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Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets

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Abstract

Lipids are vital components of many biological processes and crucial in the pathogenesis of numerous common diseases, but the specific mechanisms coupling intracellular lipids to biological targets and signalling pathways are not well understood. This is particularly the case for cells burdened with high lipid storage, trafficking and signalling capacity such as adipocytes and macrophages. Here, we discuss the central role of lipid chaperones — the fatty acid-binding proteins (FABPs) — in lipid-mediated biological processes and systemic metabolic homeostasis through the regulation of diverse lipid signals, and highlight their therapeutic significance. Pharmacological agents that modify FABP function may provide tissue-specific or cell-type-specific control of lipid signalling pathways, inflammatory responses and metabolic regulation, potentially providing a new class of drugs for diseases such as obesity, diabetes and atherosclerosis.

Fatty-acid trafficking in cells is a complex and dynamic process that affects many aspects of cellular function. Fatty acids function both as an energy source and as signals for metabolic regulation, acting through enzymatic and transcriptional networks to modulate gene expression, growth and survival pathways, and inflammatory and metabolic responses[1,2]. Furthermore, fatty acids, particularly linoleic and arachidonic acids, can be metabolized into a diverse and large family of bio-active lipid mediators called eicosanoids, which may function as pro- and anti-inflammatory mediators[3,4]. In particular, the cyclopentenone prostaglandins, such as PGA1, PGA2 and PGJ2, have potent anti-inflammatory effects through the inhibition of inflammatory kinase pathways. A critical regulatory component of eicosanoid biosynthesis is at the level of availability of unesterified fatty acids liberated from membrane phospholipids. All of these aspects depend on complex processing, shuttling, availability and removal of lipids to keep a delicate balance between lipid species at the target compartments and to regulate their engagement of signalling targets.

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DATABASES
OMIM:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Down's syndrome | obesity | type 2 diabetes | schizophrenia
UniProtKB:http://ca.expasy.org/sprot
FABP1 | FABP2 | FABP3 | FABP4 | FABP5 | FABP6 | FABP7

FURTHER INFORMATION
PRINTS:
http://www.bioinf.manchester.ac.uk/dbbrowser/PRINTS/
PROSITE:http://expasy.org/prosite/
Protein Data Bank (PDB):
http://www.rcsb.org/pdb/home/home.do
PyMOL:http://pymol.sourceforge.net/

Intracellular lipid chaperones known as fatty acid-binding proteins (FABPs) are a group of molecules that coordinate lipid responses in cells and are also strongly linked to metabolic and inflammatory pathways[5–9]. FABPs are abundantly expressed 14–15 kDa proteins that reversibly bind hydrophobic ligands, such as saturated and unsaturated long-chain fatty acids, eicosanoids and other lipids, with high affinity[8,9]. FABPs are found across species, from *Drosophila melanogaster* and *Caenorhabditis elegans* to mice and humans, demonstrating strong evolutionary conservation. However, little is known about their exact biological functions and mechanisms of action. Studies in cultured cells have suggested potential action of FABPs in fatty-acid import, storage and export as well as cholesterol and phospholipid metabolism[5,6]. FABPs have also been proposed to sequester and/or distribute ligands to regulate signalling processes and enzyme activities. In the broader context, we view FABPs as lipid chaperones that escort lipids and dictate their biological functions. Recently, through the use of various genetic and chemical models in cells as well as whole animals, the FABPs have been shown to be central to lipid-mediated processes and related metabolic and immune response pathways. Such studies have also highlighted their considerable potential as therapeutic targets for a range of associated disorders, including obesity, diabetes and atherosclerosis.

Family of FABPs

Since the initial discovery of FABPs in 1972 (REF. 10), at least nine members have been identified (TABLE 1). Different members of the FABP family exhibit unique patterns of tissue expression and are expressed most abundantly in tissues involved in active lipid metabolism. The family contains liver (L-), intestinal (I-), heart (H-), adipocyte (A-), epidermal (E-), ileal (Il-), brain (B-), myelin (M-) and testis (T-) FABPs. However, it should be noted that this classification is somewhat misleading, as no FABP is exclusively specific for a given tissue or cell type, and most tissues express several FABP isoforms (see below). The regulation of tissue-specific expression and function of various FABPs is poorly understood. The expression of FABPs in a given cell type seems to reflect its lipid-metabolizing capacity. In hepatocytes, adipocytes and cardiac myocytes, where fatty acids are prominent substrates for lipid biosynthesis, storage or breakdown, the respective FABPs make up between 1% and 5% of all soluble cytosolic proteins[5]. These amounts can further increase following periods of mass influx of lipids into these cells. Increased fatty-acid exposure leads to a marked increase in FABP expression in most cell types11. Endurance training or pathological nutrient changes, as seen in diabetes for example, can also result in high levels of FABP in skeletal muscle cells12. Similar effects have also been seen in hepatocytes and adipocytes after exposure to chronically elevated extracellular lipid levels11. These observations suggest that there is a built-in adaptive sensing system that responds to the lipid status of the target cells and regulates lipid stochiometry with the FABPs.

As small intracellular proteins, FABPs appear to access the nucleus under certain conditions, and potentially target fatty acids to transcription factors, such as members of the peroxisome proliferator-activated receptor (PPAR) family — PPAR-α, PPAR-δ and PPAR-γ — in the nuclear lumen. L-FABP, H-FABP, A-FABP and E-FABP themselves are controlled by these transcription factors, which are liganded by fatty acids or other hydrophobic agonists[13–15]. L-FABP and PPAR-α physically interact, and therefore it has been suggested that L-FABP could be considered a co-activator in PPAR-mediated gene regulation16. In a similar way, E-FABP interacts with PPAR-δ and A-FABP with PPAR-γ15. A recent study has indicated that continuous nucleocytoplasmic shuttling may underlie transcriptional activation of PPAR-γ by A-FABP[17]. However, in the case of A-FABP, its actions also provided a negative feedback to terminate PPAR-γ action, and the absence of A-FABP resulted in enhanced nuclear hormone receptor activity in the macrophage[18]. It is unclear whether such a feedback regulation occurs

with other isoforms in other cell types and how specificity is achieved in the chaperoning activity towards lipid species.

Ligand affinity and structure of FABPs

All FABPs bind long-chain fatty acids with differences in ligand selectivity, binding affinity and binding mechanism[6] as a result of small structural differences between isoforms. In general, the more hydrophobic the ligand the tighter the binding affinity — with the exception of unsaturated fatty acids. It is also possible that the needs of target cells determine the affinity and even selectivity of the major isoform present at different sites. For example, B-FABP is highly selective for very long-chain fatty acids such as docosahexaenoic acid[19]. On the other hand, L-FABP exhibits binding capacity for a broad range of ligands from lysophospholipids to haem[8].

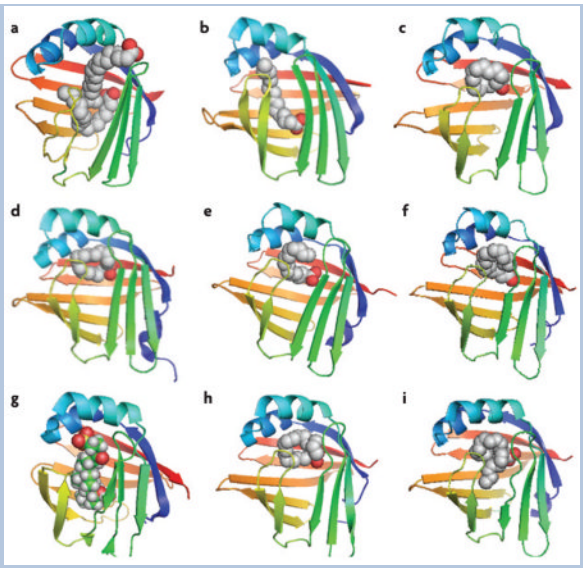
Several FABP isoforms have been structurally investigated as isolated recombinant proteins by X-ray crystallography, nuclear magnetic resonance and other biochemical and biophysical techniques. FABPs have an extremely wide range of sequence diversity: from 15% to 70% sequence identity between different members[6]. However, all known FABPs share almost identical three-dimensional structures (BOX 1). Common to all FABPs is a 10-stranded antiparallel β-barrel structure, which is formed by two orthogonal five-stranded β-sheets[6]. The binding pocket is located inside the β-barrel, the opening of which is framed on one side by the N-terminal helix-loop-helix ‘cap’ domain, and fatty acids are bound to the interior cavity. There is a conserved three-element fingerprint that provides a signature for all FABPs (PRINTS pattern FATTYACIDBP; PR00178) (BOX 2).

Box 1

Crystal structure of ligand-bound FABPs

Generally, one or two conserved basic amino-acid side chains are required to bind the carboxylate site of a fatty-acid ligand in the binding pocket of a fatty acid-binding protein (FABP)[69]. The hydrocarbon tail of the ligand is lined on one side by hydrophobic amino-acid residues and on the other side by ordered water molecules, thus creating the small differences of FABP types in the enthalpic and entropic contributions to ligand binding. Below, the crystal structures of various ligand-bound FABPs are shown (graphics were created using PyMOL).

The binding pocket of liver FABP (L-FABP; FABP1) is considerably larger than that of other FABPs, allowing the binding of two fatty-acid molecules with differing affinities **(a).** Here, two oleic acids are bound to rat L-FABP (Protein Data Bank (PDB) code: 1lfo), and show that the fatty acids are bound in opposite orientation with the carboxylate group of the second fatty acid protruding from the cavity and facing the solvent96. In rat intestinal FABP (I-FABP; FABP2), the ligand (palmitic acid) is bound in a slightly bent conformation97 (PDB code: 2ifb) **(b).** Other members generally bind a fatty acid as a twisted U-shaped entity9,[98]: a palmitic acid bound to human heart FABP (H-FABP; FABP3) (PDB code: 2hmb) **(c);** a palmitic acid bound to human adipocyte FABP (A-FABP; FABP4) (PDB code: 2hnx) **(d);** a palmitic acid bound to human epidermal FABP (E-FABP; FABP5) (PDB code: 1b56) **(e);** an oleic acid bound to bovine myelin FABP (M-FABP; FABP8) (PDB code: 1pmp) **(f).** An exception is for human ileal FABP (Il-FABP; FABP6), which binds the bile acid such as taurocholic acid (PDB code: 1o1v) **(g).** Human brain FABP (B-FABP; FABP7) binds oleic acid in the U-shaped way (PDB code: 1fe3) **(h);** however, its binding pocket can also accommodate very long-chain docosahexaenoic acid in a helical conformation[19] (PDB code: 1fdq) **(i).**



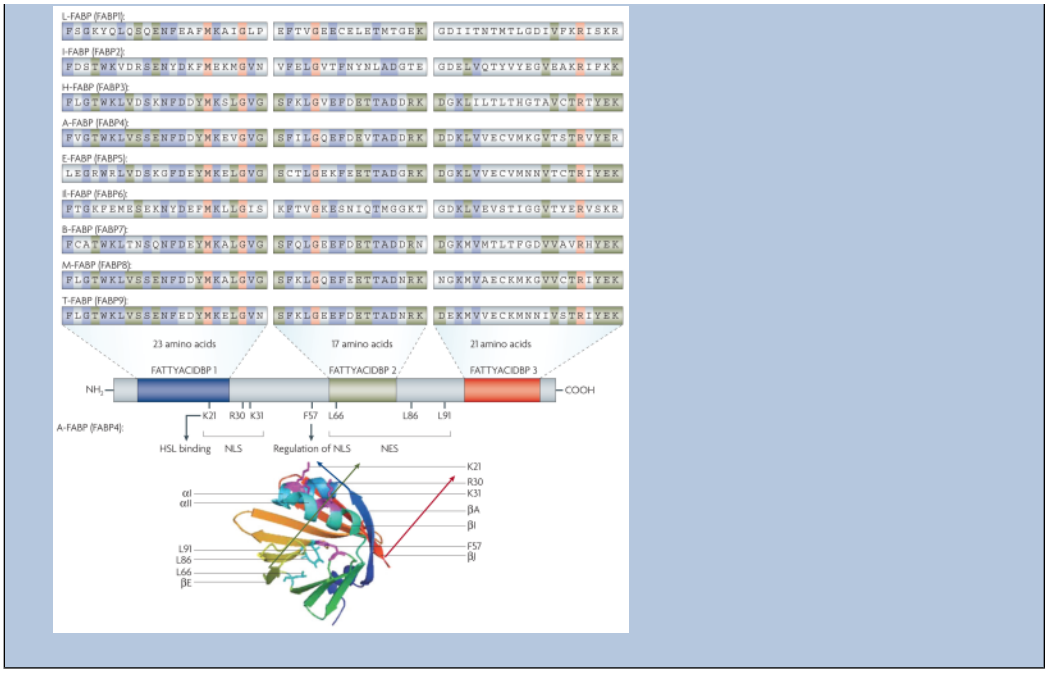
Box 2

Domain distribution of FABP family members

There is a conserved fingerprint for all fatty acid-binding proteins (FABPs) (PRINTS pattern FATTYACIDBP; PR00178), which is derived from three motifs. Motif 1 includes the G-x-W triplet, which forms part of the first β-strand (βA) and corresponds to a similar motif in the sequence of lipocalins, in which it has the same conformation and location within the protein fold[99] (see PROSITE pattern FABP; PS00214). Motif 2 spans the C terminus of strand 4 (βD) and includes strand 5 (βE). Motif 3 encodes strands 9 (βI) and 10 (βJ).

In adipocyte FABP (A-FABP; FABP4), potential functional domains include a nuclear localization signal (NLS) and its regulation site, nuclear export signal (NES) and a hormone-sensitive lipase (HSL) binding site17,26,100. The primary sequence of A-FABP does not show a readily identifiable NLS. However, the signal could be found in the 3D structure of the protein and was mapped to three basic residues (K21, R30 and K31) located in the helix–loop–helix region, whose side chains shift their orientation upon ligand binding to form a functional NLS17. The NES is also not apparent in the primary sequence, but assembles in the tertiary structure from three nonadjacent leucine residues (L66, L86 and L91) to form a motif reminiscent to that of established NES17. Activation of NLS in A-FABP involves closure of the portal loop, resulting in contraction of the binding pocket. Swinging doorway comprised of F57 perturbs a critical helix containing the NLS26. It has been suggested that activated and non-activated ligand conformations of A-FABP for NLS have different homodimeric configurations. Non-activating ligands (for example, oleate and stearate) protrude from the portal, preventing its closure and preserving the integrity of a homodimeric interface, which masks the NLS, while activating ligands (for example, troglitazone, linoleic acid and anilinonaphthalene sulphonate) favour an alternative homodimer in which the NLS is exposed26.

The representative crystal structure of FABP is human A-FABP (PDB code: 2hnx). The structural and functional domains as well as critical amino-acid residues are marked. The graphic depiction of protein structure was created with PyMOL.



Functions of FABPs

Numerous functions have been proposed for FABPs. As lipid chaperones, FABPs may actively facilitate the transport of lipids to specific compartments in the cell, such as to the lipid droplet for storage; to the endoplasmic reticulum for signalling, trafficking and membrane synthesis; to the mitochondria or peroxisome for oxidation; to cytosolic or other enzymes to regulate their activity; to the nucleus for lipid-mediated transcriptional regulation; or even outside the cell to signal in an autocrine or paracrine manner (FIG. 1). The proper engagement of targets in a spatially controlled manner requires the action of lipid chaperones. Interestingly, the functions of lipid chaperones studied so far relate to detrimental outcomes.

FABP content in most cells is generally proportional to the rates of fatty-acid metabolism11. FABPs are also involved in the conversion of fatty acids to eicosanoid intermediates and in the stabilization of leukotrienes20,21. Furthermore, a direct protein–protein interaction between hormone-sensitive lipase (HSL) activity and A-FABP or E-FABP in adipocytes has also been reported22–25. In general, the interacting protein partners for FABPs are poorly understood, and the searches for such proteins with conventional approaches have not been fruitful. Movement of FABPs into the nucleus and interaction with nuclear hormone receptors is possible, and this mechanism might potentially deliver ligands to this protein family15–17,26. Again, little is known regarding this potential action and how lipids regulate subcellular localization of FABPs. Also, how these simple chaper-ones overcome specificity or stoichiometry constraints remains elusive. Clear evidence on the specific impact of FABPs on cell biology and lipid metabolism in complex systems had been lacking until FABP-deficient mice models were created. As discussed below, consequences of genetically altered FABP expression in cells or whole animals dramatically enhanced the understanding of FABP functions (TABLES 2,3), but also raised interesting new questions and possibilities regarding systemic effects of FABPs *in vivo* and the underlying mechanisms. These studies also opened up novel possibilities to tackle a wide range of metabolic diseases through therapeutic targeting of FABPs, particularly A-FABP, with synthetic ligands.

Liver FABP

L-FABP, also known as FABP1, is abundant in the liver cytoplasm, but is also expressed in several other sites, including the intestine, pancreas, kidney, lung and stomach[6]. L-FABP in the liver can represent as much as 5% of all cytosolic proteins in hepatocytes[5]. The promoter of the L-FABP gene contains a peroxisome-proliferator response element, and accordingly the mRNA levels are increased by fatty acids, dicarboxylic acids and retinoic acid[8]. Unlike the other members of the FABP family, L-FABP is able to bind two ligands simultaneously via two different binding sites with high and low affinities[27]. Peroxisome proliferators always bind L-FABP with low affinity, whereas the strength of the binding with fatty acids depends on which affinity site is utilized. This property of L-FABP is suggested to serve as a feature enabling ligand delivery through interactions with target receptors. In addition to binding fatty acids, such as oleic acid, L-FABP can carry acyl-coenzyme A, eicosanoids, lysophospholipids, carcinogens, anticoagulants, such as warfarin, and haem, making it probably the most versatile chaperone in terms of its ligand repertoire[8].

Surprisingly, no change in appearance, gross morphology or viability was observed in *L-FABP*-deficient mice[28,29]. These mice were of normal weight, and despite a modest reduction in fatty-acid uptake, serum levels of triacylglycerols and fatty acids were unchanged[28,29]. However, metabolic parameters in mice upon exposure to high-fat/cholesterol diet differed between studies[30–32] (TABLE 2). This fragility in the phenotype points to the critical importance of the dietary exposures, gender and subtle differences in genetic background or lipid composition in the biology of L-FABP. It is also possible that the principal action of L-FABP lies elsewhere, for example in the kidney or intestine. Interestingly, recent studies have suggested that fatty acid-induced expression of L-FABP occurs in the proximal tubules and showed that urinary L-FABP in humans may be a useful clinical marker that can help predict and monitor the progression of renal diseases[33].

Intestinal FABP

I-FABP, also known as FABP2, is expressed in the epithelium of the small intestine. In the small intestine, three members of FABPs are present, namely L-FABP, I-FABP and Il-FABP (also known as FABP6), although they are distributed in different segments[34]. L-FABP is mostly expressed in the proximal region, whereas Il-FABP is restricted to the distal part of the small intestine. I-FABP is expressed throughout the intestine, but most abundantly in the distal segment. It is difficult to assess the individual contributions of these proteins to lipid absorption and metabolism at the sites at which they are present, and more work is needed in this regard.

I-FABP-deficient mice were viable and fertile[35]. Fat absorption was not affected by the loss of I-FABP, and compensation by L-FABP or Il-FABP was not observed[35]. Both genders of mice with I-FABP-deficiency exhibited elevated plasma levels of insulin, but normal levels of glucose. Male *I-FABP*$^{-/-}$ mice gained more weight, had larger livers and had significantly higher triglyceride levels regardless of diet. By contrast, female *I-FABP*$^{-/-}$ mice gained less weight, had smaller livers on a high-fat diet and exhibited no difference in plasma triglyceride levels. Although the mechanisms responsible for these gender differences remain unclear, it appears that fatty-acid uptake can be mediated by the remaining FABPs, possibly L-FABP and Il-FABP, without the need for increased total amounts of FABPs to compensate for the lack of I-FABP.

It has been reported that a polymorphism in I-FABP, an alanine to threonine substitution at codon 54 (Thr54), was associated with insulin resistance and decreased lipid oxidation in Pima Indians, a population with an extremely high prevalence of obesity and type 2 diabetes[36]. However, the association between the Thr54 allele and insulin resistance in various other populations has been modest and sometimes controversial5,6. Again, this indicates the need

to examine these genetic variations in large populations, and, more importantly, in the context of dietary and other environmental exposures.

Heart FABP

H-FABP, also known as FABP3, has been isolated from a wide range of tissues, including heart, skeletal muscle, brain, renal cortex, lung, testis, aorta, adrenal gland, mammary gland, placenta, ovary and brown adipose tissue[6,12]. The level of H-FABP was influenced by exercise, PPAR-α agonists and testosterone, and oscillates with circadian rhythm[8,14,37]. In muscle cells, H-FABP was involved in the uptake of fatty acids and their subsequent transport towards the mitochondrial β-oxidation system. Increased fatty-acid exposure *in vitro* and *in vivo* resulted in elevated H-FABP expression[11,12]. Conditions with elevated plasma lipids may result in increased H-FABP levels in myocytes, as seen in endurance training[11,12].

Studies in *H-FABP*-deficient mice showed that the uptake of fatty acids was severely inhibited in the heart and skeletal muscle, whereas plasma concentrations of free fatty acids were increased[38]. Cardiac and skeletal muscle metabolism is reported to switch from fatty-acid oxidation towards glucose oxidation when there is an inability to obtain sufficient amounts of fatty acids[39,40]. Consequently, *H-FABP*-deficient mice were rapidly fatigued and exhausted by exercise, showing a reduced tolerance to physical activity. Localized cardiac hypertrophy was also observed in the older animals[38].

The mammary gland prominently expresses H-FABP in the course of cell differentiation and formation of ductal structures during lactation[41]. In the mammary gland, mammary-derived growth inhibitor (MDGI) was identified as a growth regulator, which later turned out to be a mixture of H-FABP and A-FABP, and the amino-acid sequence of MDGI reveals 95% similarity to H-FABP[42,43]. It has been shown that H-FABP inhibits the growth of human breast cancer cells44. However, this growth inhibition appeared to be unrelated to the ligand-binding capacity of the FABPs. On the other hand, studies involving overexpression and ablation of H-FABP demonstrated that H-FABP did not play a role in regulating the development or function of the mammary gland[45,46]. Thus, the biological function of H-FABP in the mammary gland remains unclear and somewhat controversial. Similarly, little is known about the effect of lack of H-FABP in tissues other than the heart or mammary gland.

H-FABP is abundant in the myocardium and rapidly released from cardiomyocytes into the circulation after the onset of cell damage. Serum concentration of H-FABP has been proposed as an early biochemical marker of acute myocardial infarction and a sensitive marker for the detection and evaluation of myocardial damage in patients with heart failure[47,48]. However, the concentration of H-FABP is significantly influenced by renal clearance and thus has limitations in its usefulness for patients with renal dysfunction[49]. The concentration of other FABPs has also been proposed as a biomarker for the detection of tissue injury: B-FABP for brain injury and I-FABP for intestinal damage[50]. The utility of these potential biomarkers remains to be explored.

Adipocyte FABP

A-FABP, also known as FABP4, was first detected in mature adipocytes and adipose tissue[51,52]. This protein has also been termed adipocyte P2 (aP2) because of its high sequence similarity (67%) to peripheral myelin protein 2 (M-FABP/FABP8)[52]. Expression of A-FABP is highly regulated during differentiation of adipocytes, and its mRNA is transcriptionally controlled by fatty acids, PPAR-γ agonists and insulin[5,7].

A-FABP is the best-characterized isoform among the entire FABP family with the most striking biology (FIG. 2). *A-FABP*-deficient mice exhibited reduced hyperinsulin-aemia and insulin

resistance in the context of both dietary and genetic obesity, but the effect of A-FABP on insulin sensitivity was not observed in lean mice[53,54]. In adipocytes, the loss of A-FABP was compensated by overexpression of E-FABP (FABP5/mal1), which is present in the normal adipocyte only in extremely small amounts. The adipocytes obtained from *A-FABP*-deficient mice have reduced efficiency of lipolysis *in vitro* and *in vivo*[22–24]. This was initially attributed to the ability of A-FABP to bind and activate HSL, although the definitive links between HSL activation and A-FABP have not yet been established *in vivo*. It also remains to be seen whether this potential mechanism can account for the alterations in lipolysis in A-FABP-deficiency.

Recent studies have demonstrated A-FABP expression in macrophages upon their differentiation from monocytes, and following activation with phorbol 12-myristate 13-acetate, lipopolysaccharide, PPAR-γ agonists and oxidized low-density lipoprotein[55–59]. In addition, it has been reported that A-FABP is also expressed in the dendritic cells[60]. Interestingly, expression of A-FABP in macrophages was suppressed by a cholesterol-lowering statin *in vitro*[61]. Notably, adipocytes express much higher levels of A-FABP than macrophages (approximately 10,000-fold)[62]. In macrophages, A-FABP modulated inflammatory responses and cholesterol ester accumulation55, and total A-FABP deficiency conferred dramatic protection against atherosclerosis in apolipoprotein E (*ApoE*)-deficient mice with or without the additional challenge of high-cholesterol-contained Western diets[55,63]. Bone-marrow transplantation studies demonstrated that this atheroprotective effect of A-FABP is predominantly, if not entirely, related to its actions in the macrophage[55]. These results demonstrate a central role for A-FABP in the development of major components of the metabolic syndrome through its distinct actions in adipocytes and macrophages, and its ability to integrate metabolic and inflammatory responses.

In human and mouse monocyte cell lines, A-FABP expression became evident in differentiated or activated macrophages[55–59]. The 5.4 kilobase A-FABP promoter/enhancer, which is known to direct A-FABP expression in the adipocytes, was sufficient to induce the expression in macrophages as tested in three independent transgenic lines[55]. Interestingly, E-FABP was also present in macrophages and regulated in an essentially identical manner. Unlike the compensatory regulation in adipocytes, E-FABP did not appear to be significantly upregulated in macrophages derived from *A-FABP*$^{-/-}$ mice (termed *A-FABP*$^{-/-}$ macrophages)[55]. It has been suggested that A-FABP is a critical regulator of the PPAR-γ–liver X receptor-α (LXR-α)–ATP-binding cassette A1 (ABCA1) pathway and contributes to foam-cell formation in macrophages[18]. PPAR-γ activity was elevated in *A-FABP*$^{-/-}$ macrophages with stimulation of downstream targets including LXR-α and ABCA1, resulting in enhanced efflux of cholesterol[18]. In parallel, A-FABP coordinates the inflammatory activity of macrophages. In *A-FABP*$^{-/-}$ macrophages, several inflammatory signalling responses were suppressed, including production of cytokines such as tumour-necrosis factor-α (TNF-α), interleukin 1β (IL1β), IL6 and monocyte chemoattractant protein 1 (MCP1). Moreover, production and function of pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) were also suppressed[18]. It has also been demonstrated that A-FABP deficiency results in reduction in the activity of the inhibitor of kappa kinase (IKK)-nuclear factor-κB (NF-κB) pathway, which may, at least in part, underlie the alterations in cytokine expression18. Consequently, the overall reduction in foam-cell formation and modified inflammatory responses of A-FABP$^{-/-}$ macrophages was highly beneficial against the formation of atherosclerotic lesions in mouse models.

A recent study showed that A-FABP was also expressed in human bronchial epithelial cells under highly specific conditions. The induction of A-FABP was only responsive to T helper 2 (T_H2) cytokines, IL4 and IL13, which are crucial to the development of asthma, whereas the T_H1 cytokine interferon-γ (IFN-γ) resulted in a moderate suppression of A-FABP[62]. It is worth noting that the level of A-FABP expression in bronchial epithelial cells was significantly lower

when compared with adipocytes and macrophages, even after stimulation. Interestingly, PPAR-γ agonists were unable to induce A-FABP expression in bronchial epithelial cells, and transcriptional regulation was mediated, at least in part, by signal transducer and activator of transcription 6 (STAT6) activity62. Interestingly, a striking protection from airway inflammation was detected in *A-FABP*-deficient mice, indicating possible protection against asthma[62]. In this setting, there was no detectable contribution of bone-marrow-derived elements in the airway phenotype associated with FABP-deficiency. Additionally, A-FABP expression was detected in lipoblasts in lipoblastoma and liposarcoma, but not in other benign adipose tissue or malignant connective tissue or epithelial tumours[64]. A-FABP expression has also been linked to human urothelial carcinomas[65]. The significance of these associations remains to be determined.

Notably, recent studies conducted in our laboratory and by others showed that A-FABP was released from adipocytes and abundantly present in human serum. In addition, the concentration of A-FABP may be associated with obesity, type 2 diabetes and cardiovascular diseases66[–68] (G. Tuncman and G.S.H., unpublished observations). However, the biological function of A-FABP in the serum remains an unaddressed question of great importance. If the secreted form of A-FABP or any other FABP is biologically active, this might introduce a paradigm shift in the understanding of regulated lipid chaperoning and the networking of local lipid-mediated processes with systemic metabolic responses.

Epidermal FABP

E-FABP, also known as FABP5, psoriasis-associated FABP (PA-FABP) or mal1, is expressed most abundantly in epidermal cells of the skin. It is also present in other tissues, including the tongue, adipose tissue (adipocyte and macrophage), dendritic cell, mammary gland, brain, kidney, liver, lung and testis[6,7,60]. As all these tissues express additional members of the FABP family, the exact function of E-FABP is especially difficult to elucidate.

The ratio of A-FABP to E-FABP in adipocytes isolated from normal mice was approximately 99:1 (REF. 69). Although E-FABP is the minor fraction in adipocytes, the stochiometry of A-FABP and E-FABP appears to be approximately 1:1 in the macrophage under physiological conditions55. These two proteins have 52% amino-acid similarity and bind various fatty acids and synthetic compounds with similar selectivity and affinity5. Interestingly, E-FABP expression was dramatically increased in adipocytes, but not in macrophages, derived from *A-FABP*$^{-/-}$ mice[53,55]. The mechanism underlying this striking molecular compensation is not known.

Transgenic mice overexpressing the E-FABP gene in adipose tissue exhibited a minor phenotype with enhanced basal and hormone-stimulated lipolysis[25]. When fed a high-fat diet, adipose tissue-specific E-FABP overexpression in transgenic mice resulted in a reduction in systemic insulin sensitivity[70]. By contrast, absence of E-FABP in these mice led to a modest increase in insulin sensitivity[70]. The adipocytes in *E-FABP*$^{-/-}$ mice showed an increased capacity for insulin-dependent glucose transport. Other than increased H-FABP in liver[71], no compensatory increase was observed in the expression of H-FABP, A-FABP or B-FABP in adipose tissue, testis, tongue or brain in *E-FABP*-deficient mice[70].

Complete or partial lack of E-FABP in the liver during perinatal development was compensated by an overexpression of H-FABP[71]. Otherwise, there were no apparent changes in morphology and histology in the liver of *E-FABP*$^{-/-}$ mice, and this model appeared remarkably healthy[71]. The loss of E-FABP in the epidermis did not alter the fatty-acid composition of the epidermal membrane, where fatty acids are essential components of the water permeability barrier of the skin[71]. There was only a minor reduction in transepidermal water loss in *E-*

FABP-deficient mice as the water permeability barrier recovered more slowly following acetone-induced damage[71].

Interestingly, a study has shown that overexpression of E-FABP in a benign, non-metastatic rat mammary epithelial cell line may induce metastasis[72]. Hence, E-FABP seems to have the opposite effects to those reported for H-FABP (MDGI) and B-FABP (MRG), which inhibit tumour growth. E-FABP was also reported to influence survival pathways by activation of retinoic acid through PPAR-δ[73]. Taken together, there are interesting possibilities in linking FABP function to tumorigenesis, which remain largely unexplored. In addition, E-FABP is expressed in astrocytes and glia of the prenatal and perinatal brain, and, unlike B-FABP, also in neurons74. E-FABP expression was induced following peripheral nerve injury, suggesting a role in the regeneration of neurons5.

Brain FABP

B-FABP, also known as FABP7, is expressed in various regions of the mouse brain in the mid-term embryonic stage, but the expression decreases as differentiation progresses[75]. The protein is strongly expressed in radial glia cells of the developing brain, especially in the preperinatal stage, but only weakly in mature glia of the white matter. Neurons of the grey matter express H-FABP and E-FABP but not B-FABP. B-FABP is distinguished from other FABPs by its strong affinity for *n*-3 polyunsaturated fatty acids, in particular, docosa-hexaenoic acid. As this very long-chain fatty acid is an important nutrient for the nervous system, it has been considered a natural ligand for B-FABP[76].

Pathologically, B-FABP was overexpressed in patients with Down's syndrome[77] and schizophrenia[78]. Recently, *B-FABP*-deficient mice were shown to be viable with no macroscopic abnormalities[79]. Interestingly, *B-FABP*-deficient mice exhibited altered emotional behavioural responses, decreased prepulse inhibition that is a typical behaviour in schizophrenia, and attenuated neurogenesis in vivo[78,79]. It has also been suggested that B-FABP influences the correct migration of developing neurons into cortical layers[75]. Moreover, similar to H-FABP[42,43], B-FABP is prominently expressed in the mammary gland, and its overexpression inhibited tumour growth in a mouse breast cancer model[80,81].

Lipid chaperones and metabolic diseases

As described above, adipocyte/macrophage FABPs, A-FABP and E-FABP, have a central role in many aspects of metabolic diseases including obesity, diabetes and atherosclerosis. The only cells that co-express A-FABP and E-FABP are adipocytes and macrophages. However, the dramatic compensation by E-FABP in adipocytes derived from *A-FABP*$^{-/-}$ mice had masked the effects of A-FABP-deficiency on overall metabolic health[53,70]. To remove all FABP activity from these cells and address the metabolic impact of these FABP isoforms, mice with combined deficiency of A-FABP and E-FABP (*A-FABP*$^{-/-}$*E-FABP*$^{-/-}$) were also generated. The *A-FABP*$^{-/-}$*E-FABP*$^{-/-}$ mice fed on a high-fat diet or in the context of severe genetic obesity exhibited alterations in tissue fatty-acid composition and did not develop insulin resistance, type 2 diabetes or fatty liver disease, demonstrating that the protective phenotype of this model far exceeds that of individual FABP-deficiency models[82,83]. Similarly, when intercrossed into the *ApoE*$^{-/-}$ model, *A-FABP*$^{-/-}$*E-FABP*$^{-/-}$ mice developed dramatically less atherosclerosis compared with *A-FABP*-deficient or wild-type mice of the same background[84]. Remarkably, *A-FABP*$^{-/-}$*E-FABP*$^{-/-}$*ApoE*$^{-/-}$ animals also had significantly increased survival when fed a Western-type hypercholesterolaemic diet, which is probably due to increased plaque stability and significant overall metabolic health[84]. It will be interesting to test whether this increase in survival could be extrapolated into increased longevity in this model.

A-FABP$^{-/-}$, *E-FABP*$^{-/-}$ or *A-FABP*$^{-/-}$*E-FABP*$^{-/-}$ mice have one notable feature associated with obesity: a minor but significant elevation of plasma fatty acids[53,54,70,82,83]. In general, increased fatty acids are positively correlated with the development of obesity and insulin resistance, but paradoxically, adipocyte/macrophage FABP-deficient mouse models were more insulin sensitive. This observation challenges the current dogma in the mechanistic basis of fatty-acid action in the metabolic syndrome, and indicates that the distribution and availability of intracellular fatty acids (and derivatives), rather than the absolute amounts, may be more critical in pathological conditions. More detailed lipid profiling showed increased shorter-chain (C14) fatty acids and decreased longer-chain (C18 or C20) fatty acids in the muscle and adipose tissues of *A-FABP*$^{-/-}$*E-FABP*$^{-/-}$ mice. These changes favoured enhanced insulin receptor signalling, insulin-stimulated glucose uptake, adenosine monophosphate-activated protein kinase (AMPK) activity, and fatty-acid oxidation[82]. There were also alterations in liver fatty-acid composition, which differed from other sites and favoured lipid mobilization over storage and suppressed stearoyl-coenzyme A desaturase (SCD) and sterol-regulatory element-binding protein (SREBP) activities, thus reducing hepatosteosis82. The *A-FABP*$^{-/-}$*E-FABP*$^{-/-}$ mouse model has shed new light on the role of FABPs in regulating intracellular fatty-acid profiles and how these alterations are linked to specific biochemical pathways important in metabolic homeostasis.

It has recently been suggested that macrophage accumulation in adipose tissue is a feature of adipose tissue inflammatory responses triggered by obesity and hence may contribute to the metabolic consequences such as insulin resistance[85,86]. Although the impact of A-FABP on atherosclerosis was essentially exclusive to its actions in the macrophage[55], studies in cell-based experiments and bone-marrow transplantation using adipocyte/macrophage FABP-deficiency models showed that FABP action in both adipocytes and macrophages contribute to the inflammatory and metabolic responses *in vitro* and *in vivo*[101]. However, the impact of adipocyte FABP is again greater than the impact of bone-marrow-derived cells on systemic insulin sensitivity and glucose metabolism *in vivo*[101].

Therapeutic targeting of FABPs

Adipocyte/macrophage FABPs, A-FABP and E-FABP act at the interface of metabolic and inflammatory pathways. These FABPs exert a dramatic impact on obesity, insulin resistance, type 2 diabetes, fatty liver disease, atherosclerosis and asthma. The creation of pharmacological agents to modify FABP function may therefore provide tissue-specific or cell-type-specific control of lipid signalling pathways, inflammatory responses and metabolic regulation, thus offering a new class of multi-indication therapeutic agents.

Recently, a small series of A-FABP inhibitors have been identified (TABLE 4). These include carbazole-based (compounds **1** and **2**) and indole-based (compounds **3**a–c) inhibitors[87]; benzylamino-6-(trifluoromethyl) pyrimidin-4(1*H*) inhibitors (compounds **4**a–f)[88]; and a biphenyl azole inhibitor (compound **5**; also known as BMS309403)[89]. In a fluorescent 1-anilinonaphthalene-8-sulphonic acid binding displacement assay, BMS309403 had K_i values <2 nM for A-FABP compared with 250 nM for H-FABP and 350 nM for E-FABP[89]. By contrast, the endogenous fatty acids, palmitic acid and oleic acid, had A-FABP K_i values of 336 nM and 185 nM, respectively[89]. BMS309403 seems to have greater potency compared with the other reported potential inhibitors, which have IC_{50} values >0.5 μM[87–89].

In a recent study, we reported the development of an isoform-specific and biologically active synthetic A-FABP inhibitor, and demonstrated that chemical inhibition of A-FABP could be a potential therapeutic strategy against insulin resistance, diabetes, fatty liver disease as well as atherosclerosis in independent experimental models[90]. The orally active small-molecule BMS309403, a rationally designed, potent and selective inhibitor of A-FABP, interacts with

the fatty-acid binding pocket within the interior of A-FABP to inhibit binding of endogenous fatty acids (FIG. 3). Results of X-ray crystallography studies identified the specific interactions of BMS309403 with key residues, such as Ser53, Arg106, Arg126 and Tyr128, within the fatty-acid binding pocket as the basis of its high *in vitro* binding affinity and selectivity for A-FABP over other FABPs[89]. In particular, Ser53, which is a Thr in H-FABP and E-FABP, is proximal to the ethyl substituent of the pyrazole ring and might act as a critical residue to influence ligand interactions.

BMS309403 markedly reduced the extent of atherosclerotic lesions in *ApoE*$^{-/-}$ mice[90]. Cell-based studies revealed reduced macrophage foam-cell formation with decreased cholesterol-ester accumulation, increased cholesterol efflux and decreased production of several inflammatory mediators by this inhibitor in a target-specific manner. BMS309403 did not produce these effects in cells lacking A-FABP. Inhibition of A-FABP improved glucose metabolism and enhanced insulin sensitivity in both dietary and genetic mouse models of obesity and diabetes[90]. Furthermore, fatty liver infiltration and the expression of obesity-associated inflammatory mediators were also suppressed in the insulin resistant and obese *ob*/*ob* mouse model. The activity of JNK1, which is crucial in the generation of inflammatory responses and inhibition of insulin action in obesity[91,92], was also attenuated together with improved insulin action in both adipose and liver tissues upon A-FABP inhibition[90].

Previous studies suggest that the expression, regulation and metabolic function of human A-FABP may be similar to that of mice5,53,[55]. In fact, a genetic variant was identified within the promoter region of the human A-FABP gene (T-87C), which altered C/EBP binding and significantly reduced the transcriptional activity of the human A-FABP promoter, resulting in diminished A-FABP expression in adipose tissue of carriers with this allele[93]. In a large population sampling, individuals with the A-FABP variant had lower triglyceride levels, had reduced cardiovascular disease risk, and were protected from obesity-induced type 2 diabetes93. This study provided a critical proof of principle that the biological functions of A-FABP may be similar between mice and humans. Definitive genetic links will require additional large-scale population studies to determine whether this applies to different cohorts. Further studies are also needed to determine whether FABP inhibitors could be safely used in humans and show efficacy against metabolic diseases. If successful, inhibition of A-FABP in humans may become a promising new class of therapeutics against a broad range of metabolic diseases including obesity, insulin resistance, type 2 diabetes, atherosclerosis and possibly other inflammatory conditions such as asthma.

Concluding remarks

FABP-mediated lipid metabolism is closely linked to both metabolic and inflammatory processes through modulating critical lipid-sensitive pathways in target cells, especially adipocytes and macrophages. Mice under normal physiological conditions did not have a compromised phenotype when adipocyte/macrophage FABPs were deleted, but they benefited enormously when faced with systemic pathological stresses, particularly of metabolic and inflammatory origin. The phenotypes observed in the absence of adipocyte/macrophage FABPs illustrate the integrating role in metabolic and inflammatory responses, and suggest that these genes may represent an example of the “thrifty” gene hypothesis[94]. Evolutionary selection has clearly preserved the function of FABPs in that they are present in invertebrates (lower eukaryotes) up to vertebrates, including humans[95]. It may be that the close link between the inflammatory and metabolic responses underlie this conservation. The adipocyte/macrophage FABPs may be necessary to fine-tune the balance between the availability of metabolic resources and the control of inflammatory responses. That is, when humans faced feast or famine and when under pressure with pathogens, the presence of FABPs may have been beneficial by ensuring a strong macrophage immune response or by maintaining adipose

tissue energy stores as part of the “thrifty” phenotype to survive. Under the unnaturally excessive and continuous caloric intake, decreased energy expenditure, prolonged lifespan and the distinctly stressful lifestyle of contemporary humans, FABPs may not be sufficient to maintain inflammatory or metabolic homeostasis, and hence no longer be beneficial. In this scenario, their presence now facilitates the formation of obesity, diabetes, dyslipidaemia, atherosclerosis and inappropriate immune responses. In such conditions, targeting the adipocyte/macrophage FABPs, particularly A-FABP, offers highly attractive therapeutic opportunities for a broad range of pathologies in metabolic diseases by addressing an evolutionary bottleneck in the metabolic design of humans. In addition to the well-studied and characterized isoforms, FABPs in general may also offer targeting opportunities for the development of therapeutic or preventive agents for other diseases. For example, H-FABP and B-FABP may be targeted in tumours where they are heavily and aberrantly expressed, and regulate growth and survival responses. Much work is still needed in mouse models to illustrate the precise applications and indications for other isoforms. Moreover, as well as targeting these molecules directly, the ability of FABPs to modulate lipid signalling and trafficking in a tissue-specific or restricted manner could also be exploited for controlling the activity of their targets such as nuclear hormone receptors in select cell types and tissues. Development of high affinity and selective chemicals to target A-FABP provides a critical proof of principle that this class of proteins are suitable for drug development. Future studies should also increase the repertoire of synthetic ligands for the additional members of the FABP family as their biological functions become better understood.

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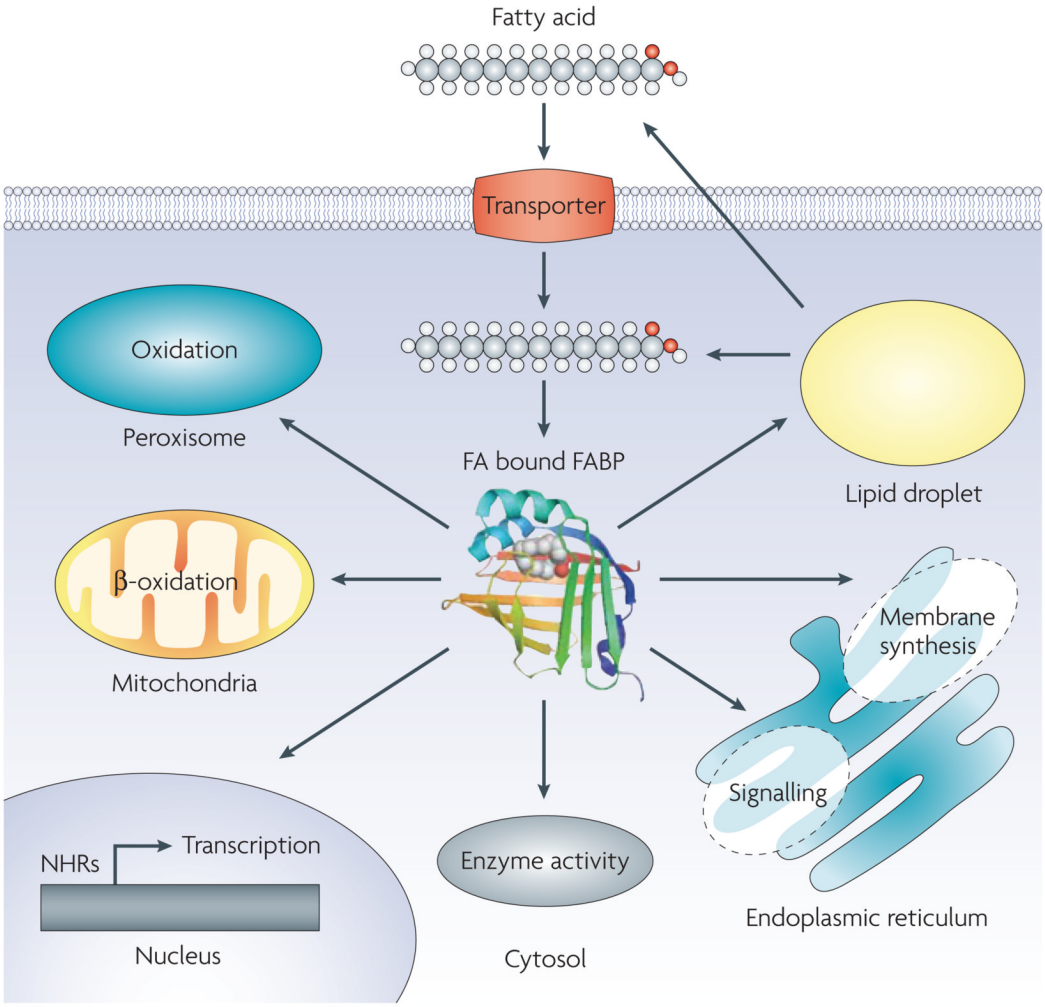

Figure 1. Putative functions of FABP in the cell

Fatty-acid (FA) trafficking accompanied by the fatty acid-binding proteins (FABPs) in the cell is shown. As lipid chaperones, FABPs have been proposed to play a role in the transport of lipids to specific compartments in the cell: to lipid droplets for storage; to the endoplasmic reticulum for signalling, trafficking and membrane synthesis; to the mitochondria or peroxisome for oxidation; to cytosolic or other enzymes to regulate their activity; to the nucleus for the control of lipid-mediated transcriptional programs via nuclear hormone receptors (NHRs) or other transcription factors that respond to lipids; or even outside the cell to signal in an autocrine or paracrine manner.

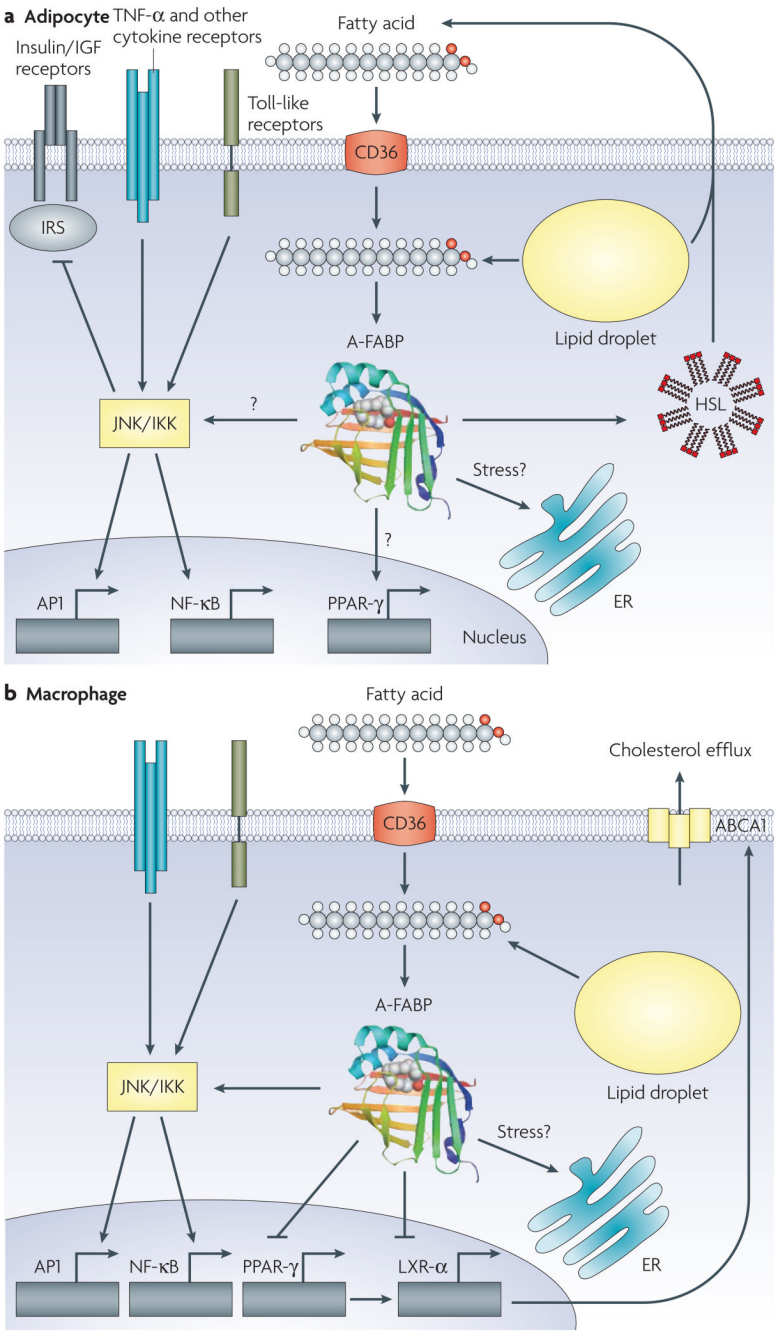

Figure 2. Functions of A-FABP in the adipocyte and macrophage

a. Other than general functions of the fatty acid-binding protein (FABP), adipocyte FABP (A-FABP; FABP4) interacts with hormone-sensitive lipase (HSL) to potentially modulate its catalytic activity and integrates several signalling networks that control inflammatory responses potentially through JNK/inhibitor of kappa kinase (IKK) and insulin action in the adipocyte. In addition to regulating fatty-acid influx, A-FABP is also important in controlling adipocyte lipid hormone production to regulate distant targets. The transcriptional events resulting from these actions are not fully understood. **b**. In the macrophage, A-FABP regulates inflammatory responses via the IKK-nuclear factor-κB (NF-κB) pathway and attenuates cholesterol efflux through inhibition of the peroxisome proliferator-activated receptor-γ

(PPAR-γ)-liver X receptor-α (LXR-α)-ATP-binding cassette A1 (ABCA1) pathway. In both macrophages and adipocytes, A-FABP has a critical role in integrating lipid signals to organelle responses, particularly in the endoplasmic reticulum (ER). AP1, adaptor protein 1; IGF, insulin-like growth factor; IRS, insulin receptor substrate; TNF, tumour necrosis factor.

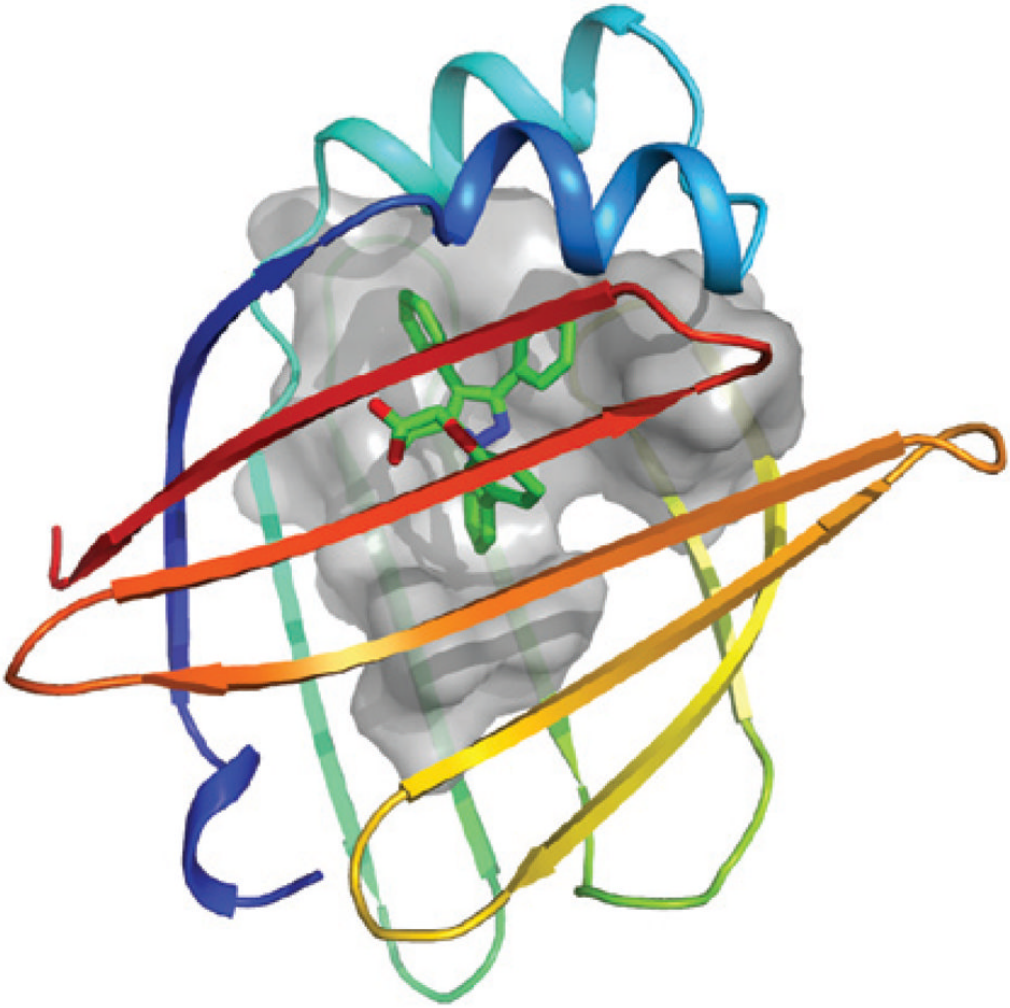

Figure 3. Crystal structure of the synthetic A-FABP inhibitor BMS309403 bound to human A-FABP

Human fatty acid-binding protein (FABP) crystallized in complex with BMS309403, a synthetic adipocyte FABP (A-FABP; FABP4) inhibitor, is shown (PDB code: 2nnq). The molecule occupies the internal binding pocket of A-FABP. One side of the internal surface of the binding pocket is shown as a grey colour where the designed surface interaction with the synthetic inhibitor takes place. The figure was created using PyMOL and provided by R. Parker, Bristol–Myers Squibb.

Table 1

Family of fatty acid-binding proteins (FABPs)

				Chromosomal location		
Gene	**Common name**	**Alternative names**	**Expression**	***Homo sapiens***	***Mus musculus***	***Rattus norvegicus***
Fabp1	Liver FABP	L-FABP	Liver, intestine, pancreas, kidney, lung, stomach	2p11	6 C1	4q32
Fabp2	Intestinal FABP	I-FABP	Intestine, liver	4q28–q31	3 G1	2q42
Fabp3	Heart FABP	H-FABP, MDGl	Heart, skeletal muscle, brain, kidney, lung, stomach, testis, aorta, adrenal gland, mammary gland, placenta, ovary, brown adipose tissue	1p32–p33	4 D2.2	5q36
Fabp4	Adipocyte FABP	A-FABP, aP2	Adipocyte, macrophage, dendritic cell	8q21	3 A1	2q23
Fabp5	Epidermal FABP	E-FABP, PA-FABP, mal1	Skin, tongue, adipocyte, macrophage, dendritic cell, mammary gland, brain, intestine, kidney, liver, lung, heart, skeletal muscle, testis, retina, lens, spleen	8q21.13	3 A1–3	2
Fabp6	Ileal FABP	Il-FABP, I-BABP, gastrotropin	Ileum, ovary, adrenal gland, stomach	5q33.3–q34	11 B1.1	10q21
Fabp7	Brain FABP	B-FABP, MRG	Brain, glia cell, retina, mammary gland	6q22–q23	10 B4	20q11
Fabp8	Myelin FABP	M-FABP, PMP2	Peripheral nervous system, Schwann cell	8q21.3–q22.1	3 A1	2q23
Fabp9	Testis FABP	T-FABP	Testis, salivary gland, mammary gland	8q21.13	3 A2	2q23

aP2, adipocyte P2; I-BABP, ileal bile acid-binding protein; MDGI, mammary derived growth inhibitor; MRG, MDGI-related gene; PA-FABP, psoriasis-associated FABP; PMP2, peripheral myelin protein 2.

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Table 2

Knockout and transgenic mouse models for FABPs

Mouse strain	Diet	Body weight	FA uptake	Serum					Ins. sens.	Fatty liver	FABPs*	Notes	Refs
				Glu.	Ins.	FFA	TG	Chol.					
Liver FABP (L-FABP/FABP1)													
L-FABP$^{-/-}$	Regular	→	↓	↓		→	→			→		Liv: chol. ↑; chol. ester ↑; phospholipid ↑; FA binding ↓	28
L-FABP$^{-/-}$	Regular	→	↓	→	↓‡	→	→	→		↓§		‡Fed state; §48 hour fasted	29
L-FABP$^{-/-}$	High fat/chol.	↑								↑		Female	30
L-FABP$^{-/-}$	High fat/chol.	↓		→	→	→	↑	→	→	↓		Male	31
L-FABP$^{-/-}$	High fat‡	↓		→		↓	↓	→		↓		Female; ‡high-saturated fat diet	32
L-FABP$^{-/-}$	Regular										E ↑ (Liv)	Female	32
Intestinal FABP (I-FABP/FABP2)													
I-FABP$^{-/-}$	Regular	↑‡		→	↑		↑‡	↓‡		→	L, II → (Liv/Int)	‡Male	35
I-FABP$^{-/-}$	High fat	↑‡/↓§		→	↑		↑‡	↓§		↑‡/↓§		‡Male; §female	35
Heart FABP (H-FABP/FABP3)													
H-FABP$^{-/-}$	Regular	→	↓	↓		↑	→	→			L, A, E, B → (Ht/Mu)	Glu. uptake: Ht ↑, Mu →; exercise intolerance, Ht: hypertrophy	38
H-FABP$^{-/-}$	High fat			↓		↑	→	→					38
H-FABP$^{-/-}$	Regular		↓								L, A, E, B → (Ht)	Ht: glu. uptake →; glu. oxidation ↑; TG →; glycogen ↑	39
H-FABP$^{-/-}$	Regular		↓									Mu: glu. oxidation ↑; TG ↓; glycogen ↓	40
H-FABP$^{-/-}$	Regular											No regulation: development/function of mammary gland	45
H-FABP$^{BLG\text{-promoter}}$	Regular										H ↑ (Ma)	No regulation: development/function of mammary gland	46
Epidermal FABP (E-FABP/FABP5)													
E-FABP$^{-/-}$	Regular	→		→	→	↑	↓	↓	→		H, A, B → (‡)	Ad‡, testes, tongue, brain	70
E-FABP$^{-/-}$	High fat	↓		↓	→	↑‡	→	→	↑	→		‡Marginally	70
E-FABP$^{-/-}$	Regular										H ↑ (Liv)	FA composition → (skin), TEWL: basal ↓; recovery ↓	71
E-FABP$^{-/-}$*ob/ob*	Regular	→		↓	↓‡	↑	↓	↓	↑	→		‡Marginally	70

Mouse strain	Diet	Body weight	FA uptake	Serum					Ins. sens.	Fatty liver	FABPs*	Notes	Refs
				Glu.	Ins.	FFA	TG	Chol.					
E-FABP$^{aP2\text{-promoter}}$	Regular	→				→					E ↑ (Ad); A ↓ (Ad)	Basal and stimulated lipolysis ↑; FA composition → (Ad)	25
E-FABP$^{aP2\text{-promoter}}$	High fat	→		↑	→	→	→	→	↓		E ↑ (Ad); A ↓ (Ad)		70
Brain FABP (B-FABP/FABP7)													
B-FABP$^{-/-}$	Regular										L, I, H, A, E → (Br)	Anxiety ↑; fear memory ↑; DHA ↓ (neonate)	79
B-FABP$^{-/-}$	Regular											Prepulse inhibition ↓; neurogenesis ↓	78

*Type of fatty acid-binding proteins (FABPs) are: A, adipocyte; B, brain; E, epidermal; H, heart; I, intestinal; II, ileal; L, liver. Ad, adipose tissue; Br, brain; Chol., cholesterol; DHA, docosahexaenoic acid; FA, fatty acid; FFA, free fatty acid; Glu., glucose; Ht, heart; Ins. sens., insulin sensitivity; Liv, liver; Ma, mammary gland; Mu, muscle; TEWL, transepidermal water loss; TG, triglyceride.

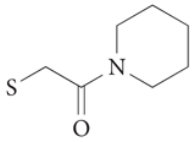
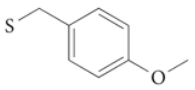
Table 3

Knockout mouse models for A-FABP (FABP4)

Mouse strain	Diet	Body weight	FA uptake	Serum					Ins. sens.	Fatty liver	Athero.	FABPs*	Notes	Refs
				Glu.	Ins.	FFA	TG	Chol.						
A-FABP														
A-FABP$^{-/-}$	Regular	→		→	→	↑‡	↓	→	→			E ↑ (Ad)	‡Marginally	53
A-FABP$^{-/-}$	High fat	↑		↓	↓	↑‡	↓	→	↑↑	→			‡Marginally	53
A-FABP$^{-/-}$	Regular												Stimulated lipolysis ↓; insulin secretion ↓; HSL level →	23
A-FABP$^{-/-}$	Regular		→									E ↑ (Ad)	Stimulated lipolysis ↓; adipose FAs ↑	24
A-FABP$^{-/-}$	Regular												Allergic airway inflammation ↓	62
A-FABP$^{-/-}$ *ob/ob*	Regular	↑		↓	↓	↑	↓	↓	↑↑			E ↑ (Ad)		54
A-FABP$^{-/-}$ *ApoE*$^{-/-}$	Regular			→	→		→	→	↑‡		↓	E →(Mφ)	‡Female	55
A-FABP$^{-/-}$ *ApoE*$^{-/-}$	High fat/chol.	↑		→		→	→	→	→		↓			63
A-FABP inhibitor (BMS309043) as reference														
A-FABP$^{+/+}$ *E-FABP*$^{+/+}$	High fat	→							↑					90
A-FABP$^{-/-}$ *E-FABP*$^{-/-}$	High fat	→							→					90
ob/ob	Regular	→		↓	↓	↑‡	↓	→	↑	↓		A, E → (Ad)	‡Marginally	90
ApoE$^{-/-}$	High fat/chol.	→		→	→	→	→	→	→		↓			90
A-FABP/E-FABP														
A-FABP$^{-/-}$ *E-FABP*$^{-/-}$	Regular	↓	↑‡/↓§	↓	→	↑	→	→	↑			L, I, H, B → (‖)	Altered FA composition (‖); ‡C12:0; §C18:0; ‖Ad, Mu, Liv	82
A-FABP$^{-/-}$ *E-FABP*$^{-/-}$	High fat	↓		↓	↓	↑	→	→	↑↑↑	↓				82
A-FABP$^{-/-}$ *E-FABP*$^{-/-}$ *ob/ob*	Regular	↑		↓	↓	↑	↓	↓	↑↑↑	↓				83

Mouse strain	Diet	Body weight	FA uptake	Serum					Ins. sens.	Fatty liver	Athero.	FABPs*	Notes	Refs
				Glu.	Ins.	FFA	TG	Chol.						
A-FABP$^{-/-}$ *E-FABP*$^{-/-}$ *ApoE*$^{-/-}$	Regular	↓‡		→		→	↓	↓	↑		↓↓		‡Male	84
A-FABP$^{-/-}$ *E-FABP*$^{-/-}$ *ApoE*$^{-/-}$													Survival ↑	84

*Type of fatty acid-binding proteins (FABPs) are: A, adipocyte; B, brain; E, epidermal; H, heart; I, intestinal. Ad, adipose tissue; ApoE, apolipoprotein E; Athero., atherosclerosis; C12:0, lauric acid; C18:0, stearic acid; Chol., cholesterol; E-FABP, epidermal FABP (also known as FABP5); FA, fatty acid; FFA, free fatty acid; Glu., glucose; HSL, hormone-sensitive lipase; Ins. sens., insulin sensitivity; Liv, liver; Mφ, macrophage; Mu, muscle; TG, triglyceride.

Compound name	X group	IC_{50} (μM)*				PDB code	Refs
		A-FABP	H-FAPB	E-FABP	I-FABP		
1	–	0.57	<0.6	6.7	>100	1tow	87
2	–	1.1	9.9	9.1	42	–	87
3a	3-Me	1.5	–	–	–	–	87
3b	6-Me	1.3	–	–	–	–	87
3c	5-Br	1.3	9.8	14	3.9	–	87
4a		1	–	–	–	1tou	88
4b		0.6	17	–	–	–	88

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Compound name	X group	IC_{50} (μM)*				PDB code	Refs
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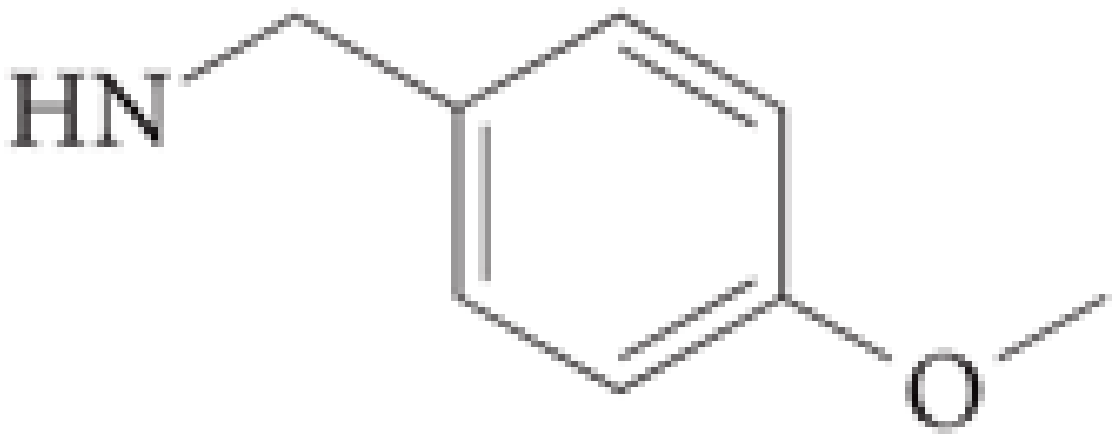
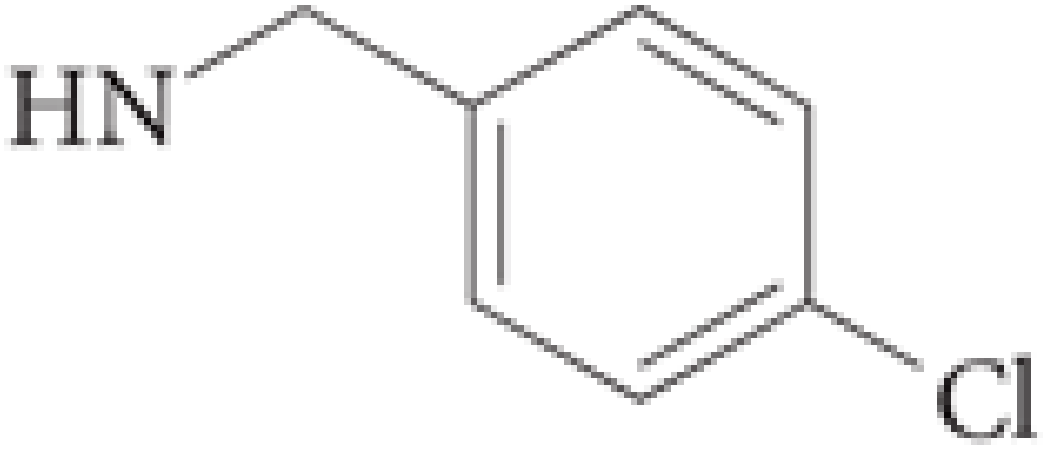
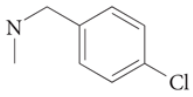
4c		3.9	>100	–	–	–	88
4d		2.9	>100	–	–	–	88
4e		4.0	>100	–	–	–	88

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Compound name	X group	IC_{50} (μM)*				PDB code	Refs
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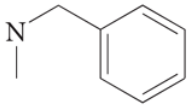
4f		24	>100	–	–	–	88
5 (BMS309403)	–	<2*	250*	350*	–	2nnq	89,90

ABP, heart FABP (FABP3); I-FABP, intestinal FABP (FABP2).