Proposed title: Fatty acid-binding proteins: tissue-specific functions in health and disease.

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Abstract:

Purpose of review: To review recent evidence for the role of the cytosolic fatty acid-binding proteins (FABP) as central regulators of whole-body metabolic control.

Recent findings: Dysregulated FABPs have been associated with a number of diseases, including obesity and non-alcoholic fatty liver disease (FABP1, FABP2, FABP4), cardiovascular risk (FABP3) and cancer (FABP5, FABP7). As underlying mechanisms become better understood, FABPs may represent novel biomarkers for therapeutic targets. In addition, the role of FABPs as important signalling molecules has also been highlighted in recent years; for example, FABP3 may act as a myokine, matching whole-body metabolism to muscular energy demands, while FABP4 functions as an adipokine regulating macrophage and adipocyte interactions during inflammation.

Summary: In addition to their traditional role as fatty acid trafficking proteins, increasing evidence supports the role of FABPs as important controllers of global metabolism, with their dysregulation being linked to a host of metabolic diseases.

Keywords: Fatty acid metabolism; NAFLD; obesity; metabolic syndrome; cancer

Introduction

The human intra-cellular fatty acid-binding proteins (FABP) are expressed in most of the major tissues, likely reflecting their critical biological roles. They are small (~15 kDa) cytosolic proteins that bind un-esterified long-chain fatty acids, and other ligands, with nanomolar affinity. It has been proposed that this reflects their biological roles as central regulators of lipid metabolism, inflammation and energy homeostasis through the control of fatty acid transport, metabolism and storage. It is intriguing that there are at least eight separate human isoforms that, while possessing only moderate sequence homology, have similar protein structures and ligand binding properties (1). In this review, we have excluded discussions of FABP as potential biomarkers of tissue damage, focusing instead on interesting recent data that broaden our understanding of these proteins, while also posing new questions regarding their role in health and metabolic diseases.

FABP1 (liver FABP, LFABP)

FABP1, first isolated from liver tissue, plays a central role in the hepatic β -oxidation of un-esterified fatty acids, both through fatty acid trafficking and the regulation of gene expression through interactions with PPAR α (1). Recent reports continue to implicate FABP1 down-regulation in steatotic livers and non-alcoholic fatty liver disease (NAFLD) (2)(3)(4)(5). In particular, the work of Chen and colleagues (4) demonstrates that, in mice, FABP1 is required to maintain intracellular lipid droplets in hepatic stellate cells (HSC). Typically quiescent, HSCs store vitamin A in lipid droplets; however, down-regulation of FABP1 resulted in their activation, proliferation, loss of lipid droplets and HSC secretion of collagen and extracellular matrix proteins, leading to hepatic fibrogenesis.

In the intestine, FABP1 has a role distinct from that of FABP2 (intestinal FABP, see below). FABP1 mediates the formation of pre-chylomicron transport vesicles (PCTV) through the fusion of FABP1 with the endoplasmic reticulum (ER) (6). Siddiqi and Mansbach have suggested a model in which FABP1 is held in the cytosol in a hetero-tetrameric complex containing FABP1, Sar1b, Sec13 and the

small VCP/p97-interactive protein (6). Phosphorylation of Sar1b by the atypical protein kinase C, PKC ζ , in the presence of ATP leads to the disruption of this complex leading to FABP1 fusion with the ER membrane, ER budding and generation of the PCTVs (6). A separate study by the Storch group showed that FABP1-/- knockout animals became obese and preferentially used lipids as an energy source, even though they displayed reduced fatty acid oxidation and decreased monoacylglycerol incorporation into triacylglycerol (7).

Several recent NMR-based studies have expanded our understanding of the properties and dynamics of FABP1 ligand binding (8)(9)(10)(11). Of particular interest is work demonstrating that FABP1 has a high affinity for multiple PPAR isoform-selective drugs and can interact directly with the ligand-binding domain of PPAR α (11). As PPAR α and FOXA1 are dominant trans-activators of FABP1 expression (3), this may indicate a positive feedback loop for FABP1 expression, whereby delivery of FABP1 ligands to PPAR α increases FABP1 expression. The role of C/EBP α in regulating FABP1 levels is less clear, with recent data supporting roles for it as both a repressor (3), and as an inducer (12) of FABP1 expression.

FABP2 (intestinal FABP, IFABP)

Intestinal enterocytes express FABP2, commonly described as intestinal FABP, in addition to FABP1. Recent work shows that FABP2-/- knockout mice lose weight in response to high fat feeding, decreased incorporation of fatty acids into triacylglycerols relative to phospholipids and preferentially utilised carbohydrates as an energy source (7). Considering the important role of the intestine in terms of nutrient uptake, it is rather surprising that more studies have not focussed on the functions of FABPs (including FABP6) in this tissue.

FABP3 (heart/muscle FABP, HFABP)

In addition to its expression in cardiac and skeletal muscle tissues, where its primary role is the trafficking of fatty acids, FABP3 is also expressed in a wide range of other tissues, albeit at significantly lower levels; these include testes, brain, kidney, lung, adrenal gland and lymphocytes (1). It is increasingly recognized that skeletal muscle does not exist as an isolated functional unit, but can contribute to paracrine and endocrine signalling, regulating energy demands through the secretion of key signalling molecules (myokines). FABP3 has been proposed as one such myokine, with exercise-associated increases observed in human skeletal muscle (13), as well as increased secretion from rat gastrocnemius muscle (14).

Recent work has highlighted a distinct role for FABP3 in apoptosis. For example, knockdown of FABP3 expression *in vitro* is associated with reduced proliferation and increased apoptosis in the P19 cardiac cell line (15), an effect that can be prevented through the use of the natural antioxidant α -lipoic acid (16). This implies that FABP3 may have a role in protection against oxidative stress. Studies in the model species zebrafish have replicated such findings, demonstrating that cardiac muscle-specific knockdown of FABP3 resulted in mitochondrial dysfunction, increased reactive oxygen species generation and increased apoptosis (17). Furthermore, cardiac organogenesis was severely impaired when FABP3 functioning was disrupted during the early stages of development. The exact mechanism for these effects is still not clear, although the Wnt, RAR and mTORC2 signalling pathways have been implicated (17)(18)(19).

FABP4 (adipocyte FABP, AFABP)

The main cells expressing FABP4 are differentiated adipocytes and macrophages (1), with substantial crosstalk between these cell types occurring in adipose tissue (20). In addition to its traditional role in trafficking of non-esterified fatty acids within cells, for example to and from PPAR γ and hormone-sensitive lipase (HSL) (1)(21), FABP4 is now recognized as an adipokine secreted from adipocytes and

macrophages (21). Increasing evidence exists for a link between lipid metabolism and inflammation, and FABP4 may mediate these effects, thus impacting on disease conditions such as metabolic syndrome, insulin resistance, NAFLD and atherosclerosis (22)(23)(21)(24)(25)(5)(26)(27) (28). For example, hepatic Kupffer cells are intimately involved in NAFLD pathogenesis and recent data has demonstrated that FABP4 is increased in Kupffer cells of NAFLD patients, and may be linked to increased pro-inflammatory cytokines and liver inflammation (5).

Further support for the role of FABP4 as an adipokine has been provided by *in vitro* studies demonstrating that interaction between adipocytes and macrophages increases the secretion of FABP4 into culture medium (27), while serum levels of FABP4 have been directly correlated with levels of adiposity (29), metabolic syndrome, atherosclerosis (21) and the long-term prognosis of cardiovascular mortality (23). The expression of FABP4 has also been linked to the rupture of atherosclerotic plaques (30), production of pro-inflammatory leukotriene C₄ (31), IL6/VEGF expression (26), angiogenesis in endothelial cells (32), and increased adipogenic differentiation of primary osteoblasts (33).

Paradoxically, pharmacological inhibition of fatty acid binding to FABP4 reversed NAFLD (5), while decreased FABP4 expression in adipocytes increased lipolysis (27). These studies reinforce previous studies showing that FABP4 has an important role in fatty acid storage, in the form of triacylglycerols. However, as pointed out by Ohira et al (27) an increase in lipolysis from adipocytes may contribute to the development of insulin resistance. Together, these suggest that reduced functionality of FABP4 mediated by short-chain fatty acids, statins, peptides, knockdown strategies or pharmacological compounds (5)(27)(34)(35)(36), may have beneficial effects, although tissue-specific inhibition by pharmacological agents may prove challenging.

FABP5 (epithelial FABP, keratinocyte FABP, EFABP, KFABP)

FABP5 has been found at detectable levels in adipocytes, macrophages, endothelial cells, lung epithelium, neural tissues and breast tumour (1)(37)(38). The role of FABPs in regulating cell proliferation is also seen with FABP5, where levels are up-regulated in breast tumours, promoting proliferation and metastasis in cultured cells, most likely through interactions with PPAR δ (37). A link between FABP5 and the immune system has also been recently demonstrated in a study investigating the response of lung epithelial cells to infection by influenza virus. Interestingly, a biphasic expression of FABP5 was observed in this study, with an initial down-regulation as part of immune response initiation, followed by recovery of expression levels to aid attenuation of the inflammatory response, possibly in conjunction with increased expression of PPAR γ (39). A specific inhibitor of FABP5, namely AM404, was used to show that FABP5 enhances the action of *N*-acylethanolamine, a PPAR α agonist, by increasing its uptake and nuclear translocation in Hela cells (38). Thus, several studies have shown that FABP5 interacts with the PPAR class of nuclear receptors and we speculate that these interactions are cell- and tissue-dependent, while probably also driven by substrate supply and the metabolic requirements of the specific cells.

FABP7 (brain FABP, BFABP)

The brain expresses three FABP isoforms in a dynamic spatio-temporal fashion, namely FABP3, FABP5 and FABP7 (1). Recent work with FABP5 and FABP7 knockout mice has demonstrated that both proteins are required for proliferation of neural stem cells, but negatively affect the survival of immature neurons in the postnatal hippocampus (40). Consistent with these observations, aberrant expression of FABP7 is detected in human glioma biopsies and is associated with invasion and progression of this malignancy (41,42). FABP7 is almost exclusively expressed in glioblastoma-derived neurospheres, which are believed to contain the stem-like cells responsible for tumour recurrence, with down-regulation of FABP7 expression resulting in reduced neurosphere migration (41). Related to this, Liu and colleagues demonstrated that the Pax6 transcription factor, which is

also expressed in brain tumour tissue and tumour neurospheres, is an inducer of FABP7 expression; a reduction of Pax6 expression reduced FABP7 levels in malignant glioma cells (42).

Separately, aberrant expression of FABP7 has been associated with poor prognosis of triple-negative breast cancer (43). Interestingly, this association is not through FABP7 expression directly, but rather through the sub-cellular localisation of this protein. A tissue microarray screening of almost 1,500 invasive breast cancers (44) revealed heterogeneity in sub-cellular localization, with cytoplasmic versus nuclear FABP7 having different prognostic implications dependent on breast cancer type. FABP7 expression exclusively in the cytosol or nucleus showed a better prognosis for tumours with nucleus-only expression, although the mechanistic rationale for this finding are unclear (44).

It has recently been demonstrated that FABP7 translation is regulated in a circadian fashion through alterations in poly(A) tail processing (45). This finding implies that subcellular trafficking of fatty acids, as mediated by FABP7, may be affected by circadian and/or sleep cycles (45), a topic that is of broad interest as disruption of these processes has been linked to increased occurrence in metabolic disease.

Clinically relevant polymorphisms within the FABP family

Given the important roles of FABPs, it is perhaps not surprising that polymorphisms in FABP genes are associated with the increased incidence of diseases within the obesity-metabolic syndrome-insulin resistance-type 2 diabetes spectrum (Table 1). As such, it is important to view these variants in light of their potential role in the spectrum of these disorders, rather than just with a single disease phenotype. Equally, the identification of a FABP2 polymorphism linked to cancer (Table 1) can also be understood through the role of several FABPs in this disease spectrum, as described above.

Several studies show FABP genetic variants may affect an individual's response to life-style interventions designed to reduce the risk of obesity-related diseases. For example, obese individuals with the FABP2 (Ala54Thr) variant responded better to hypocaloric diets than controls (Ala54Ala) in terms of anthropometric (e.g. BMI, waist circumference) and biochemical (e.g. HOMA-IR, total cholesterol) factors (46)(47). In addition, the exact fat composition appears to be critical for an optimal response, as improved anthropometric changes were replicated in Ala54Thr individuals fed a hypocaloric diet that was high in monounsaturated fats, while under this paradigm biochemical factors responded significantly poorer than controls (48). In a similar vein, Pishva et al (49) demonstrated that individuals with the Ala54Thr variant showed an improved response to eicosapentaenoic acid (EPA), with higher plasma levels of ω -3 and ω -6 fatty acids (49). These studies suggest that FABP variants do affect the response to life-style management, although this is highly dependent on the fatty acid composition within the diet and hence may be difficult to reproduce in the general population.

Zhang et al have recently shown that the promoter methylation status of FABP3 is significantly altered in individuals with metabolic syndrome, suggesting that epigenetic regulation may also play an important role in FABP physiology (50). The role of epigenetic modifications on gene functioning is a rapidly emerging field and one that promises to fill in many gaps in the understanding an individual's predisposition to disease and will complement studies on the impact genetic variation on disease aetiology.

Conclusion

The historically held view that FABPs are of minimal interest, acting merely as biologically silent traffickers of fatty acids, is dispelled by the above studies. It is becoming increasingly clear that the FABPs are important constituents of cellular and systemic metabolic networks, with functions in most of the major tissues that impact a wide range of disease aetiologies. Such roles will be further

elucidated through the use of untargeted studies focussed on, amongst others, the transcriptome, proteome and metabolome, technologies that have been poorly applied to FABP biology to date.

Key points:

- FABP1, FABP2 and FABP4 are implicated in steatosis, NAFLD, atherosclerosis, insulin resistance and the metabolic syndrome.
- FABP1 and FABP2 have different roles in the intestine, with divergent whole-body downstream effects at the level in terms of energy metabolism and obesity.
- FABP1, FABP4 and FABP5 are indirect regulators of gene expression through interactions with PPAR α and PPAR γ .
- FABP4 is involved in the metabolic cross-talk of Kupffer cells with hepatocytes in the liver and macrophages with adipocytes in the adipose tissue.
- FABP3, FABP4 and FABP7 are important in cell differentiation and the development of cancers.

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There are no conflicts of Interest.

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