations were performed essentially as described previously (14). Briefly, paraformaldehyde-fixed dehydrated sections were hybridized with ^{35}S-radiolabeled (5×10^7 cpm/ml) cRNA probes generated from the open reading frame of FATP6. After hybridization, slides were washed and dehydrated. To detect the localization of mRNA transcripts, the slides were dipped in Kodak NBT-2 photoemulsion and exposed for 7 days at 4 °C followed by development with Kodak Dektol developer. Slides were counterstained with hematoxylin and eosin and photographed. Controls for the *in situ* hybridization experiments included the use of a sense probe, which showed no signal above background in all cases.

Northern Blotting—Human mRNA blots were obtained from Clontech. Blots were probed with ^{32}P-labeled DNA probes generated by PCR from the 5′-untranslated region of FATP6 using the Rapid-Hyb buffer (Amersham Biosciences).

Immunofluorescence Microscopy—Unfixed rhesus monkey or mouse heart was washed with Hanks' buffered salt solution containing 1 mM EDTA, infused with 2.3 M sucrose solution, and embedded in O.C.T. 4583 compound. The material was cut into thick sections (15–40 μm). The sections were washed in phosphate-buffered saline containing 1% bovine serum albumin, 10% fetal calf serum, and 1% normal donkey serum to block nonspecific binding. Primary and secondary antibodies were diluted in blocking solution and incubated for 1 h. The sections were mounted in 90% glycerol/phosphate-buffered saline containing 1 mg/ml paraphenylinediamine and examined with a Zeiss LSM10 confocal system.

Antibodies—Anti-FATP6 serum was raised by immunization of rabbits with the last 90 C-terminal amino acids fused to GST. Serum was affinity-purified over protein A columns and found to have minimal cross-reactivity against other FATP family members. Monoclonal anti-caveolin 3 antibodies and anti-CD31 were purchased from BD Biosciences. The anti-CD36 monoclonal antibody was a generous gift from Dr. Maria Febbraio.



	hsFATP4	hsFATP1	hsFATP5	hsFATP6	hsFATP2	hsFATP3
hsFATP4	/	62.3	37.3	28.4	37.4	38.6
hsFATP1		/	38.3	36.8	38.8	40.5
hsFATP5			/	43.4	46.4	44.8
hsFATP6				/	51.1	45.2
hsFATP2				44.6	/	44.6

FIG. 1. **FATP6 is a heart-specific FATP.** *A*, alignment of human FATPs. Full-length protein sequences of all six human FATPs were aligned using the Clustal algorithm in the DNA Star MegAlign program. The calculated percent identity is shown. Full-length FATP sequences were independently aligned using ClustalX to generate a phylogenetic tree, which was plotted using TreeViewPPC. The *bar* indicates the number of substitutions per residue with 0.1 corresponding to a distance of 10 substitutions/100 residues. *B*, FATP6 expression pattern. Northern blot analysis of human FATP6 expression was performed using human tissue poly(A) mRNA blots (Clontech). The probe was generated from the 5′-untranslated region of hsFATP6. *C*, tissue Western blot. Equal amounts of mouse organ lysates (10 μg/lane) were separated by electrophoresis on 8–16% gradient gels, blotted, and probed with an FATP6-specific antiserum. The apparent molecular mass of the FATP6 signal is 70 kDa.

RESULTS

Cloning and Chromosomal Localization of FATP6—We initially reported the 3′ sequence of a sixth human FATP gene using BLAST screens of FATP1 against the NCBI public data bases (10). Using the known 3′ FATP6 sequence, we screened public data bases of human expressed sequence tags and identified a full-length cDNA for FATP6. The cDNA clone was confirmed by sequencing and was found later to be identical to a cDNA sequence deposited in GenBank™ as VLCS-H1 (AF064254). The FATP6 cDNA encodes for a 619-amino acid protein with a predicted molecular weight of 70.1 kDa. Alignments of the full-length FATP6 protein with the full-length sequences of all other known human FATPs were done using the ClustalW algorithm. Fig. 1*A* shows that FATP6 is a member of the FATP family and is most closely related to FATP2 (51.1% identity). FATP6 is part of a larger group including FATP5 and FATP3 that is clearly distinct from the FATP1 and FATP4 genes (Fig. 1). Using radiation hybrid mapping, we localized hsFATP6 to human chromosome 5q23 (D5S1896). hsFATP6 sequence and localization was also confirmed by the human genome project, which showed that the coding region of the gene is distributed over 10 exons spanning 67 kb on chromosome 5q. Using alignments of hsFATP6 against the translated mouse genome, we were able to identify a murine homologue (mmFATP6). The mmFATP6 protein is 78% identical to hsFATP6 and is also encoded in 10 exons spanning 55.6 kb on mouse chromosome 18.

FATP6 Expression Is Heart-specific—An FATP6-specific probe from the 5′-untranslated region of the gene was used to detect its expression pattern using Northern blot analysis of human tissue mRNAs. FATP6 was strongly expressed in heart but was absent from the lung, spleen, brain, rectum, colon, liver, muscle, stomach, ileum, jejunum, and pancreas (Fig. 1*B*). Moderate levels of FATP6 (approximately 20–40 times lower than in the heart by densitometric quantification of Northern blot data) were found in the placenta (Fig. 1*B*), testis, and adrenal glands (data not shown). FATP6 mRNA was present at very low levels in kidney, bladder, and uterus (Fig. 1*B*). A tissue Western blot of 12 murine organs revealed that mmFATP6 is predominantly expressed in the heart in this species (Fig. 1*C*). Weak mmFATP6 expression was observed in the testis (Fig. 1*C*).

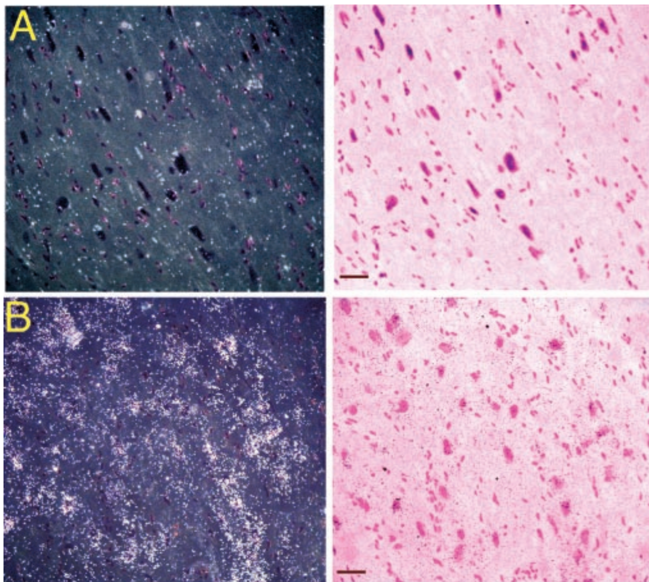


FIG. 2. **FATP6 is localized in cardiac myocytes by *in situ* hybridization.** Dark field (*left panels*) and phase contrast (*right panels*) of *in situ* hybridization of human heart sections with either a sense control (*A*) or with an FATP6-specific antisense probe (*B* and *C*) is shown. *Bar* represents 200 μM.

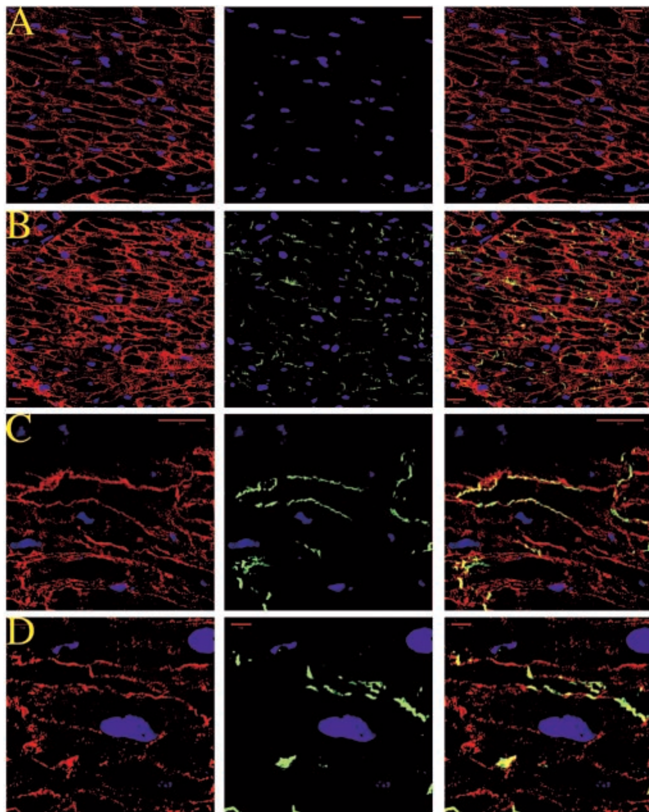


FIG. 3. **FATP6 is localized on the sarcolemma.** Fresh-frozen rhesus monkey heart sections were stained with either anti-caveolin 3 antibodies (*left panels*) or FATP6- specific anti-serum (*middle panels*), and an overlay projection is shown in the *right panels*. *A*, caveolin 3 and FATP6 antisera were preincubated with FATP6-GST fusion proteins. The *bar* represents 20 μM. *B* and *C*, sections were stained with caveolin 3 and FATP6 antisera. The *bar* represents 20 μM. *D*, sections were stained with caveolin 3 and FATP6 antibodies. *Bar* represents 5 μM.

FATP6 Is Expressed by Cardiac Myocytes—To identify the cell type that expresses FATP6, *in situ* hybridizations were performed with human heart sections. A sense probe showed only a very low background signal (Fig. 2*A*), whereas the corresponding FATP6-specific antisense probe showed a strong signal with silver grain accumulations over cells identified by morphology as cardiac myocytes (Fig. 2*B*).

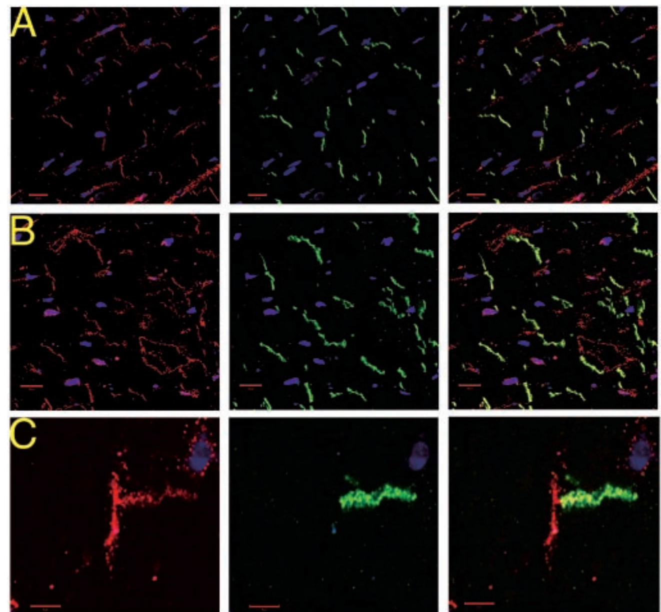
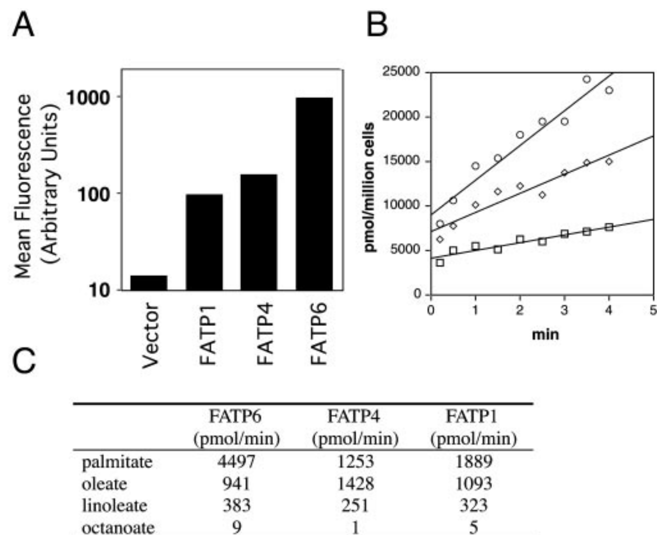


FIG. 4. **FATP6 is localized adjacent to blood vessels.** Fresh-frozen rhesus monkey heart sections were either stained with anti-CD31 antibodies (*left panels*) or an FATP6-specific antiserum (*middle panels*), and an overlay projection is shown in the *right panels*. The *bar* represents 20 μM in *A* and *B* and 5 μM in *C*.

Localization of the FATP6 Protein to Cardiac Plasma Membrane Specializations—To further study the subcellular localization of FATP6, we raised an antiserum against the C-terminal portion of FATP6. Sections of rhesus monkey hearts were co-incubated with anti-FATP6 serum and anti-caveolin 3 antibodies (Fig. 3). Caveolin 3 is highly expressed by cardiac myocytes and was used as a plasma membrane marker (21). Confocal microscopy showed FATP6 in virtually all cardiac myocytes (Fig. 3, *middle panels*). Staining was FATP6-specific, because preincubation of the FATP6 and caveolin 3 antisera with the FATP6 fusion protein antigen abolished FATP6 but not caveolin 3 staining (Fig. 3*A*). At higher magnifications (Fig. 3, *C* and *D*), FATP6 protein was found almost exclusively on the sarcolemma. Unlike the caveolin 3 staining, however, FATP6 was not evenly distributed along the membrane but was concentrated in shorter segments. Myocytes derive most of their LCFA from the interstitial space adjacent to the microcapillaries. To test whether FATP6 was concentrated on sarcolemma sections in the direct vicinity of blood vessels, we costained heart sections with FATP6 and a marker for endothelial cells, CD31 (Fig. 4, *left panels*). FATP6 expression was clearly observed in the areas directly adjacent to the microvasculature, whereas expression was absent in the areas of larger blood vessels (Fig. 4, *A* and *B*). This expression pattern was apparent at higher magnifications as shown in Fig. 4*C*, where a small branch of a blood vessel is surrounded by FATP6 expression on the myocytes above and below the blood vessel. This expression pattern is consistent with a role of FATP6 in the uptake of LCFAs from the interstitial space into cardiac myocytes.

FATP6 Mediates the Uptake of Long Chain Fatty Acids—To confirm that FATP6, like the other FATP family members, facilitates the uptake of long chain fatty acids, we transiently transfected COS cells with mammalian expression vectors containing either FATP1, FATP4, or FATP6 into 293 cells (Fig. 5*A*). Transfected cells were identified by CD2 cotransfection, and uptake of BODIPY-labeled LCFA was determined as de-

scribed previously (10, 14). Stable cell lines overexpressing FATP6 were generated by the transfection and selection of 293 cells. Initially, approximately 30 independent FATP6 clones were isolated. However, the cell lines with the highest uptake rates lost the ability to take up fatty acids after a few generations possibly because of fatty acid toxicity. Uptake of ^{14}C-labeled oleate by one of the stable FATP6 cell lines with intermediate uptake rates is shown in Fig. 5*B* along with uptake by cells stably expressing FATP1 or the expression construct alone. Fig. 5, *A* and *B*, demonstrates that overexpression of FATP6 can indeed increase uptake of LCFAs. We further tested the substrate preference of hsFATP6 in comparison with hsFATP4 and hsFATP1 using stably transfected cell lines (Fig. 5*C*). Interestingly, FATP6 and FATP1 had a higher preference for palmitate and linoleate compared with FATP4, the major intestinal LCFA transporter (Fig. 5*C*). As expected, none of the FATPs tested increased the uptake of fatty acids with chain length shorter than C10 (Fig. 5*C*).



	FATP6 (pmol/min)	FATP4 (pmol/min)	FATP1 (pmol/min)
palmitate	4497	1253	1889
oleate	941	1428	1093
linoleate	383	251	323
octanoate	9	1	5

FIG. 5. **FATP6 transports long chain fatty acids.** *A*, 293 cells were cotransfected with mammalian expression vectors pCDNA-CD2 either alone (control) or in combination with one of the FATP-containing expression vectors (pMET7-hsFATP1, pMET7-hsFATP4, or pMET7-hsFATP6). BODIPY-fatty acid uptake assays were performed as described under "Experimental Procedures." *Bars* represent the mean BODIPY-fatty acid fluorescence of CD2-positive cells. *B*, the rate of ^{14}C-oleate uptake by 293 cells, stably expressing either hsFATP6 (*diamonds*) or hsFATP1 (*circles*), was compared with that of cells containing the vector with no insert (*squares*). *C*, specific uptake of different fatty acid substrates by 293 cell lines stably expressing human FATP6, FATP4, or FATP1. The uptake rates in pmol/min/million cells after subtraction of background are shown. Background uptake was measured using a 293 cell line that stably expressed pcDNA 3.1 without inserted cDNA. Uptake of palmitate, oleate, linoleate, and octanoate by the control cell line was 564, 662, 640, and 0 pmol/min/million cells, respectively. All fatty acids were at a 50 μM final concentration.

FATP6 Is the Predominant FATP in the Heart—Because both FATP1 and FATP6 are expressed in the heart, we wanted to compare their overall abundance. To this end, we performed Western blots with equal amounts of WAT and heart lysates from mice next to titrations of known amounts of FATP1 or FATP6 antigen. The blots were probed with FATP1 and FATP6 sera, respectively, and signals were quantitated by densitometry. FATP6 was absent from WAT but was robustly expressed in the heart. FATP1 was more than 10 times more abundant in WAT than in the heart (Fig. 6). After calibrating the Western blot signals to the antigen titrations, we were able to directly compare the FATP1 and FATP6 signals in the heart (Fig. 6*B*). FATP1 was expressed at ~100 pg/ml heart lysate (1 mg/ml total protein), whereas FATP6 was more than 20 times (2139 pg/mg lysate) more abundant (Fig. 6*B*), which indicates that FATP6 is the predominant FATP in the heart.

FATP6 Colocalizes with CD36 on the Myocyte Membrane—Because both FATP6 and CD36 are plasma membrane proteins that have been implicated in the uptake of LCFAs into cardiomyocytes, we wanted to test a possible interaction between these proteins. To this end, we stained sections of mouse hearts with antibodies against FATP6 (*red channel*), CD36 (*green channel*), caveolin 3 (*blue channel*) and a DNA-specific dye (4′,6-diamidino-2-phenylindole, *pink channel*). As in sections of primate hearts, murine FATP6 was present in subregions of

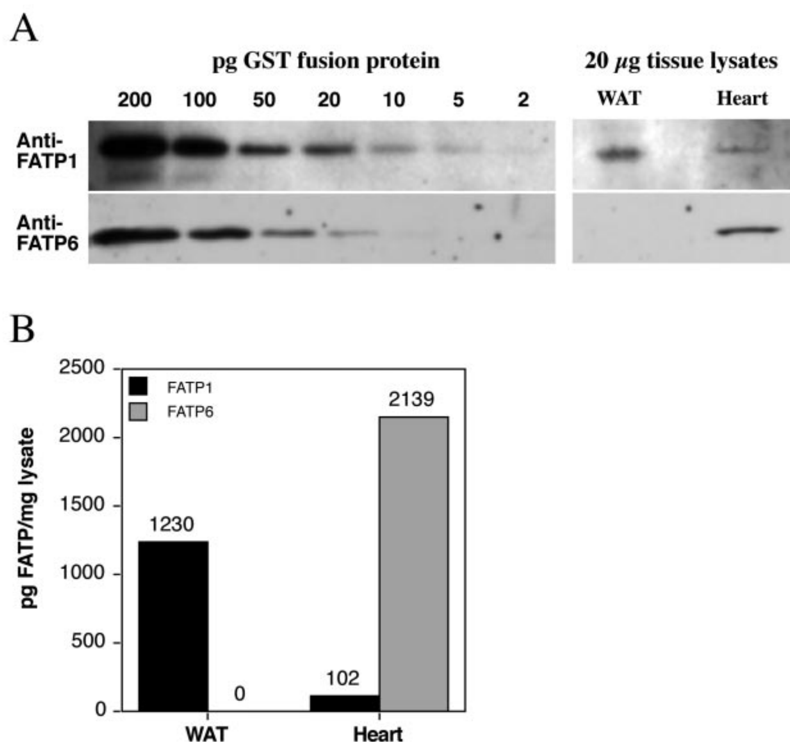


FIG. 6. **FATP6 is the predominant FATP in the heart.** *A*, the indicated amounts of FATP1-GST fusion protein (*upper row*), FATP6-GST fusion protein (*lower row*), mouse WAT, or mouse heart were separated by PAGE and blotted with FATP6 or FATP1 antibodies. All blots were exposed on the same film. *B*, ECL signal strength of the GST fusion titrations for FATP1 and FATP6 were determined by densitometry and plotted as a function of protein amount (not shown). Linear regressions from these plots were used to calculate protein amounts for FATP1 and FATP6 in the adipose tissue and heart lysates expressed as picogram of antigen per milligram of lysate.

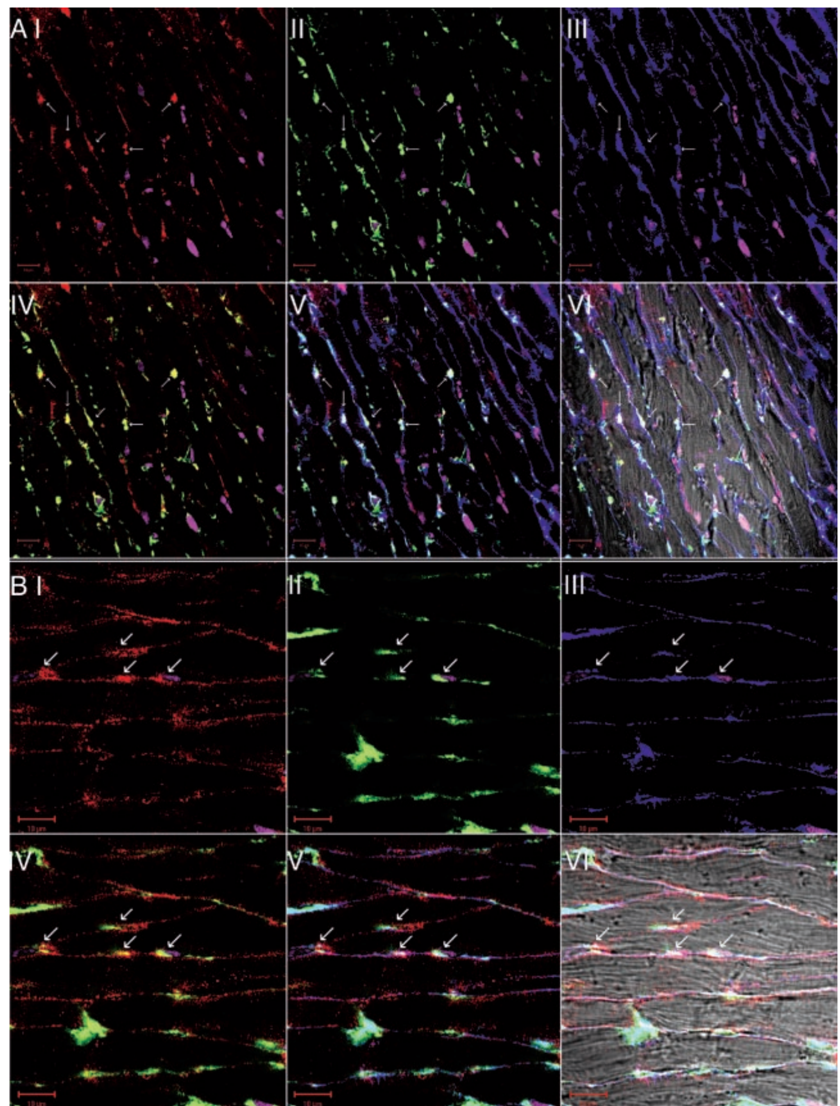


FIG. 7. **FATP6 partially colocalizes with CD36.** Thin sections of mouse hearts were stained for FATP6 (*I*), CD36 (*II*), and caveolin 3 (*III*). Two different magnifications (*A* and *B*) are shown (*bars* represent 10 μM). Colocalization between FATP6 and CD36 shows as *yellow* in the superimposition of *sections I* and *II*. Superimposition of all three channels without (*V*) or with a bright field image (*VI*) shows colocalization of FATP6, CD36, and caveolin 3 (*arrows*) in the *white* areas.

the plasma membrane (Fig. 7, *A*, *panel I* and *B*, *panel I*). Staining of the same sections with an anti-CD36-specific monoclonal serum showed a similar staining pattern (Fig. 7, *A*, *panel II*, and *B*, *panel II*), with streaks on the sarcolemma and pronounced globular aggregates (Fig. 7, *white arrows*). In contrast, caveolin 3 was evenly distributed along the plasma membranes of all myocytes (Fig. 7, *A*, *panel III*, and *B*, *panel III*). The overlay of FATP6 and CD36 signals (Fig. 7, *A*, *panel IV*, and *B*, *panel IV*) showed that FATP6 was distributed somewhat more broadly along the sarcolemma. Significant colocalization of FATP6 with CD36 was most apparent in the globular aggregates (Fig. 7, *white arrows*). The overlay of FATP6, CD36, and caveolin staining (Fig. 7, *A*, *panel V*, and *B*, *panel V*) showed further that all three molecules are present in these membrane specializations (Fig. 7, *white arrows*) as indicated by the appearance of the white areas. These data provide evidence suggesting that members of the FATP family may interact with CD36.

DISCUSSION

Fatty acids are a major source of energy for cardiac myocytes, and changes in fatty acid metabolism have been implicated in cardiac disease. The mechanism by which fatty acids from the interstitial space enter myocytes is not well understood, but it has been proposed that the bulk of this uptake occurs via protein-mediated transport (6–9). Here we report the cloning and characterization of a novel member of the fatty acid transport protein family, termed FATP6, in humans and mice. Heart muscle expresses other FATP family members, most notably FATP1 as well as FATP6. FATP6 is heart-specific, however, whereas FATP1 is expressed in a variety of other organs including adipocytes, skeletal muscle, and the brain (9, 10, 22). Further supporting the notion that FATP6 is the predominant cardiac FATP is our finding that the protein is more than 20 times more abundant than FATP1 in mouse heart lysates. The heart also has a very distinct uptake pattern of fatty acids and shows, in contrast with WAT, a preference for palmitate compared with oleate (23). Interestingly, this trend is reflected by the LCFA uptake pattern of the FATP6-stable cell line, which is consistent with the idea that a significant part of the cardiac LCFA uptake is mediated by FATP6.

Amino acid sequence comparisons of the FATP family show that human FATP6 is most closely related to hsFATP2, a fatty acid transporter predominantly expressed in the liver and kidneys. FATP2 is the homologue of a rat gene previously identified by others as a very long chain acyl-CoA synthase (24). This notion was subsequently challenged by the finding that FATP2 can function as a fatty acid transporter (10). It is unlikely that FATP6 is a peroxisomal very long chain acyl-CoA synthase, because our immunofluorescence studies of FATP6 distribution in cardiac myocytes clearly demonstrated that FATP6 is almost

exclusively localized to the plasma membrane of cells. However, the mechanism by which FATPs transport LCFAs across phospholipid bilayers is poorly understood, and long chain as well as very long chain acyl-CoA activities have been demonstrated for several mammalian FATP and yeast FATP (16, 17). Therefore, the possibility that uptake is coupled to CoA activation of LCFA, either directly by FATPs or by a closely associated long-chain acyl-CoA synthetase, cannot be excluded (13). In this context, it is noteworthy that recent studies of the yeast FATP homologue FAT1 (18) have demonstrated that specific mutations in FAT1 can distinguish the fatty acid import from the very long chain acyl-CoA synthetase activities. Zou *et al*. (18) noted that two mutations (S258A and D508A) greatly diminished long chain and very long chain acyl-CoA synthesizing activity and that these residues are conserved in FAT1 and FATPs 1 through 5. Alignment of murine and human FATP6 sequences with the other family members shows that both residues are also conserved in FATP6 (data not shown), which suggests that these mammalian proteins could also function as LCFA transporters in the absence of catalytic activity. Most importantly, direct measurements of long chain (C16:0) and very long chain (C24:0) acyl-CoA activity of hsFATP6 by Steinberg *et al.* (25) showed no activity above background when the protein was overexpressed in COS-2 cells. Combined with the data presented here, this finding demonstrates clearly that acyl-CoA activity is not required for FATP6-mediated LCFA uptake.

FATP6 is exclusively targeted to areas of the sarcolemma that are directly juxtaposed to microvasculature. This characteristic of FATP6 contrasts with the insulin-sensitive glucose transporter Glut4, which on translocation to the sarcolemma is evenly distributed on the plasma membrane (26), and possibly reflects the faster diffusion rate of glucose compared with albumin-bound LCFAs.

Although FATP overexpression alone leads to an increase in LCFA uptake, it is likely that *in vivo* several proteins interact to facilitate efficient uptake of fatty acids in the heart. In addition to FATPs, several other proteins have been implicated in LCFA uptake by cardiac myocytes, most notably CD36 and fatty acid-binding proteins, and it has been suggested that these proteins may interact to facilitate efficient LCFA uptake (13). Here we demonstrate for the first time that FATPs are in close physical proximity to CD36 on the plasma membrane. This fact supports the idea that scavenger receptors may help to sequester LCFAs on the plasma membrane and subsequently pass them on to FATPs for uptake.

Changes in heart fatty acid metabolism have been linked to various cardiac disorders, especially cardiac hypertrophy (27) and ischemic injury (28). Although normal hearts use fatty acids as their primary energy source, hearts of patients with cardiac hypertrophy rely on glucose metabolism accompanied by a dramatic decrease in fatty acid oxidation (27, 29). Deletion of the genes involved in fatty acid use in the heart has in fact been shown to cause cardiomyopathy (6, 30). Fatty acid use can interfere with recovery from ischemic injury, and agents that block fatty acid oxidation, such as etomoxir and dichloroacetate, improve the recovery of contractile function after ischemic injury in rats (28). A recent study comparing FATP1 expression levels in healthy hearts with hearts from patients with cardiomyopathy found no changes in mRNA levels for this transporter (31). FATP6 expression was not measured, however. It will be of great interest to determine whether FATP6 is altered during the development of cardiac abnormalities and whether overexpression or inhibition of the transporter can affect cardiac disease.

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