

# Structural and functional analysis of fatty acid-binding proteins

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**Abstract** The mammalian FA-binding proteins (FABPs) bind long-chain FA with high affinity. The large number of FABP types is suggestive of distinct functions in specific tissues. Multiple experimental approaches have shown that individual FABPs possess both unique and overlapping functions, some of which are based on specific elements in the protein structure. Although FA binding affinities for all FABPs tend to correlate directly with FA hydrophobicity, structure-function studies indicate that subtle three-dimensional changes that occur upon ligand binding may promote specific protein-protein or protein-membrane interactions that ultimately determine the function of each FABP. The conformational changes are focused in the FABP helical/portal domain, a region that was identified by in vitro studies to be vital for the FA transport properties of the FABPs. Thus, the FABPs modulate intracellular lipid homeostasis by regulating FA transport in the nuclear and extra-nuclear compartments of the cell; in so doing, they also impact systemic energy homeostasis.—Storch, J., and L. McDermott. Structural and functional analysis of fatty acid-binding proteins. *J. Lipid Res.* 2009. 50: S126–S131.

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The family of cytoplasmic FA-binding proteins (FABPs) evolved by successive gene duplications generating a large number of tissue specific homologs. The mammalian family includes nine FABPs, the cellular retinoid binding proteins, and a newly discovered retinal form whose ligand binding properties are not known (1, 2). Tissues with high rates of FA uptake and lipid metabolism have high expression of one or more FABPs. The large diversity of FABPs, which contrasts sharply with other lipid-binding proteins, has long been suggestive of functional specialization. It is now clear that there are both unique and overlapping functions for specific FABPs (2). In this brief review, we will focus on those functions of different FABPs where the

structural elements that may underlie these functions are beginning to be understood.

Despite modest amino acid sequence homologies, the FABPs exhibit very similar tertiary structures. Their 10 anti-parallel  $\beta$ -strands are organized into 2 nearly orthogonal  $\beta$ -sheets that form a slightly elliptical  $\beta$ -barrel, with 2 8-10 residue helices linking the first 2  $\beta$ -strands (3, 4) (Fig. 1A). The helix-turn-helix motif, from which the ligand-binding cavity extends, is thought to act as a portal for FA access and egress (3), with the  $\alpha$ -II helix forming long-range interactions with the  $\alpha$ -II turn between  $\beta$ -strands C and D.

The FABP binding cavity is considerably larger than its ligand (3). All the FABPs bind FA with its carboxylate group oriented inside the cavity, interacting with interior Arg residues and other side chains (5). Solution structures of apo FABPs reveal specific regions of disorder in the portal domain, compared with holo-FABP structures (5, 6). Thus, it is likely that a conformational change in the portal region occurs during FA binding or release. FABP-membrane interactions or protein-protein interactions may catalyze this conformational change.

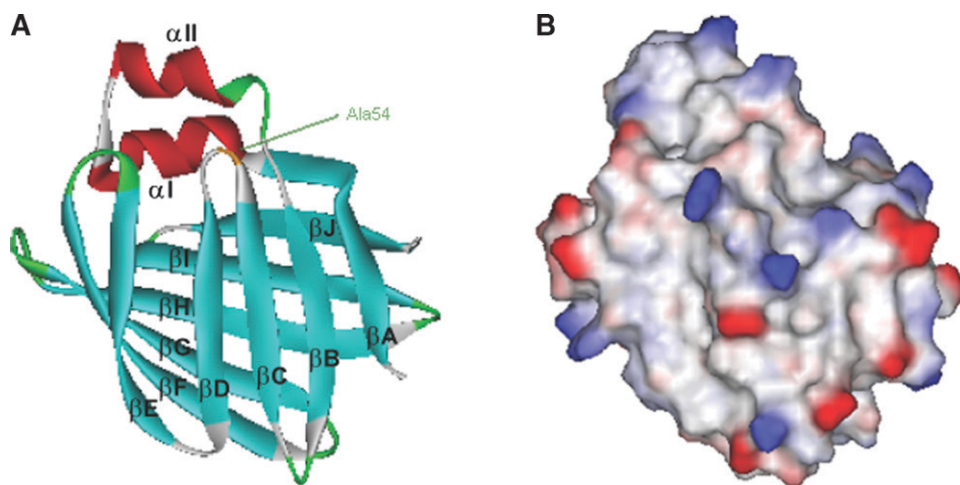
Despite its similar fold, the liver FABP (LFABP) alone can bind an additional FA, as well as other larger hydrophobic molecules (6). All FABPs bind both saturated and unsaturated long-chain ( $\geq 14$ C) FA. Binding affinity values obtained using the ADIFAB method indicate dissociation constant ( $K_d$ ) values in the nanomolar range. None of the FABPs show a distinct specificity for a particular FA, and the binding affinities for all FABPs correlate directly with FA hydrophobicity (7). Thus, a paradox is apparent:

Abbreviations: AFABP, adipocyte FA-binding protein; CRABP II, cellular retinoic acid binding protein II; DHA, docosahexaenoic acid; DKO, double knockout; FABP, FA-binding protein; HFABP, heart/muscle FA-binding protein; IFABP, intestinal FA-binding protein; HSL, hormone-sensitive lipase; KFABP, keratinocyte FA-binding protein; LFABP, liver FA-binding protein; NLS, nuclear localization signal; PPAR, peroxisome proliferator activated receptor; RA, retinoic acid; RAR, retinoic acid receptor.

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**Fig. 1.** NMR-derived structure of human IFABP (3IFB) (5). Structures generated with Accelrys DS Visualizer ([www.accelrys.com](http://www.accelrys.com)). A: Flat ribbon structure; Ala<sup>54</sup> is highlighted in yellow. B: Solvent surface colored by electrostatic potential, probe radius 1.4 Å. Blue: positively charged; red: negatively charged; white: neutral residues.

why are there multiple FABPs if their ligand binding capacities and specificities, with LFABP as a possible exception, are roughly the same? We hypothesize that unique functional properties of individual FABPs may be dictated in large part by structural characteristics of the proteins' surfaces rather than strictly by ligand binding specificity.

In vitro studies have shown that different FABPs transfer FA to membranes by two different transfer mechanisms. LFABP transfers ligand to and from membranes by aqueous phase diffusion (8). In marked contrast, a larger number of the FABPs, including the adipocyte, keratinocyte, intestinal, brain, myelin, and heart/muscle types, transfer their FA by directly interacting with a membrane (8). Evaluation of the structural elements underlying the two in vitro transfer mechanisms has identified the FABP helix-turn-helix/portal domain as the major determinant of its FA transfer mechanism (2, 8). Protein-membrane interactions are supported by the net positive surface electrostatic potential across the portal region of collisional FABPs (9) and the amphipathic character of their  $\alpha$ -I helices in particular (2, 9) (Fig. 1B).

As the physiological roles of individual FABPs have begun to emerge in recent years, it is becoming possible to link their functional properties with an understanding of the structural characteristics that underlie their mechanisms of action. As with the in vitro FA transfer studies, the available data point to the helix-turn-helix/portal region of the FABPs as a critical domain determining many of the functions of this diverse family of proteins. In the following sections, the structure-function relationships that appear to define specific functions of different FA-binding FABPs will be discussed.

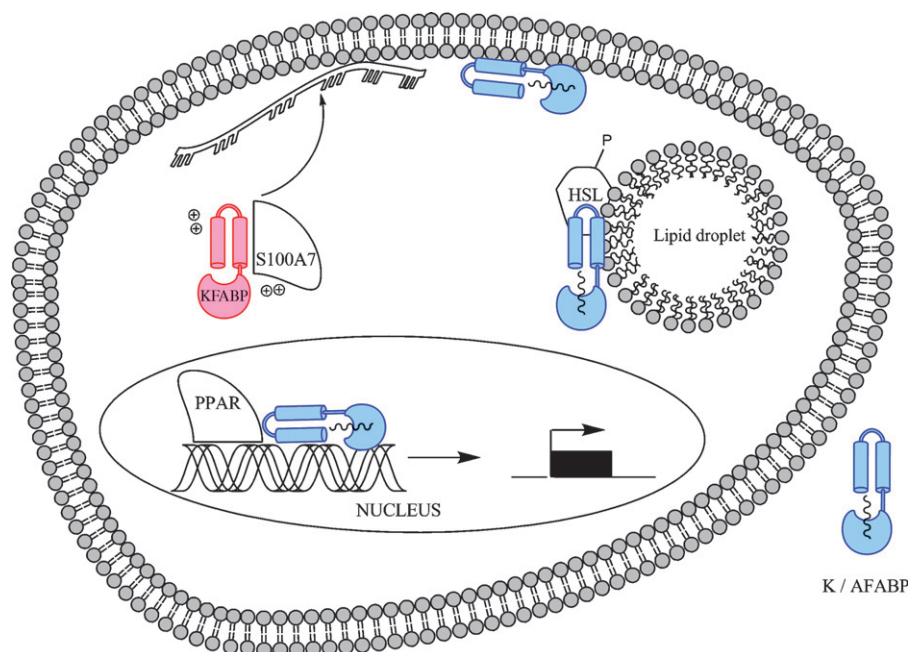
#### AFABP (ADIPOCYTE-TYPE FABP; FABP4)

Adipocyte FABP (AFABP) and the keratinocyte FABP (KFABP) are both expressed in adipocytes and macrophages. AFABP is in far greater abundance in fat cells, while

equivalent levels of AFABP and KFABPs are found in macrophages. Described below (and in Fig. 2) are similarities in the regulation and function of AFABP and KFABPs; individual properties of KFABP are described thereafter.

Both AFABP and KFABPs transfer FA to membranes via collisional interaction (8). Basic residues in the helix-turn-helix domain of AFABP, in particular K21 and K31, were identified as vital for the collisional transfer process (10). AFABP interacts with hormone-sensitive lipase (HSL) and K21 is required for interaction (11). HSL phosphorylation, oleic acid binding by AFABP, and charged residues in AFABP's  $\alpha$ -helical domain (D17, D18, and R30) are also necessary for HSL interaction (12). These four portal residues are conserved in KFABP, which also interacts with HSL, but not in intestinal FABPs (IFABPs) and LFABPs, which do not (12). Mutagenesis studies show that D18 on AFABP forms an ion pair with K196 on HSL, and K21 on AFABP interacts with E193 on HSL (12).

The phenotypes of AFABP, KFABP, and combined AFABP/KFABP null mouse models have provided clues to their cellular and systemic functions. While the individual gene knockouts showed only modest effects, mice null for both A and KFABPs were found to be strongly protected against insulin insensitivity and hepatic steatosis (2, 13). Recently, a comparison of lipid profiles from wild-type and double knockout (DKO) mice showed that adipose tissue and plasma from DKO had elevated levels of the MUFA palmitoleate (16:1 $\Delta$ 9) (14). When 16:1 $\Delta$ 9 and the saturated palmitate (16:0) were directly compared by incubation with cultured hepatocytes and myocytes and by systemic infusion into mice, the results suggested that adipose-derived 16:1 $\Delta$ 9 could regulate metabolic pathways in liver and muscle, leading to the protection of DKO mice from metabolic syndrome symptoms. This is an interesting possibility, and additional studies, particularly comparing 16:1 $\Delta$ 9 to the other major product of  $\Delta$ 9 desaturation by stearoyl CoA desaturase-1, oleate (18:1 $\Delta$ 9), will further indicate the unique properties of the FABP ligand, 16:1 $\Delta$ 9. Based on an evaluation of the binding affinities of 7 FABP



**Fig. 2.** AFABP and KFABP demonstrate unique and overlapping functions. KFABP interacts with the calcium binding protein S100A7 in the presence of divalent cations and relocates to peripheral membrane adhesion-like structures. The helical portal domains of A and KFABPs allow for direct interact with membranes, HSL, and PPARs (see text for details).

types for 19 different FA, including 16:1 $\Delta$ 9, it is not evident that 16:1 $\Delta$ 9 would have an unusual interaction with AFABP (7). As noted earlier, FA binding affinities correlate with ligand hydrophobicity; thus, 16:1 $\Delta$ 9 and 18:1 $\Delta$ 9 have lower affinities than their immediate precursors 16:0 and 18:0, and 6 other FAs were found to have dissociation constants within 2-fold of that found for 16:1 $\Delta$ 9 (7). However, as discussed below, specific ligands that do not differ in affinity may nevertheless result in functionally important structural alterations on the FABP surface.

Three isoforms of peroxisome proliferator activated receptors (PPARs),  $\alpha$ ,  $\beta$ , and  $\gamma$ , are important regulators of lipid metabolism and energy homeostasis. AFABP was shown to selectively enhance the activity of PPAR $\gamma$ , and KFABP of PPAR $\beta$ . Green fluorescent protein-labeled A and KFABPs move to the nucleus in specific response to ligands for PPAR $\gamma$  and PPAR $\beta$ , respectively, and direct AFABP:PPAR $\gamma$  and KFABP:PPAR $\beta$  interactions were demonstrated. The tertiary structures of AFABP bound to PPAR $\gamma$  ligands troglitazone and linoleic acid revealed stabilized AFABP conformations in which three nonadjacent, basic portal residues were exposed: K21 on helix  $\alpha$ I and R30 and K31 on  $\alpha$ II. Together, these form a nuclear localization signal (NLS). In contrast, AFABP complexed with oleate or stearate, ligands that do not activate PPAR $\gamma$ , did not show a stable NLS (15). Furthermore three nonadjacent leucine residues (L66, L86, and L91), positioned close to junctions of turn elements connecting the  $\beta$ -sheets, form a nuclear export signal in the tertiary structure (16).

These studies indicate that FABP functional properties are not governed by FA binding properties alone, as the

binding of specific ligands to A or KFABPs causes subtle conformational changes in their portal surfaces, allowing for specific functional interactions to occur. It will be of interest to determine whether 16:1 $\Delta$ 9 causes distinct surface structural changes that could account for its suggested function as an FABP-modulated lipid mediator.

#### KFABP (KERATINOCYTE-TYPE FABP; FABP5; EFABP, CFABP)

In addition to adipocytes and macrophages, KFABP is expressed in skin, liver, brain, lung, and cancerous tissue (2) and appears to play tissue-specific roles in each.

KFABP binds retinoic acid (RA) with a  $K_d$  of  $\sim$ 35 nM, similar to its binding affinity for FA (17), and this observation has implications for its suggested role in cancer. RA inhibits cell growth by binding to the nuclear RA receptor (RAR); however, it can also promote cell growth by binding to and activation of PPAR $\beta$ / $\gamma$  (17). The underlying mechanism of these divergent RA effects are related to interactions of RAR and PPAR $\beta$ / $\gamma$  with FABPs: RA delivery to either PPAR $\beta$  or  $\gamma$  or RAR is determined by the ratio of KFABP-cellular RA binding protein II (CRABP II), with a high KFABP-CRABP II ratio leading to RA activation of PPAR $\beta$ / $\gamma$  and a low ratio to RAR activation (18). Using a RA-resistant mouse model of breast cancer, it was shown that decreasing the KFABP-CRABP II ratio in mammary tissue diverted RA from PPAR $\beta$ / $\gamma$  to RAR and suppressed tumor growth (18).

KFABP is distinguished from other members of the FABP family by a large number of cysteine residues, and



it has been suggested to play a role in regulating the cellular redox state (19). In murine KFABP, Cys 120 and 127 form a disulphide link within the ligand binding cavity and are positioned in close proximity to the bound FA hydrocarbon chain. It has been shown that Cys120 can be covalently modified by 4-hydroxynonenal, a lipid produced in response to oxidative stress and aging (20), suggesting that KFABP functions as an antioxidant protein by scavenging reactive lipids through covalent modification of Cys120 (20).

KFABP has been shown to form a divalent cation-dependent complex with S100A7, a calcium-regulated signaling protein (21). In cultured keratinocytes, coexpression of S100A7 and KFABP resulted in the protein-protein complex relocating from the cytoplasm to peripheral adhesion-like structures upon addition of calcium (21). The functional significance of these observations and the structural basis for the KFABP-S100A7 interaction are unknown.

### LFABP (LIVER-TYPE FABP; FABP1)

LFABP has been hypothesized to be involved in lipid absorption by the enterocyte and in hepatocyte lipid transport and lipoprotein metabolism. Its unique binding and surface characteristics are likely to contribute to its specific functional properties.

In contrast to the stoichiometric binding of long-chain FA by other FABPs, LFABP binds two FA, one in a manner similar to other FABPs, with the carboxylate moiety interacting with R122, S124, and S39 in the internal binding cavity, and the second with its carboxyl group interacting with K31 and S56 located near the protein surface in the portal region (6). Binding of the second surface ligand is unique to LFABP, and binding of the internal FA precedes binding of the second (22). The binding affinities of the two FA sites are similar for saturated fatty acids, but the internal site has approximately 10-fold higher affinity for unsaturated FA than the surface site (23). LFABP also binds a variety of other small hydrophobic ligands such as lysophospholipids, heme, and vitamin K (8). The accommodation of these alternative ligands is at least in part attributable to the larger cavity volume of LFABP relative to other FABPs (24).

LFABP is the only FA-binding member of the mammalian FABP family to transfer FA to membranes by aqueous diffusion. Studies with chimeric FABPs show that the helix-turn-helix domain of LFABP can impart a diffusional mechanism of FA transfer to the binding pocket of an otherwise collisional FABP (2, 8). This can be attributed in large part to the fact that neither  $\alpha$ -helix of LFABP is amphipathic. LFABP does, however, associate with membranes to a limited extent in cells, perhaps indicating protein-protein interactions. Several studies have revealed a partial nuclear localization for LFABP (25). Furthermore, direct interactions with PPAR $\alpha$  have been reported, and PPAR $\alpha$  transactivation by FA was found to be directly correlated with cellular LFABP concentration (25). Thus, it is possible that the regulation of gene expression is a common function of the FABP family. At present, the structural basis of putative

LFABP-PPAR interaction has not been determined, and the NLS-forming residues identified on A and KFABPs are not conserved in LFABP.

LFABP null mice show both tissue-specific and secondary effects, as with other FABP knockout models. Little or no compensation with IFABP or other FABPs occurs in LFABP null mice, underscoring unique functions for these proteins. *Lfabp*<sup>-/-</sup> mice show a defect in fatty acid  $\beta$  oxidation, which is likely to represent a defect in FA transport, because no relevant changes in gene expression are found (26, 27). Moreover, while wild-type mice developed fatty liver on a high-fat diet or following fasting, the *Lfabp*<sup>-/-</sup> mice were protected from hepatic steatosis in both situations (26, 27). The protection occurred only when the diet was high in saturated FA, however, but not when a high PUFA diet was fed (28). This divergence may not be related to ligand binding properties, because LFABP has increased specificity for binding unsaturated rather than saturated FA. Taken together, the results indicate that LFABP may be involved in partitioning of FA to specific lipid metabolic pathways.

An important function of LFABP in chylomicron biogenesis is suggested by decreased postprandial lipid secretion in *Lfabp*<sup>-/-</sup> mice (27) and by cell-free studies of intestine, where LFABP was shown to be essential for the budding of prechylomicron transport vesicles from the endoplasmic reticulum (29).

### IFABP (INTESTINAL-TYPE FABP; FABP2)

Small intestinal enterocytes express both I and LFABPs. The clear differences in ligand binding properties and FA transfer mechanisms are based on several structural differences between the two FABPs. The volume of the binding cavity of IFABP is <50% of the LFABP cavity (24) as a result of bulkier side chains that protrude into the ligand pocket, contributing to the strict specificity of IFABP for long-chain FA and not other endogenous lipid molecules (6). The collisional mechanism of FA transfer between IFABP and membranes has been shown by mutagenesis to be determined in large part by electrostatic interactions between positively charged lysines in the helical domain of the protein and negative charges of phospholipid membranes; Lys residues in the  $\alpha$ -II segment are of particular importance (2).

*Ifabp*<sup>-/-</sup> mice exhibited, under certain circumstances and with an apparent gender dimorphism, increased serum triacylglycerol levels, greater weight gain, hepatic steatosis, and insulin resistance relative to wild-type mice (30). This phenotype supports a role in intestinal lipid processing and indicates that IFABP may be protective against development of the metabolic syndrome. A polymorphism in the human IFABP gene resulting in an Ala to Thr substitution at residue 54 is associated with obesity, decreased insulin sensitivity, elevated serum leptin levels, and dislipidemias in several populations (31), providing additional support for a role in energy assimilation and the metabolic syndrome. Thr<sup>54</sup>-IFABP binds FA with greater affinity than

the predominant Ala<sup>54</sup> form, yet Thr<sup>54</sup> homozygous subjects displayed higher serum FA levels after eating (8, 32). Thus, the higher FA binding affinity does not translate into reduced lipid export from the enterocyte, suggesting perhaps a more specific role for IFABP in FA targeting. Residue 54 in IFABP, in the turn between  $\beta$ -strands C and D, is part of the ligand portal domain, forming long-range interactions with the  $\alpha$ -II helix (Fig. 1B). Comparative solution structures of the Ala<sup>54</sup> and Thr<sup>54</sup> forms demonstrate that structural alterations occur only in the locale of the substitution, with the larger side chain of Thr likely reducing the rate of dissociation of FA from the binding pocket; hence, the higher affinity (4). What remains unknown is how this structural and binding alteration in IFABP might be preventive of the systemic metabolic syndrome.

#### OTHER FABPS

Structural understanding of the potential functions of other FABPs is limited. In vitro FA transfer from the heart/muscle FABP (HFABP; FABP3; MDGI) to membranes is collisional, with the helical/portal region a key determinant of its ligand transfer mechanism (8). That HFABP functions in the transport and metabolism of FA is clear from the phenotype of the *Hfabp*<sup>-/-</sup> mouse, which shows reduced FA uptake into the heart and reduced muscle FA oxidation (2).

Incubation of mammary epithelial cells with HFABP inhibited cell proliferation, and ectopic expression of HFABP in breast cancer cells reduced their tumorigenicity in nude mice, indicating a role for HFABP in cell growth and differentiation (33). It has been proposed that the structural element responsible for these HFABP effects is the C-terminal undecapeptide of the protein. When expressed in breast cancer cell lines, this 11-residue peptide, which comprises the  $\beta$ -J strand of HFABP, reduced colony formation in vitro and tumor growth in inoculated nude mice (34). This implies that such effects of HFABP may be entirely independent of their FA ligand.

While brain development and morphology in the BFABP null mouse are normal (35), *N*-methyl-D-aspartate receptor activity in response to the  $\omega$ 3 FA docosahexaenoic acid (DHA) was decreased, and diminished DHA content was found in BFABP<sup>-/-</sup> brain (35). DHA is found in high concentrations in brain, and initially BFABP was reported to have a 40-fold greater affinity for DHA than for arachidonate, an  $\omega$ 6 FA; subsequent reports showed either much lesser specificity or no difference in affinity between DHA and 20:4 (7). As noted, however, equilibrium binding properties may not be solely predictive of FABP function. It was suggested that the structural basis of any specificity for DHA may be due to an interior Phe residue at position 104, which interacts with the unsaturated bonds in the DHA chain (36).

The myelin P2 protein (also designated as FABP8, MFABP) is unique in having been shown to be an extrinsic membrane protein; thus, its membrane interaction properties, seen to some extent with all collisional transfer FABPs are likely to

be substantial and may dictate its function in peripheral nerve myelin (8).

#### SUMMARY

The FABPs function in intracellular lipid homeostasis, thereby also affecting systemic lipid metabolism. Individual FABPs possess unique and overlapping functions that are generally related to transport and metabolism of long-chain FA. Elegant structure-function studies of A and KFABPs suggest that subtle three dimensional changes that occur upon ligand binding may promote specific FABP-protein or FABP-membrane interactions that ultimately determine the particular function of the FABP. The conformational changes are focused in the FABP helical/portal domain, a region that was identified by in vitro studies to be crucial for the FA transport properties of specific FABPs. **EB**

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