TISSUE-SPECIFIC FUNCTIONALITY IN THE FABP (FATTY ACID-BINDING PROTEIN) FAMILY[#]

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Running head: Tissue-specific FABP functions

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The fatty acid-binding proteins (FABPs) are abundant intracellular proteins expressed in almost all tissues. They exhibit high affinity binding of a single saturated or unsaturated long-chain fatty acid (LCFA; $\geq$14 carbons), with the exception of the liver FABP, which binds two fatty acids or other hydrophobic molecules. Despite only moderate amino acid sequence homology they have highly similar tertiary structures consisting of a 10-stranded anti-parallel β-barrel and N-terminal helix-turn-helix motif. Research emerging in the last decade has suggested that the FABPs have tissue-specific functions that reflect tissue-specific aspects of lipid and fatty acid metabolism. Proposed roles for the FABPs include the assimilation of dietary lipids in the intestine via targeting to specific metabolic pathways and biogenesis of chylomicrons; targeting of liver lipids to catabolic and anabolic pathways; the regulation of lipid storage and release, and lipid-mediated gene expression in adipose tissue and macrophages; fatty acid targeting to β-oxidation pathways in muscle, and the maintenance of phospholipid membranes in neural tissues. The regulation of these diverse processes is reflected by the expression of different and sometimes multiple FABPs in these tissues, and may be driven by protein-protein and protein-membrane interactions.

The fatty acid-binding proteins (FABPs) are abundant intracellular proteins expressed in almost all tissues; nine separate genes for FABPs have been identified in mammals. FABPs were named after the tissue in which they were discovered or are prominently expressed. This nomenclature can be misleading since several FABPs are expressed in more than one tissue, and a numerical nomenclature for the various FABPs has been introduced (1-6). All FABPs exhibit high affinity binding of a single saturated or unsaturated long-chain fatty acid (LCFA; $\geq$14 carbons), with the exception of liver FABP (LFABP, FABP1), which binds two fatty acids or other hydrophobic molecules. Binding affinities correlate directly with fatty acid hydrophobicity (1-6). These small proteins (~15 kDa) show only moderate amino acid sequence homology, ranging from 20%-70%, yet they have highly similar tertiary structures. All have in common a 10-stranded anti-parallel β-barrel structure which is formed by two orthogonal five-stranded β-sheets (Figure 1). The ligand-binding pocket is located inside the β-barrel, and is framed on one side by the N-terminal helix-turn-helix motif, consisting of two short α-helices between the first two β-strands, that is thought to act as the major portal for LCFA entry and exit (1-6).

Why are there multiple FABPs, then, when all have a similar fold and all bind LCFA? Other classes of lipid-binding proteins are, typically, ubiquitously expressed from a single gene. As will be discussed below, recent research has suggested that the FABPs have individual functions in their specific tissues. While all FABPs are involved in fatty acid disposition, it is likely that the diverse nature of fatty acid function is reflected in the diversity of FABP expression in different tissues. These divergent functions may be driven, in part, by protein-protein and protein-membrane interactions that are tissue specific. This review

will present currently held hypotheses regarding the functions of FABPs in different tissues, evaluating the evidence obtained from culture cells, structure-function analyses, and gene knockout mice.

Tissue specific FABP functions:

Adipose tissue

Adipose tissue has long been known as a key organ of energy homeostasis, being the major reservoir of stored calories in the form of triacylglycerol (TG). It has become increasingly apparent that adipose tissue is also an important endocrine organ, releasing many bioactive small molecules, including numerous cytokines involved in inflammation (7). Adipose tissue metabolism, therefore, has important effects on systemic energy metabolism and inflammatory processes. Adipocytes express very high levels of the adipocyte FABP (AFABP, FABP4) and very low levels of the skin-type FABP (KFABP, FABP5). Studies of AFABP support a role in both the TG storage and inflammatory functions of the adipose tissue. Ablation of AFABP expression results in marked compensatory upregulation of KFABP expression (1,2), and is accompanied by relatively minor metabolic alterations in the adipose tissue, with small or no effects on TG hydrolysis or lipid synthesis processes observed (1,2). In vitro, AFABP and KFABP display similar ligand specificity and similar mechanisms for the transport of fatty acids to membranes, and these functional similarities are likely to underlie the mild phenotype observed in AFABP null adipose tissue (1,2). Simultaneous deletion of both FABPs, however, reveals their importance in maintaining systemic energy balance, with double-null animals displaying a marked protection against the development of insulin resistance and the metabolic syndrome, and against a variety of inflammatory diseases (2).

The molecular mechanisms by which AFABP and KFABP function in adipose tissue are emerging, and studies to date point to multiple areas of potential involvement. AFABP has been shown to interact with the hormone-sensitive lipase (HSL), with charged residues in the helix-turn-helix domain of AFABP interacting with oppositely charged residues on HSL. While a role in stimulating lipolysis by relieving lipase end-product inhibition was initially proposed, only the apo-AFABP was found to interact with HSL. Moreover, the AFABP-HSL complex is present in both cytosol, where HSL is inactive, and on the surface of lipid droplets, when the lipase is active (1).

AFABP may also function in the adipocyte by regulating the fatty acid species abundance in plasma, thus impacting systemic metabolism. Higher levels of the low-abundance palmitoleate were reported in adipose tissue and plasma of AFABP/KFABP double-null mice, and incubation of cultured liver and muscle cells with palmitoleate, in comparison to the saturated palmitate (PA; C16:0), led to changes consistent with protection against insulin resistance(8). The mechanism of palmitoleate action, and a direct comparison of palmitoleate with oleate (OA; C18:1 ω9), remains to be investigated (1).

AFABP may also function in adipose tissue at the level of gene transcription. Structure-function studies have shown that AFABP binding of specific ligands leads to subtle conformational changes in the helical domain that promote nuclear localization via importins, and subsequent binding to the nuclear transcription factor PPARγ. Nuclear localization and PPARγ interaction occur only for those ligands that activate PPARγ target gene transcription, while non-activating ligands, though still binding to AFABP, do not cause nuclear localization (2,9).

Macrophages

Unlike adipose tissue, differentiated macrophages express high levels of both AFABP and KFABP, and KFABP expression in the macrophage remains unchanged following AFABP ablation, suggesting that the two proteins are likely to have distinct functions in this tissue. Macrophage-specific knockdown of AFABP in the ApoE deficient mouse has been shown to offer dramatic protection against the development of diet-induced atherosclerosis, even though animals remain hypercholesterolemic (1,2).

It is likely that alterations in inflammatory cytokine production underlie the beneficial effects of AFABP knockdown, and several mechanisms are under investigation. Recently it was demonstrated that macrophage inflammatory

responses leading to cytokine production via c-Jun N-terminal kinase (JNK) and activator protein-1 (AP1) require AFABP, whose transcription is in turn mediated by JNK (10). AFABP has also been shown to be necessary for macrophage endoplasmic reticulum (ER) stress response to inflammatory signals including lipid accumulation (11). As mentioned above, KFABP as well as AFABP, has been shown to exhibit a subtle conformational change in the helical domain that reveals a cryptic nuclear localization signal upon binding of a PPAR-activating ligand, resulting in translocation and PPAR-mediated transcriptional activation (2,9). Direct interaction of AFABP with JAK2 has also been reported and, similar to HSL interaction in the adipocyte, involves charged residues in the AFABP helix-turn-helix domain and requires fatty acid binding. Functional consequences of this interaction are inferred from alterations in JAK2 (Janus-activated kinase 2) signaling in macrophages from AFABP$^{-/-}$/KFABP$^{-/-}$ mice (12).

Muscle

LCFA contribute a large portion of the energy required in cardiac muscle, in skeletal muscle at rest, and to varying degrees in skeletal muscle during exercise (13). The major FABP in muscle tissues is heart FABP (HFABP, FABP3).

HFABP expression is up-regulated during cardiomyocyte differentiation and associated with the inhibition of cardiomyocyte proliferation. A marked decrease in PA oxidation was observed in HFABP null cardiac muscle, although β-oxidation capacity was not affected, suggesting that HFABP is required for LCFA transport to maintain efficient mitochondrial β-oxidation. HFABP ablation also causes a dramatic switch in cardiac fuel selection from LCFA to glucose, resulting in reduced tolerance to exercise and cardiac hypertrophy in older animals. HFABP null mice displayed alterations in both cardiac LCFA uptake and esterification into TG and phospholipids (PL) (5). Relative levels of PA were increased in the heart PL pool relative to the neutral lipid pool. While arachidonic acid (AA, C20:4 ω6) incorporation into both TG and PL was decreased, the phosphatidylinositol and phosphatidylserine pools were not affected, thus implying that HFABP plays a role in trafficking fatty acids into specific PL pools that may be linked to lipid-mediated signal transduction (5). There were no compensatory increases in expression of other FABPs in HFABP$^{-/-}$ cardiomyocytes, indicating that HFABP function is unique in this cell type (5).

The up-regulation of HFABP expression during skeletal muscle differentiation is correlated with increased utilization of LCFA for both β-oxidation and esterification (3,5). HFABP null mice showed a decrease in the rate of muscle fatty acid uptake, however the skeletal muscle had an increased mitochondrial density compared to wild-type and could therefore maintain efficient utilization of fatty acids (3,5). Unlike the dramatic increase in glucose oxidation in cardiac muscle, glucose oxidation can be either increased or inhibited in HFABP null soleus muscle depending on physiological conditions that may be related to the TG content of the muscle tissue, thus the effects of HFABP loss are not as acute in the skeletal as compared to cardiac muscle (3;5).

The positive effects of HFABP on LCFA utilization have been proposed to occur at the substrate level, to enhance LCFA supply to β-oxidation and lipid synthesis pathways; and also at the regulatory level, by interacting with allosterically modulated enzymes as well as transcription factors (5). Studies have shown that the HFABP α-helical domain is involved in the transfer of LCFA from HFABP to acidic membrane domains, in a process requiring transient collisional interactions between HFABP and membranes, and it has been suggested that similar interactions could take place between HFABP and acidic peptide domains to facilitate protein-protein interactions, as have been observed between HFABP and plasma-membrane LCFA transporters (6,13). HFABP may also interact with peroxisome proliferator-activated receptor α (PPARα), a nuclear receptor, to induce the expression of mitochondrial and peroxisomal β-oxidation pathways (6,14).

Nervous system

Neural membrane PL containabundant long-chain polyunsaturated fatty acids (PUFA) such as docosahexaenoic (DHA) and AA, as well as saturated PA, components that have been linked to brain development and function. In addition, fatty acids and their metabolites are involved in

intracellular signaling, neurotransmission, and the regulation of gene transcription. Given the multiplicity of cell types and of LCFA functions in the nervous system, it is perhaps not surprising that multiple FABPs are also found. The central nervous system (CNS) expresses HFABP in the adult brain, while brain FABP (BFABP, FABP7) and KFABP are detected mainly in the pre- and peri-natal brain, respectively, with lower levels of expression in the adult brain. In contrast, myelin FABP (MFABP, Myelin P2, FABP8) is only found in the peripheral nervous system (PNS) (15,16). The expression of these four different FABPs in nerve tissues, each with distinct spatio-temporal distributions, suggests that they differentially moderate the actions of LCFA on specialized brain functions (16).

In human brain the concentration of HFABP is ≥ 10 times higher than that of BFABP in each part of the brain (16,17), suggesting that HFABP expression may be associated with the maintenance of the differentiation status of adult brain cells (16,17). Studies with HFABP null mice have shown that HFABP expression is necessary to maintain the $\omega 6/\omega 3$ PUFA balance in adult brain cells through the uptake and utilization of AA, and that decreased HFABP expression lowers the incorporation of AA into brain phospholipids, in particular phosphatidylinositol. Thus, HFABP appears to play a role in directing AA to specific classes, as well as in maintaining the steady state levels of AA in these phospholipids (18). An imbalance in the $\omega 6/\omega 3$ ratio of brain membranes is thought to be a factor in the pathogenesis of several neurological and psychiatric disorders (19), and decreased HFABP expression is found in the brains of patients with Down syndrome and Alzheimer's disease, providing indirect evidence of a connection between HFABP and neurological function (16).

Neurogenesis includes three contiguous phases, namely proliferation, migration and differentiation, and maturation and integration of the precursor cells (20). The expression of BFABP is highest in the mid-term embryonic stages of development, and is associated with the proliferation of neural progenitor cells during early cortical development (16). BFABP$^{-/-}$ mice have been shown to promote neural differentiation (3,16). Therefore the up-regulation of BFABP (and also KFABP) is likely related to the proliferation and initial differentiation of neural cells, rather than their maturation and integration (20). BFABP preferentially binds $\omega 3$ PUFA, e.g. DHA (16,21-23). DHA is a major component of brain phosphatidylethanolamine and phosphatidylserine and is highly enriched in the PL of the synaptic plasma membrane and synaptic vesicles (16). An increase in BFABP expression is correlated with an increase in DHA utilization, and BFABP null mice display decreased DHA incorporation into phospholipids, with an increase in AA and PA incorporation (2,16). Interestingly, BFABP expression levels are increased in schizophrenia, bipolar disorder, and Down syndrome, and have been associated with increased anxiety and depression and altered emotional behavior (3,16,21); these disorders are proposed to be linked to $\omega 3$ PUFA deficiency via alterations in dopaminergic and serotonergic processes (19). BFABP has also been proposed to be involved in the stimulation Jak3 (Janus-activated kinase 3) and Stat5 (signal transducers and activators of transcription 5) and activation of the RXR nuclear receptor by increasing the levels of $\omega 3$ PUFA (16). Antibodies against BFABP block cultured glial/neuronal cell differentiation and outgrowth, which has been interpreted to indicate that BFABP is expressed on the cell surface where it can be involved in LCFA uptake, cell-cell interactions or protein-protein interactions with cell surface receptors (16).

KFABP is expressed mainly at the late embryonic stages and its expression is upregulated during the differentiation of human embryonic stem cells into motor neurons or astrocytes, as well as in various pathological conditions, including peripheral nerve injury (16). Thus KFABP may be required for the mobilization of the LCFA substrates necessary for active synthesis of lipids and membranes in the processes of neurite outgrowth, axon development and neural cell regeneration (16). KFABP has similar affinities for a range of saturated and unsaturated long-chain fatty acids, such as PA, AA and DHA, and in PC12 cells neurite extension can be stimulated by the expression of KFABP and a simultaneous supply of AA and DHA, supporting a role in membrane biogenesis during neurite outgrowth and axon development (16). It has been proposed that KFABP exerts its cell- and tissue-specific roles via ligand binding and transport, as well as

ligand-specific interactions with PPARβ/δ (2,14,22). Indeed, KFABP has been shown to bind retinoic acid (RA) and deliver this lipid hormone to PPARβ/δ, thus partitioning RA away from the classical retinoic acid receptor and leading to the transcription of genes related to cell survival rather than growth inhibition (22).

MFABP is expressed exclusively in the PNS myelin sheath during development and is absent from the CNS (15). Proposed roles include the generation and maintenance of lipid composition of the myelin membranes (15,23). The detection of plasma antibodies to MFABP in Guillain-Barré syndrome have been proposed to be linked to demyelination (24), although a specific function for MFABP in demyelination has not been elucidated. MFABP is extrinsically associated with membranes in peripheral nerve (6), a characteristic that has also been shown in CNS for BFABP; it is therefore tempting to speculate that these two FABPs have similar functions in the CNS and PNS.

Liver

The liver is active in lipid anabolism as well as catabolism, being the major site of very low density lipoprotein biogenesis, cholesterol and bile acid synthesis and bile production, and fatty acid oxidative pathways. It nevertheless expresses only a single FABP at high level, the liver FABP (LFABP, FABP1). In the LFABP null mouse, furthermore, essentially no compensation with other FABPs is found. This singular expression in such a multifunctional organ may be related to the ligand binding properties of LFABP, which are unique in the protein family in that two rather than one LCFA is bound to LFABP, and, moreover, a variety of other small hydrophobic ligands have been shown to bind in its relatively large ligand-binding pocket (1,2,4).

A consistent finding in the LFABP^{-/-} mice is defective fatty acid β-oxidation that is not due to diminished oxidative capacity or decreased expression of relevant genes, supporting the hypothesis that LFABP acts as a LCFA transporter, specifically targeting ligand to β-oxidation pathways (5,25,26). Despite the decrease in LCFA oxidation, however, the LFABP null mouse does not develop hepatosteatosis following either a high fat diet or an overnight fast, as found

for wild type controls, indicating protection against development of the metabolic syndrome, although others report an exacerbation of obesity (27). Recently, it was shown that LFABP null mice were highly susceptible to the development of cholesterol gallstones, with the effect likely secondary to increased liver cholesterol levels and increased enterohepatic bile acid pool size (28).

LFABP may in part be exerting its functional effects via regulation of gene transcription. Several reports indicate direct interactions between LFABP and PPARα (14,33), a nuclear receptor involved in the induction of hepatic β-oxidation (29), and it has been suggested that LFABP is specifically delivering LCFA or perhaps other ligands to the nucleus. A number of studies have shown that a portion of hepatocyte LFABP is localized in the nucleus, and a redistribution of some LFABP from the nuclear interior to the nuclear envelope in isolated hepatocytes from LFABP^{-/-} mice was recently reported (14,30). Unlike what has been shown for AFABP and KFABP, however, the LFABP helix-turn-helix domain does not appear to contain structural information promoting nuclear localization, thus the molecular basis for LFABP delivery of ligand to the nucleus, as well as the structural basis for the putative LFABP-PPARα association, remain to be determined. It was recently shown that PPARβ/δ may also be a LCFA-responsive transcription factor in liver (31); whether LFABP might interact similarly with PPARβ/δ is presently unknown.

Intestine

The small intestine is responsible for the assimilation of dietary lipid as well as the reuptake of bile acids via the enterohepatic circulation. Differentiated enterocytes of proximal small intestine express high levels of two FABPs, the liver-type LFABP as well as the intestine-specific form, intestinal FABP (IFABP, FABP2). In rodents, both are expressed at roughly equal levels although in humans, LFABP is more abundant. The distal small intestine expresses a third member of the FABP family, ileal bile acid binding protein (ILBP, FABP6) (1,2,4). There appears to be no compensatory upregulation of LFABP upon ablation of IFABP, nor vice versa, again indicating unique functional roles. However, LFABP null

mice display an increase in the mRNA levels of ILBP, which may be part of the mechanism underlying the increased bile acid pool size and increased gallstone susceptibility (28).

A unique feature of LFABP in the intestine is its role in chylomicron biogenesis. Cell-free transport studies demonstrated that LFABP is necessary for the release of specific ER-generated vesicles containing nascent TG-rich chylomicrons, the so-called pre-chylomicron transport vesicles (PCTV). Budding of the PCTV, which subsequently fuse with Golgi membranes, is dependent on LFABP, which cannot be replaced by IFABP (32). Recently, the intestinal ER-derived PCTV budding machinery was shown to be a >600 kDa complex containing not only LFABP but also VAMP7, apoB48, CD36, and COPII proteins (33).

As found in the liver, the LFABP null mouse also displays defective fatty acid β-oxidation in the intestine. Total mucosal oxidative capacity is not decreased, nor are there changes in the expression of genes involved in β-oxidation, thus in intestine as well as in liver, LFABP is likely playing a lipid transport/targeting role.

Certain unique roles for the two proximal enterocyte FABPs in intracellular lipid metabolism have also been found. LFABP ablation does not substantially alter the incorporation of radiolabeled LCFA into TG or PL, but radiolabeled monoacylglycerol (MG) metabolism is shifted toward greater TG incorporation in the LFABP$^{-/-}$ mucosa, suggesting that LFABP is involved in partitioning of MG toward PL biosynthesis. In contrast, IFABP null animals display no changes in MG metabolism, consistent with the lack of MG binding by IFABP, but rather display a reduced incorporation of OA into TG relative to PL, suggesting that IFABP is involved in partitioning of LCFA toward TG synthesis. The metabolic changes observed in both LFABP and IFABP null models appear to occur by a non-transcriptional mechanism, supporting the hypothesis that the enterocyte FABPs are specifically trafficking bound ligands to their respective metabolic fates in a targeted manner.

As discussed above for LFABP, the actions of IFABP in the enterocyte may lead to systemic metabolic effects, although, as with LFABP, reports are not entirely consistent and underlying mechanisms not clear. IFABP null mice, under certain conditions related to age, gender, or diet, appear to be more prone to developing obesity, hypertriglyceridemia, and increased liver TG accumulation (34,35), characteristics of the metabolic syndrome (36). A potential role for IFABP in the development of the metabolic syndrome is also supported by a single nucleotide polymorphism in the IFABP gene that leads to the substitution of threonine for alanine at position 54. The Thr54 isoform binds LCFA with greater affinity, indicating that the elevated serum TG levels are not secondary to greater sequestration of LCFA in the enterocyte but rather may be related to the aforementioned specific role of IFABP in intestinal TG synthesis and/or transport (1,2,4).

Summary and Perspective

The FABP family includes nine separate gene products, each with a unique tissue distribution. As the functions of fatty acids and other lipids are often highly tissue-specific, so it is becoming clear that the FABPs function in a tissue-specific manner as well. Thus, despite similar ligand binding characteristics and highly homologous tertiary structures, each FABP appears to have unique functions in specific tissues. Overall, the FABPs function as intracellular trafficking proteins, delivering or receiving LCFA and in some cases other small hydrophobic lipids to and from particular subcellular sites. The transport properties of the FABPs are governed in part by specific protein-protein and protein-membrane interactions, and the helix-turn-helix domain of the FABPs appears to specify these interactions. Several of the FABPs have been shown to deliver their ligands to nuclear transcription factors, thereby modulating gene expression in a tissue-specific manner. Cellular changes in gene expression and lipid metabolism brought about by the FABPs leads to changes in whole body energy homeostasis. Given the role of aberrant lipid metabolism in most if not all of the metabolic syndrome disorders, the FABPs may be envisioned as central regulators of lipid disposition at the cell and tissue levels that have profound impact on systemic energy metabolism.

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FOOTNOTES:

The authors apologize for not citing all relevant primary publications; reviews have been used as the main citation sources due to space limitations.

The abbreviations used are: AA, arachidonic acid, C20:4 ω6; AFABP, adipocyte FABP, FABP4; BFABP, brain FABP, FABP7; CNS, central nervous system; DHA, docosahexaenoic acid, C22:6 ω3; FABP, fatty acid binding protein; HFABP, heart FABP, FABP3; IFABP, intestinal FABP, FABP2; ILBP, ileal bile acid binding protein, FABP6; KFABP, keratinocyte FABP, FABP5; LCFA, long chain fatty acid; LFABP, liver FABP, FABP1; MFABP, myelin FABP, FABP9; MG, monoacylglycerol; OA, oleic acid, C18:1 ω9; PA, palmitic acid, C16:0; PL, phospholipid; PNS, peripheral nervous system; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RA, retinoic acid; TG, triacylglycerol.

[*] Lagokos, W.S. and Storch, J (2010). Unpublished observations.

FIGURE LEGENDS

Fig. 1. The crystal structure of human heart FABP (HFABP) containing an oleic acid ligand (1HMS.pdb). The protein structure is similar for all the FABPs and shows the β-barrel domain and the N-terminal helix-turn-helix motif (37).

β-barrel domain

Helix-turn-helix motif

Oleic acid ligand