Recent insights into the biological functions of liver fatty acid binding protein 1

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Abstract Over four decades have passed since liver fatty acid binding protein (FABP1) was first isolated. There are few protein families for which most of the complete tertiary structures, binding properties, and tissue occurrences are described in such detail and yet new functions are being uncovered for this protein. FABP1 is known to be critical for fatty acid uptake and intracellular transport and also has an important role in regulating lipid metabolism and cellular signaling pathways. FABP1 is an important endogenous cytoprotectant, minimizing hepatocyte oxidative damage and interfering with ischemia-reperfusion and other hepatic injuries. The protein may be targeted for metabolic activation through the cross-talk among many transcriptional factors and their activating ligands. Deficiency or malfunction of FABP1 has been reported in several diseases. FABP1 also influences cell proliferation during liver regeneration and may be considered as a prognostic factor for hepatic surgery. FABP1 binds and modulates the action of many molecules such as fatty acids, heme, and other metalloporphyrins. The ability to bind heme is another cytoprotective property and one that deserves closer investigation. The role of FABP1 in substrate availability and in protection from oxidative stress suggests that FABP1 plays a pivotal role during intracellular bacterial/viral infections by reducing inflammation and the adverse effects of starvation (energy deficiency).—Wang, G., H. L. Bonkovsky, A. de Lemos, and F. J. Burczynski. Recent insights into the biological functions of liver fatty acid binding protein 1. J. Lipid Res. 2015. 56: 2238–2247.

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OVERVIEW OF FATTY ACID BINDING PROTEIN 1

Liver fatty acid binding protein (FABP), also known as L-FABP or FABP1, is a 14 kDa soluble protein abundantly found in the cytoplasm of hepatocytes, and to a lesser extent in the nucleus (1, 2) and outer mitochondrial membrane (1, 3). FABP1 is also present in many other tissues, although in less abundance, e.g., enterocytes (4, 5), tubular cells of the kidney, and alveolar epithelium of the lung, among other tissues (6). Species differences exist in the presence or absence of FABP1 in various organs and in its content; e.g., FABP1 is present in human but not mouse kidneys (7, 8). In normal human liver, FABP1 accounts for as much as 7–11% of cytosolic proteins, nearly 2-fold more than in mouse liver (9). Unlike other members in the FABP family, each molecule of FABP1 is capable of binding two molecules of long-chain fatty acids (LCFAs) (Fig. 1) (10). The primary and secondary fatty acid binding sites appear to be interdependent, because both aliphatic chains form favorable hydrophobic interactions. This binding property may directly affect interactions with ligands, enzymes, or membrane systems (11). In addition to binding LCFAs, FABP1 binds fatty acyl-CoAs, peroxisome proliferators, prostaglandins, bile acids, bilirubin, heme, hydroxyl and hydroperoxyl metabolites of fatty acids, lyso-phosphatidic acids, selenium, and other hydrophobic ligands. Recent work has shown that FABPs may be involved in the transport of endocannabinoids (12, 13) and possibly monoacylglycerols (14). The extensive ligand binding property suggests that FABP1 has multiple functional roles (15). FABP1 can work as a trafficking and delivery controller of various ligands to cellular destinations such as enzymes, membranes, and nucleus. In many respects FABP1 appears to represent the intracellular equivalent to serum albumin, participating in the intracellular storage and transport of fatty acids and their acyl-CoA esters and influencing the metabolic utilization and compartmentalization of LCFAs (16). FABP1 also may be a possible carrier

Abbreviations: FABP, fatty acid binding protein; GFP, green fluorescent protein; HCC, hepatocellular carcinoma; HMOX, heme oxygenase; LCFAs, long-chain fatty acid; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus.

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of certain hydrophobic reactants in their passage from cytosol to chromatin (17), and thus may have a direct or indirect effect on cell growth. Moreover, the level of immunostained FABP1 is markedly increased during all stages of mitosis (18, 19), and FABP1 mRNA expression and levels were significantly increased during liver regeneration after 70% hepatectomy in rats. The regeneration activity and hepatic LCFA uptake rates were directly correlated to FABP1 level (20).

FABP1 is speculated to have an important cytoprotectant role by binding potentially toxic fatty acids, heme, and other molecules that, when unbound, may cause severe cytotoxicity. FABP1 can, therefore, affect enzyme function by its effect on ligand availability and targeting (21), modulate enzyme activity by changing membrane structure and fluidity (22), and regulate gene expression through activating nuclear receptors (23). PPARα and FABP1 are both found in the nucleus and likely interact directly as part of a signal transduction pathway (23, 24). Thus, FABP1 is likely involved in the signaling pathways for PPARα and PPARγ by transporting their agonists (25). The intracellular concentrations of FABP1 directly correlate with the activities of PPARα and PPARγ, suggesting that FABP1 is a positive regulator of PPAR expression. In the treatment of hypercholesterolemia, statins inhibit cholesterol synthesis and also decrease plasma triglyceride and nonesterified fatty acid levels. FABP1 is upregulated by and involved in the effects of statin treatment on hepatocytes. A molecular mechanism for this induction is suggested by the fact that statins transactivate the PPARα promoter (26). PPARα agonists enhance the transcriptional rate of the FABP1 gene and cause a rise in FABP1 mRNA and protein level (27). The upregulation of FABP1 is significantly correlated with protein content and peroxisomal fatty acid oxidation (28). This finding provides another molecular basis for the hypolipidemic effect of these drugs. The design of drugs affecting gene regulation usually focuses on ligand-activated receptors. However, it should be recalled that cellular chaperones/delivery systems function to transport drugs to their target sites. Therefore, FABP1 and other FABPs could serve as novel therapeutic targets that modulate nuclear receptor activity.

FABP1 concentration in hepatocytes is variable and responsive to changes in physiological and pharmacological conditions. Hepatic levels of FABP1 are gender specific (higher in females than males), increase during pregnancy and lactation (29, 30), decrease with age, and are also regulated by growth hormone (31). The gender influence on FABP1 corresponds to the effects of sex steroid hormones. Testosterone decreases, whereas estrogen increases, FABP1 levels in rats (32). The higher level of FABP1 in female rats, as well as the increased FABP1 content in male animals treated with clofibrate, is not related to differences in the turnover rate of FABP1, but appears to be correlated with an increased content of tissue FABP1 mRNA (33). Starvation and high-fat content diets also have clear and reciprocal effects on FABP1 levels (34–36). A high-carbohydrate diet increases FABP1 content in the liver and intestine (37). Low dose chronic alcohol consumption induces a marked increase of FABP1 in the livers of rats (38, 39). Methionine/choline-deficient diets decreased FABP1 significantly in a rat model of nonalcoholic steatohepatitis (NASH) (40), while dexamethasone has been reported to downregulate FABP1 by an indirect endocrine effect (41). Additional details regarding the occurrence distribution, ligand specificity, gene and protein structure, regulation, role in hepatic fatty acid uptake and transportation, and other potential physiological functions of FABP1 have recently been reviewed (42–44). Accordingly, the remainder of this review focuses on some new functions of FABP1.

**FABP1 AS A CELLULAR ANTIOXIDANT**

Liver diseases, such as cirrhosis, hepatitis, iron and copper overload, porphyrias, and hepatocellular carcinoma (HCC), are associated with notable changes in cellular lipid metabolic homeostasis, which usually correlate with changes in cellular FABP levels (45). FABP1 may play a regulatory or protective role by: a) controlling availability of LCFA and their oxidative metabolites, or other ligands such as heme that are potentially cytotoxic (46, 47), thus limiting the free LCFA fraction [in this manner FABP1 serves to protect the cytosol from the otherwise detergent effects of these molecules. Similarly, binding of molecules, such as heme, limits their availability to take part in reactive oxygen species (ROS) production (48)]; b) modulating the interaction of
LCFAs or other ligands with nuclear receptors (24); and e) trapping or scavenging ROS (49–52).

ROS may result from metabolic processes such as the metabolism of LCFAs, which may lead to the generation of highly reactive oxygen and hydroxyl radicals (53) or those derived from interrupted oxygen metabolism (hypoxia-ischemia/reperfusion). As well, unbound heme becomes highly cytotoxic in the presence of other molecules such as tumor necrosis factor (48). As primary defense mechanisms, binding proteins and antioxidant enzymes in cells such as superoxide dismutase, catalase, and glutathione peroxidase are present to scavenge these reactive species. Prolonged exposure to ROS, however, may deplete the cellular antioxidant capacity and cause cellular oxidative stress (54). FABP1 has been found to contain a cysteine group, which is known to be an effective antioxidant agent participating in S-thiolation/dethiolation reactions (55), and several methionine groups. Methionine residues have nucleophilic sulfur atoms and are regarded as cellular scavengers of activated xenobiotics such as carcinogens (56). Oxidative damage to cellular components may be suppressed by oxidation of the methionines in FABP1 to sulfoxides, which can be reduced back to methionine residues by methionine sulfoxide reductase (57, 58). Methionine sulfoxide reductase is highly expressed in liver (59) and is considered a regulator of cellular antioxidative defense (60, 61). Thus, redox cycling of the FABP1 methionine groups by methionine sulfoxide reductase causes a net scavenging effect by FABP1 for ROS, delineating an important antioxidant defense mechanism in cellular regulation (62) (Fig. 2). The mechanism of FABP1’s antioxidant activity is thought to be through inactivation of the free radicals by FABP1’s methionine and cysteine amino acids (63). FABP1 also binds many lipid peroxidation products (46, 49) and is present at high concentrations (approximately 0.4–0.8 mM) in hepatocytes. For these reasons FABP1 might serve as an endogenous cellular protectant (64–66).

Antioxidant activity of FABP1 was shown to be greatest when free radicals were released in the hydrophilic domain rather than in the lipophilic domain (63), suggesting that the cell is better protected by FABP1 in the cytosol. Using a hepatoma cell line, Yan et al. (67) reported that a reduction in FABP1 expression using FABP1 siRNA was associated with increased levels of ROS following H$_2$O$_2$-induced oxidative stress. In a rat model of cholestasis in which the common bile duct was ligated, PPAR agonist treatment increased FABP1 expression, and this correlated with a reduction of liver oxidative stress and risk of mortality (68). In a FABP1 gene knockout mouse model, mice exhibited higher sustained hepatic oxidative stress during chronic ethanol ingestion than the control group, suggesting that FABP1 is an antioxidant protein and that its downregulation may be important in the pathogenesis of alcoholic liver disease (69). In a glutathione depletion-induced oxidative stress rat model, upregulation of FABP1, along with upregulation of PPARα-regulated gene transcripts (i.e., acyl-CoA thioesterase-2 and -4), indicated that PPARα activation is involved in hepatocellular protection (70). Wang and colleagues had earlier suggested that FABP1 levels could be targeted through appropriate pharmacological treatment to minimize cellular damage (66, 68). Thus, FABP1 may be a new therapeutic strategy to suppress ROS levels occurring in the liver (71) during chemotherapy (72, 73) or drug-induced liver injury (74, 75).

FABP1 is also constitutively expressed in proximal tubular cells of kidney (76). Renal FABP1 plays a protective role against oxidative stress in kidney and reduces tubulointerstitial and glomerular injury and nephrotoxicity (7, 77–79). Expression of human FABP1 in mice (79) significantly reduced the number of macrophages (F4/80) infiltrating the interstitium, the levels of monocyte chemotactic protein-1 and -3, the degree of tubulointerstitial injury, and the deposition of type I collagen in the kidneys of unilaterally ureteral-obstructed mice (lipid peroxidation products were not observed in kidneys within 7 days of unilateral ureteral obstruction).

FABP1 also acts as a heme binding protein, thus limiting its availability in ROS production by shielding its highly reactive Fe-heme group. The regulatory heme pool normally controls cellular heme homeostasis in hepatocytes. A small but critical pool of bound heme regulates expression of 5-aminolevulinate synthase-1, the rate-controlling enzyme for heme synthesis, and heme oxygenase (HMOX), the rate-controlling enzyme for heme breakdown. The size and activity of the regulatory heme pool in hepatocytes may be linked to cytosolic heme-binding proteins. FABP1 has a 10-fold higher affinity for heme than for oleic acid, as well as other organic anions including other (metallo)porphyrins and bilirubin (80, 81). Compared with the binding affinity of human serum albumin for heme, FABP1 has a slightly higher binding affinity with dissociation constants of $K_d$ (FABP1) = 0.15 μM versus $K_d$ (albumin) = 0.5 μM (80, 82). Heme binds at the same binding site as oleate and thus, acts as an inhibitor for the binding of fatty acids. Ferroheme is a 3-fold stronger competitor of oleate binding than ferriheme; however, the oxidation states of heme do not affect the diffusion of heme in the presence of FABP1 because of its high binding affinity (83). Binding of heme to FABP1 might be an important determinant for drug efficacy by modulating the availability of drugs to their nuclear targets through competitive and allosteric mechanisms. Heme is synthesized in mitochondria and must be translocated to the cytoplasm and endoplasmic reticulum for hemoprotein
syntheses (e.g., cytochrome P450s, cytochrome b5, tryptophan pyrrolase, catalase, peroxidase, etc.). This efflux depends on the presence of a cytosolic protein (84). FABP1 likely facilitates heme efflux from mitochondria and cellular translocation (85). However, it is currently unknown whether intracellular FABP1 expression levels affect heme synthesis and metabolism. Whether there are altered levels or activities of FABP1 in hepatic porphyria and whether such levels play a role in modulating symptoms or clinical severity of porphyria are also unknown. Our recent in vitro study found that overexpression of FABP1 in hepatocytes reduces heme-induced cytotoxicity (Wang et al., unpublished observations). HMOX1, the rate-controlling enzyme for heme catabolism, has been found to have cytoprotective and anti-oxidant effects (86). In rats, hepatic glutathione depletion resulted in increased expression of both HMOX1 and FABP1 protein (70), suggesting that FABP1 and HMOX1 may have complementary or synergistic antioxidant effects. It will be very interesting to elucidate the role of FABP1 in heme-mediated cellular oxidative stress and the possible role of FABP1 in modulating the clinical expression of hepatic porphyria.

In summary, there is convincing evidence that FABP1 exerts cytoprotection in liver and kidney that FABP1 is an effective endogenous antioxidant.

**FABP1 IN METABOLIC DISEASES**

Nonalcoholic fatty liver disease (NAFLD) is the major hepatic manifestation of the metabolic syndrome and is associated with markedly increased risk for development of overt type 2 diabetes mellitus (T2DM), atherosclerotic heart disease, and cardiovascular disease. Approximately 10–20% of NAFLD patients have biochemical and histological evidence of hepatic progressive inflammatory and fibrogenic disorder, often referred to as NASH. Unlike NAFLD, which tends to be a benign condition, NASH patients are at risk for progressing to fibrosis or cirrhosis and developing HCC (87). Although the etiology and pathogenesis of these hepatic manifestations are not well understood, high levels of fatty acids in the liver and the known hepatotoxic effects of these agents raise the possibility that disturbances in hepatic fatty acid binding or oxidation may play a role in the pathogenesis of these conditions.

The importance of FABP1 in regulating a variety of cellular processes (inflammation, immunity, metabolism, and energy homeostasis), together with its role in binding fatty acids, would suggest that inactivation and/or loss of this protein might modulate susceptibility to NAFLD/NASH and perhaps other traits of the metabolic syndrome. Decreased expression of FABP1 not only occurs in rare human genetic lipid malabsorption syndromes such as abetalipoproteinemia and Anderson’s disease (88), but also occurs in more common human metabolic conditions such as NAFLD. FABP1 was overexpressed in simple steatosis patients compared with nonsteatotic patients and was shown to be decreased in NASH patients (89). Expression of FABP1 in NAFLD correlates with an altered expression of its transcription factors, mainly FOXA1 and PPARα (90). Significantly lower FABP1 levels were observed in steatotic rat or mouse models established by administration of methionine choline-deficient diet or 17α-ethynylestradiol (40, 91, 92). Conversely, FABP1 may be involved in a compensatory mechanism to counteract hepatocellular steatosis. Hepatic FABP1 levels are increased nearly 6.9-fold in a sterol carrier protein knockout mouse model of Refsum disease (93). In the liver of streptozotocin-nicotinamide-induced diabetic rats, FABP1 was reduced by ~4.7-fold. Restoration of hepatic FABP1 by receiving a fish oil diet was associated with lowered serum triglycerides and VLDL cholesterol levels and elevated serum high density lipoprotein cholesterol levels, as well as downregulated expression of TNF-α and IL-6, in livers of diabetic rats (94). FABP1 ablation significantly impacted hepatic fatty acid β-oxidative genes mediated by PPARα activation of the dietary n-3 PUFAs (rich fish oil), an even more prominent effect in the context of high glucose (95). Higher dose alcohol consumption is associated with impaired peroxisomal β-oxidation and FABP1 responses to PPARα in rats, and the severity of fatty liver correlated inversely with the level of FABP1. Treatment with clofibrate, a potent PPARα-activating ligand, prevented ethanol-induced oxidative stress, fat accumulation, and inflammatory changes in the liver (96). If these results in rats hold true for humans, targeting FABP1 by dietary therapy or man-made PPARα agonists has a therapeutic value in preventing irregularities in lipid metabolism in T2DM and alcoholic liver disease. The likelihood of NAFLD progression to advanced fibrosis or HCC is also impacted by age, gender, ethnicity, other genetic factors, other risk factors, etc. It is noteworthy to study how FABP1 is involved in this progression in human subjects. Direct parallels between the effects of human variants and observations in FABP1 ablation mice cannot yet be drawn. Uncertainties on the role of FABP1 in the pathology of human obesity and fatty liver include whether FABP1 functions or the extent that it is modulated during the pathogenesis. This underscores the importance of studying FABP1 in human subjects, as well as in murine models of disease.

**FABP1 VARIANTS AND KNOCKOUT MODELS**

A common human FABP1 genetic variation at sequence position 94, a threonine to alanine amino acid replacement (T94A), has been identified (97). Carriers of this SNP have higher baseline plasma free fatty acid levels, lower body mass index, and a smaller waist circumference than T94/T94 homozygotes. A significant trend of higher plasma triglyceride (98, 99) and LDL-cholesterol concentrations was also observed (100). This genetic variation alters the protein structure, stability, and interaction with fatty acids as well as PPARα agonists, and subsequently impacts fatty acid metabolism and PPARα activation (99, 101, 102). Therefore, FABP1 T94A missense mutation could influence obesity indices and the risk to exhibit residual hypertriglyceridemia following lipid-lowering therapy. A study of the association of FABP1 SNPs and NAFLD demonstrated that genetic variations within
FABP1 impact blood lipoprotein/lipid levels and responses to lipid-lowering therapy with fenofibrate (a cholesterol synthesis inhibitor) and glycogenolysis, which may contribute to a higher risk of NAFLD (98) as well as T2DM and insulin resistance (103). FABP1 polymorphism in a Chinese population was also shown to be associated with increased risk of NAFLD. The study population associated with two SNPs was reported to be at significantly higher risk for developing NAFLD than individuals with one SNP (98). These reports show the influence and importance that FABP1 SNPs have on modulating NAFLD risk.

In order to further understand the importance of FABP1 in cellular processes, FABP1 gene knockout mice have been generated on the C57BL/6 background from two independent laboratories, one referred to as the FABP1−/− mouse (104) and the other as the FABP1−/−-green fluorescent protein (GFP) mouse (105). Both lines of mice exhibit some similar phenotypes with the human FABP1 T94A variants, such as defective hepatic fatty acid uptake, oxidation, VLDL secretion, and triglyceride metabolism (100, 104–110). However, results of studies on the roles of FABP1 in obesity and fatty liver in mice fed with different types of high-fat/cholesterol diets have often proven contradictory (Table 1). For example, FABP1−/− mice were observed to gain more body weight and fat tissue mass relative to wild-type mice when fed high-fat/cholesterol diets (110–114). This result was reproducible by others using the same line of mice (21). However, in contrast, FABP1−/−-GFP mice fed high-fat diet showed less body weight gain and low risk of hepatic steatosis (115–119). Two recent review articles expressed opposing views about whether FABP1 may play an important role in preventing diet-induced obesity and/or steatosis (42, 120). Although dietary exposure, gender, and environmental factors all affect metabolic parameters in mice, design of gene-targeting construct, backcrossing to mouse substrains, and control mice (FABP1+/+ wild-type or FABP1+/−-GFP) in studies may be critical to interpretation of experimental observations. Moreover, GFP has 238 amino acid residues with a 26.9 kDa molecular mass, which is almost double the size of FABP1. Whether such an exogenous GFP replacement of FABP1 in hepatocytes would abundantly alter metabolic phenotypes in mice is not clear. Furthermore, overexpression of GFP in cells has

### Table 1. FABP1 gene knockout mouse models and comparison of their phenotypes in response to different diets

| Mouse Strains | Gender | Diet       | Body Weight | Fat Mass | FA Uptake | FFA Ser/Liv | TG Ser/Liv | Chol Ser/Liv | PL Liv | Liv Steatosis |
|---------------|--------|------------|-------------|----------|-----------|-------------|------------|-------------|--------|--------------|
| FABP1−/−-GFP backcross to C57BL/6J | Female | Regular | ↔ | ↔ | ↓ | ↔/↔ | ↔/↔ | ↔/↔ | ↔ | ↓ | Eight and 14 wks old, liv TG and PL ↓ in 48 h-fasted mice | 105 |
| | | High-fat | ↓ | ↓ | ↓/↔ | ↓/↔ | ↔/↔ | ↔/↔ | ↔ | ↓ | Twelve wks old, fed 20–36 wks, no difference in HFU fed | 118, 119 |
| | | High-fat/chol | ↓ | ↓ | ↔/↔ | ↑/↓ | ↔/↑ | ↓ | ↓ | ↓ | Twelve wks old, fed 18–26 wks, 4 h-fasted mice | 115 |
| | | | | | | | | | | | Eight wks old, fed 10–12 wks, no difference in HFU and low chol fed | 118, 119 |
| | Male | Regular | ↔ | ↔ | ↓ | ↔/↔ | ↔/↔ | ↔ | ↔ | ↓ | Eight and 14 wks old, liv TG and PL ↓ in 48 h-fasted mice | 105 |
| | | High-fat | | | | | | | | | Twelve wks old, fed 18–26 wks, 4 h-fasted mice | 115 |
| | FABP1−/− backcross to C57BL/6N | Female | ↔ | ↔ | ↑/↔ | ↔/↑ | ↑ | ↑ | ↑ | ↑ | Greater than or equal to 8 mo old, 12 h-fasted mice | 104, 106 |
| | | High-fat | ↑ | ↑ | | | | | | | Eight wks old, fed 12 wks, TG ↑ in LFD, ↓ in HFU | 111 |
| | | High-fat/chol | ↑ | ↑ | ↑/↑ | ↑/↑ | ↑ | ↑ | ↑ | ↑ | Eight wks old, fed 5 wks, 12 h-fasted mice | 113 |
| | Male | Regular | ↑ | ↑ | ↔/↑ | ↔/↓ | ↔/↔ | ↔ | ↔ | ↑ | Two mo old, fed 1–16 mo, 12 h-fasted mice, ser TG and lipids ↑ with age | 106, 110 |
| | | High-fat | ↑ | ↑ | ↔ | ↑/↓ | ↔ | ↔ | ↔ | ↑ | Three mo old, fed 12 wks, TG ↑ in LFD, ↓ in HFU | 21 |
| | | High-fat/chol | ↑/↑ | ↑/↔ | ↑/↑ | ↔ | ↔ | ↔ | ↑ | Eight wks old, fed 5 wks, 12 h-fasted mice | 114 |

All results were comparisons to wild-type mice; cells without symbols have no results reported. chol, cholesterol; HFU, high-unsaturated fat; liv, liver; mo, months; PL, phospholipids; ser, serum; wks, weeks; ↑, increase; ↓, decrease; ↔, no change relative to wild-type.
been found to have some biological effects (121, 122) and could specifically affect in vivo nucleic acid metabolism, energy utilization, amino acid catabolism, and immune responses (123, 124). Also, composition of diets, gender, and age of animals all vary between studies. For example, use of a high-fat diet containing hydrogenated coconut oil, containing medium-chain fatty acids that are weakly bound to FABP1 (125), has been reported to be associated with reduced weight gain (126). Moreover, growth and sex steroid hormones regulate FABP1 expression during the entire life span. It is not clear whether ablation of the FABP1 gene affects the hormones that correlate to metabolic phenotypes. There are no systematic data to show what potential compensatory genes are regulated due to ablation of FABP1 and/or in response to high-fat or high-cholesterol diets in these mouse models. In summary, although recent studies of these two FABP1 ablation mouse models do provide new insights to the functions of FABP1, the role of FABP1 in diet-induced obesity and steatosis is divergent. These results highlight the complications in interpretation of genetically altered mouse models. The relevance of results in murine knockout models to humans with metabolic syndromes is uncertain. Thus, direct parallels between the effects of human variants and observations in FABP1 ablation mice cannot yet be drawn.

Uncertainties on the role of FABP1 in the pathology of human obesity and fatty liver include whether FABP1 functions or the extent that it is modulated during the pathogenesis. This underscores the importance of studying FABP1 in human subjects, as well as in murine models of disease.

Recent studies demonstrate that LCFAs and their metabolites can modulate the action or localization of many transcriptional factors, including PPARs, liver X receptors, and hepatocyte nuclear factor (127). FABP1 has a similar binding spectrum with these proteins and may be targeted for metabolic activation through the cross-talk of these transcriptional factors and the ligands that activate them. A putative cyclic regulation seems to exist for FABP1 gene expression (Fig. 3) in which FABP1 binds a specific ligand, the complex stimulates a transcription factor, which then upregulates FABP1 expression. FABP1 overexpression may reduce ligand

![Fig. 3. A partial model of FABP1 in gene and metabolic activation.](image)

The ligand is transported through the cytoplasm to the nucleus by FABP1. Upon entering the nucleus, the FABP1:ligand complex binds to the PPAR receptor. The ligand-activated receptor, in turn, regulates the expression of FABP1, as well as other genes involved in fatty acid degradation or storage and embryonic development. GPCR, G protein-coupled receptors; CD36, cluster of differentiation 36, also known as fatty acid translocase (FAT); FATP, fatty acid transport protein; FABPpm, plasma membrane-associated FABP; RXR, retinoid X receptors; ACO, acyl-CoA oxidase; CPT-1, carnitine palmitoyl transferase; HNF, hepatocyte nuclear factor; HSL, hormone-sensitive lipase.

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availability and slow activation of the transcription factor. Therefore, FABP1 may be either a positive or negative factor in FABP1 expression regulation. FABP1 enhances LCFA uptake and intracellular LCFA transport and targets bound LCFA and/or LCFA-CoA to intracellular organelles’ esterification (endoplasmic reticulum), storage (lipid droplets), secretion (VLDL), or, most importantly, normal biological oxidation (in mitochondria, peroxisomes) (104, 128–131). As described above, FABP1 exerts appreciable antioxidant and/or detoxification effects, especially under conditions of increased oxidative stress (66, 68). Loss of FABP1 in liver may render hepatocytes more susceptible to the deleterious effects of LCFA and impact the capacity of hepatic lipid oxidation, thus contributing to the development of inflammation, steatohepatitis, and NAFLD progression. However, overexpression of FABP1 may induce unnecessary hepatic lipid accumulation. Thus, FABP1 likely works as a fine tuner in hepatic lipid metabolism.

CONCLUSION

The modern sedentary lifestyle of humans today too often is characterized by high caloric intake, low energy expenditure, ingestion of numerous and diverse xenobiotics, and highly stressful work or activities that lead to an unbalanced inflammatory and metabolic homeostasis that results in oxidative stress. Conservation of FABP1 from worms to humans, suggests that FABP1 is of fundamental importance. The roles of FABP1 in energy regulation/production, in response to oxidative stress, and in binding of heme and other metalloporphyrins suggest that FABP1 plays pivotal roles in resistance to infection and the adverse effects of starvation (energy deficiency) (68, 132, 133). FABP1 has been reported in many metabolic disease processes, such as cholestatic liver disease, cancer, diabetes, obesity, and atherosclerosis. Thus, in view of its highly conserved and central role in lipid metabolism and transport of heme and other ligands, the role of FABP1 in normal and pathological processes is in need of further study. The possible key questions to be answered would include: a) what effects do different levels of FABP1 exert on human diseases such as alcoholic liver disease, NAFLD, NASH, cirrhosis, HCC, and hepatic porphyria; b) should efforts be made to down- or upregulate FABP1 in liver in order to prevent or treat NAFLD; and c) should efforts be made to upregulate FABP1 prior to or post hepatectomy and liver transplant? Answers to these fundamental questions will shape therapeutics for liver diseases.

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