

Lipids and lipid binding proteins: A perfect match

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Review

Lipids and lipid binding proteins: A perfect match

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ABSTRACT

Lipids serve a great variety of functions, ranging from structural components of biological membranes to signaling molecules affecting various cellular functions. Several of these functions are related to the unique physico-chemical properties shared by all lipid species, i.e., their hydrophobicity. The latter, however, is accompanied by a poor solubility in an aqueous environment and thus a severe limitation in the transport of lipids in aqueous compartments such as blood plasma and the cellular soluble cytoplasm. Specific proteins which can reversibly and non-covalently associate with lipids, designated as lipid binding proteins or lipid chaperones, greatly enhance the aqueous solubility of lipids and facilitate their transport between tissues and within tissue cells. Importantly, transport of lipids across biological membranes also is facilitated by specific (membrane-associated) lipid binding proteins. Together, these lipid binding proteins determine the bio-availability of their ligands, and thereby markedly influence the subsequent processing, utilization, or signaling effect of lipids. The bio-availability of specific lipid species thus is governed by the presence of specific lipid binding proteins, the affinity of these proteins for distinct lipid species, and the presence of competing ligands (including pharmaceutical compounds). Recent studies suggest that post-translational modifications of lipid binding proteins may have great impact on lipid-protein interactions. As a result, several levels of regulation exist that together determine the bio-availability of lipid species. This short review discusses the significance of lipid binding proteins and their potential application as targets for therapeutic intervention.

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1. Introduction

The significance of lipids has generally been recognized throughout the years. Lipids are vital components of many biological processes and serve as building blocks of biological membranes (e.g., phospholipids, sphingolipids) or of specific proteins (e.g., myristoylation, palmitoylation), as substrate for metabolic energy production (long-chain fatty acids), and as signaling compounds (long-chain fatty acids and fatty acid metabolites). All lipid species are characterized by their virtual insolubility in aqueous solutions, i.e., their hydrophobic or amphiphilic nature, which property severely hampers the transport of lipids in aqueous compartments such as blood plasma, interstitium and the cellular soluble cytoplasm. However, these compartments contain proteins capable of reversibly and non-covalently binding lipids – therefore designated ‘lipid binding proteins’ – which dramatically enhance the availability and aqueous transport of specific lipid species. These proteins include a.o. plasma albumin and cytoplasmic lipid binding proteins such as cytoplasmic fatty acid binding proteins

(FABP_c), retinol/retinoic acid binding proteins, and oxysterol binding protein [1–3]. The plasma membrane also contains several proteins capable of reversibly and non-covalently binding long-chain fatty acids, collectively referred to as membrane-associated fatty acid binding proteins [4–6]. Together, the soluble and membrane-associated lipid binding proteins determine the bio-availability of their lipid ligands in a temporal and spatial manner, and thus directly influence the metabolism or signaling effect of these compounds. This short review focuses on the significance of cellular fatty acid binding proteins in health and disease and their potential application as drug targets.

2. Cytoplasmic fatty acid binding proteins

The intracellular or cytoplasmic FABPs were first discovered in 1972 [7] and are now known to form a group of 9 distinct proteins of 14–15 kDa with each type displaying a characteristic pattern of tissue distribution [1,3,8]. For instance, heart-type FABP_c (H-FABP or FABP3) occurs not only in heart but also in (red) skeletal muscle, brain and kidney. Likewise, liver-type FABP_c (L-FABP or FABP1) is found in both liver, small intestine and kidney. However, intestinal-type FABP_c

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(I-FABP or FABP2) is specifically expressed in intestinal enterocytes and brain-type FABP (B-FABP or FABP7) specifically in glial cells of the brain. The FABPs are abundantly expressed with cellular concentrations up to 300 μM [1]. Similar to plasma albumin, the FABPs each bind (long-chain) fatty acids with such high affinities that the total concentration of fatty acids present in the soluble cytoplasm is enhanced by several orders of magnitude (Fig. 1). Thus, while the estimated non-protein bound fatty acid concentration in the cytoplasm is only 1–5 nM, the total fatty acid concentration is up to 50 μM (depending of the metabolic state of the cell) [9–11]. As a result, throughout the soluble cytoplasm, cytoplasmic FABP provides a buffer for fatty acids as each fatty acid that is metabolized or undergoes transmembrane transport to another compartment is immediately replenished by the release of another fatty acid from the protein binding site. Therefore, and in view of the small size and free movement of the FABPs through the cytoplasm, a local subcellular deficit of fatty acids is unlikely to occur. Importantly, the abundance of FABP in the soluble cytoplasm (150–300 μM in hepatocytes and cardiomyocytes) presents with a total buffering capacity that markedly exceeds the total fatty acid concentration in each compartment [11] (Fig. 1). The latter assures that the non-protein bound fatty acid concentration remains low, even under mild pathological conditions (e.g. mild ischemia in the heart), so as to keep fatty acids from exerting detrimental effects [12].

The cytoplasmic FABPs can be seen as intracellular counterparts of plasma albumin and function as a sink for fatty acids taken up into the cell. Studies with genetically manipulated mouse models have shown that the absence of cytoplasmic FABPs markedly impairs cellular fatty acid uptake and utilization e.g., [13]. Luiken et al. [14] studied fatty acid uptake into skeletal muscle of mice with either a homozygous or heterozygous deletion of (heart-type) FABP to find that in homozygous mice the fatty acid uptake rate was reduced by approximately 45% while in skeletal muscle from heterozygous mice, in which the FABP protein expression was 34% of that of wild-type mice, fatty acid uptake was not altered compared to that in wild-type animals (Fig. 2) [14]. These data indicate that—at least in muscle—cytoplasmic FABP plays an important, yet permissive (rather than a regulatory) role in fatty acid uptake.

The three-dimensional protein structure of the FABPs is almost identical for all nine FABP types [3,15]. Common to all FABPs is a 10-stranded antiparallel β -barrel structure, which is formed by two orthogonal five-stranded β -sheets [16,17]. The binding pocket is located inside the β -barrel, the opening of which is framed on one side by an N-terminal helix–loop–helix ‘cap’ domain. Fatty

acids are bound in the interior cavity. The binding pocket of L-FABP is considerably larger than that of the other FABPs, allowing the binding of two fatty acid molecules with differing affinities. Other FABP types bind a single fatty acid molecule.

Pharmacological agents have been developed that interact with the lipid binding by FABPs and thus modify their function. These agents thus may act as tools to provide tissue-specific or cell type-specific control of lipid trafficking or of lipid-signaling pathways (reviewed [17]). For instance, a synthetic inhibitor was developed for adipocyte FABP (A-FABP or FABP4) that, both *in vitro* and *in vivo*, markedly influenced the interaction of A-FABP with its ligands in adipocytes and macrophages, thereby acting on metabolic and inflammatory pathways [18]. It was suggested that such chemical inhibition of A-FABP could be a potential therapeutic strategy against insulin resistance, type 2 diabetes, fatty liver disease and atherosclerosis [18]. More recent work by Hoo et al. [19] indeed demonstrated that chronic treatment with this pharmacological compound alleviates both acute liver injury and non-alcoholic steatohepatitis in mice as induced by exposure to a high-fat/high-cholesterol diet

3. Membrane-associated fatty acid binding proteins

Despite the fact that long-chain fatty acids can easily enter and diffuse within biological membranes, there now is ample evidence that their transport across membranes is facilitated by membrane-associated fatty acid binding proteins (reviewed in [20]). In particular, these membrane proteins facilitate the desorption of the fatty acids from the membrane which represents the rate-limiting step of transmembrane transport [21]. To date, at least three distinct types of membrane proteins have been identified that facilitate the cellular uptake of fatty acids. First, plasma membrane fatty acid-binding protein (FABP_{pm}) is a peripheral protein of approximately 43 kDa with a ubiquitous tissue occurrence [22–24]. Second, a family of so-called ‘fatty acid-transport proteins’ (FATP; 63 kDa) consists of 6 members (FATP1–6) each displaying a characteristic tissue distribution [6]. The FATPs are trans-membrane proteins showing acyl-CoA synthetase activity and merely function in the uptake of very long-chain fatty acids (chain length > 22) which then are converted directly into very long-chain acyl-CoA esters [5,6]. Third, CD36, also referred to as fatty acid translocase (FAT), is a class B scavenger receptor protein with multiple functions such as the binding of thrombospondin, oxidized low-density lipoprotein (LDL), and anionic phospholipids, and its action as a gustatory lipid sensor [5,25,26]. CD36 has a hairpin membrane topology with two transmembrane spanning regions, and is heavily glycosylated bringing the 472-amino acid protein (53 kDa) to 88 kDa.

With respect to the molecular mechanism of cellular fatty acid uptake (heart, muscle, and adipose tissue), the prevalent view is that the fatty acid transporter CD36 acts as an acceptor for fatty acids whereafter the fatty acids make their way through the cell membrane by simple diffusion. At the inner site of the membrane, the (transmembrane) protein may provide a docking site for H-FABP_c or for enzymes that act on fatty acids such as acyl-CoA synthetase [5]. Thus, CD36 may function to sequester fatty acids in the membrane, and help organize them within specific membrane domains so as to make the fatty acids readily available for subsequent aqueous transport and/or enzymatic conversion.

At the extracellular site CD36 shows protein–protein interaction with plasma membrane fatty acid-binding protein (FABP_{pm}), and at the intracellular site with cytoplasmic FABP that acts as a lipid chaperone by binding the incoming fatty acids and facilitating their transport to sites of utilization, as discussed above. While FABP_{pm} has been shown to facilitate cellular fatty acid uptake

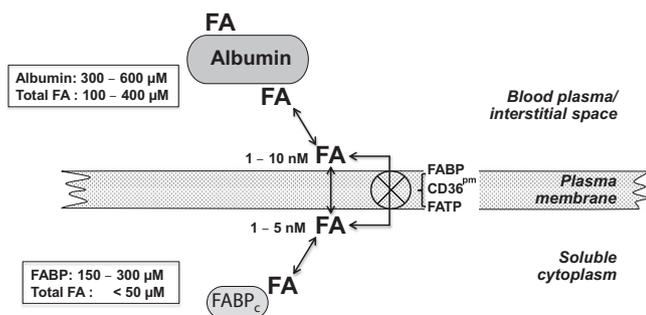


Fig. 1. Schematic presentation of the involvement of various lipid binding proteins in the cellular uptake of long-chain fatty acids. The concentrations of soluble binding proteins, i.e., albumin (68 kDa) in plasma (approximately 600 μM) or interstitial space (approximately 300 μM), and cytoplasmic FABP (15 kDa) in the cellular cytoplasm, and of (non-protein bound) fatty acids on both sides of the plasma membrane are given (data are for hepatocytes or cardiac myocytes, see [11]). The membrane-associated proteins FABP_{pm}, CD36 and/or FATP assist in the transmembrane transport and subsequent desorption of fatty acids. FA, long-chain fatty acid; FABP_c, cytoplasmic fatty acid-binding protein; FABP_{pm}, plasma membrane fatty acid-binding protein; FATP, fatty acid transport protein.

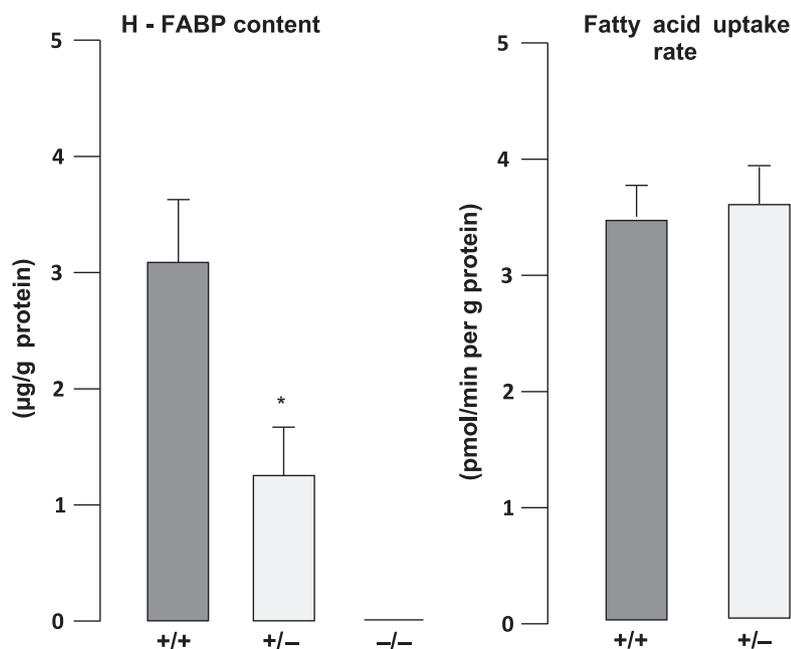


Fig. 2. H-FABP protein contents and fatty acid uptake rates of skeletal muscle from wild-type mice (+/+) and from heterozygous (+/-) and homozygous (-/-) H-FABP null mice. H-FABP contents were determined in tissue homogenates by ELISA. Palmitate uptake rates were measured in giant vesicles prepared from hindlimb muscles. These vesicles do not contain subcellular compartments (such as mitochondria), thus enabling the study of the uptake process separate from metabolism. Palmitate uptake was determined during 15 s at a physiologically relevant 1:1 M ratio with albumin, resulting in a non-protein bound fatty acid concentration of 5 nM. Data are means \pm SD for 7 experiments and were obtained from reference [14]. H-FABP, cytoplasmic heart-type fatty acid-binding protein. *Significantly different from wild-type animals ($P < 0.05$).

[27], the precise nature of this role is still obscure [5]; for instance, it may function to help create a local high concentration of fatty acids to drive their uptake or to localize CD36 to domains of the plasma membrane where fatty acid uptake preferentially would occur. Such latter role is also envisaged for the caveolins, small integral membrane proteins (22 kDa) that are the defining protein constituents of caveolae (specialized microdomains of the plasma membrane). Caveolins have been suggested to be potential fatty acid transporters [28], but may function in fatty acid uptake in an indirect manner, i.e., by offering plasma membrane docking sites for CD36 [5].

In case of the FATPs, the acyl-CoA synthetase activity of these transporters converts the fatty acids directly into their acyl-CoA ester, resulting in so-called metabolic trapping of fatty acids. This facilitatory action of the FATPs on cellular fatty acid uptake is also referred to as 'vectorial acylation' [6].

CD36 was found not only to facilitate but also to regulate fatty acid uptake in (cardiac and skeletal) muscle by a mechanism that resembles that of GLUT4-mediated cellular glucose uptake [29]. Thus, following an acute stimulus (insulin, muscle contraction) CD36 translocates from an intracellular store (endosomes) to the plasma membrane (Fig. 3). This recycling of CD36, together with the similar recycling of the glucose transporter GLUT4, appears to be pivotal for the proper regulation of cellular substrate uptake, for instance to clear lipids from the circulation postprandially and to rapidly facilitate substrate provision when the metabolic demands of muscle are increased by contractile activity [5]. Recent data indicate that this function of CD36 is controlled not only by intracellular recycling but also by post-translational modification, in particular *N*-glycosylation [30] and ubiquitination [31,32].

Several chronic diseases with genetic and lifestyle components (e.g., dietary factors) are characterized by a perturbed fatty acid (lipid) metabolism. For instance, excess cellular uptake of fatty acids is implicated as early driver in the etiology of lipotoxicity, type 2 diabetes, and heart failure. Evidence is accumulating that these conditions can be treated by the acute or chronic (partial) inhibition of CD36-mediated transport. For example, pharmacological inhibition

of CD36 transport by the small molecules AP5055 and AP5258 ameliorated atherosclerosis (46% decrease in plaque volume) and diabetes (50% decrease in plasma glucose) in rodent models, with potent reductions in blood triacylglycerol concentrations [33]. Similarly, the CD36 peptide ligand EP 80317 protected against ischemic myocardial injury in mice [34], while antibody inhibition of CD36 improved cardiomyocyte function in a cell model of high-fat induced insulin resistance by metabolic modulation towards glucose utilization rather than fatty acids [35]. Interestingly, complete genetic deficiency of CD36 in humans is mostly asymptomatic [36], suggesting that its pharmacological inhibition would not be harmful yet lead to a redistribution of lipids in the body that is beneficial to the functioning of key organs like heart and liver without affecting other organs.

4. Concluding remarks

A dynamic interplay exists among lipids and their cognate binding proteins. These lipid binding proteins act as chaperones for their lipid ligands, facilitating their transport in aqueous environments as well as across (and perhaps within) biological membranes thereby determining their bio-availability. Importantly, lipid binding proteins also protect against potentially detrimental effects of high concentrations of lipids (e.g., the detergent-like action of long-chain fatty acids). It is clear that the functioning of lipids in the various biological pathways (metabolism, signaling, etc.) in both invertebrates and mammals cannot be considered without taking these lipid binding proteins into account. It will be a challenge for the future to unravel further the dynamic interplay among the various lipid species and their metabolites with the various lipid binding proteins under both health and disease conditions. The complexity of these studies can be illustrated from recent insights that the functioning of the lipid binding proteins is controlled at several levels. For instance, the cellular expression of CD36 is under the control of lipid-responsive genes, its trafficking towards and from the plasma membrane is

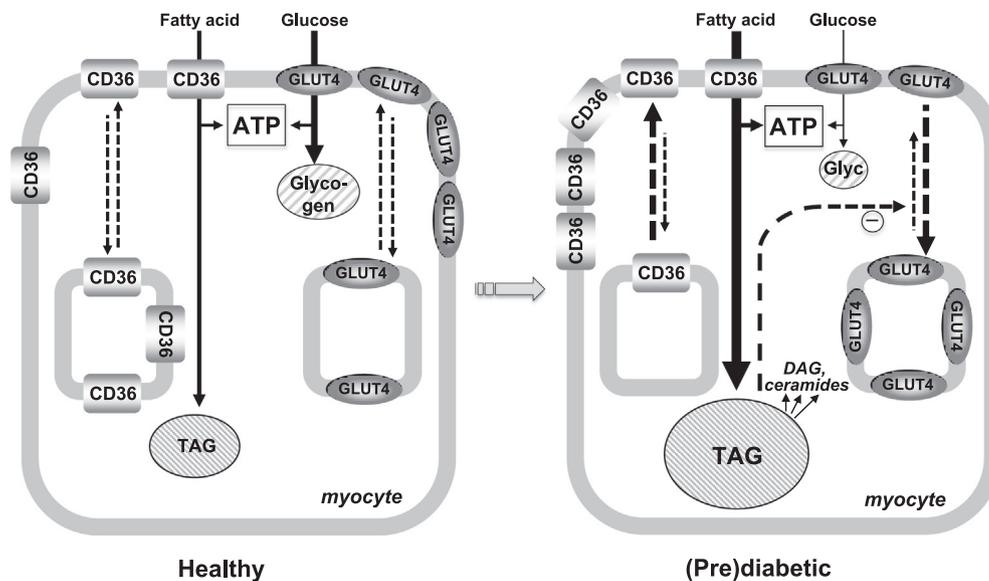


Fig. 3. Comparison of changes in subcellular localization of the substrate transporters CD36 (for fatty acids) and GLUT4 (for glucose) and in substrate utilization in myocytes during the transition from a healthy (*left panel*) to the (pre)diabetic state (*right panel*). In the healthy state, both CD36 and GLUT4 are about equally distributed between endosomes and sarcolemma, which results in a similar contribution of fatty acids and glucose to total energy production. In the (pre)diabetic state, there is a shift in CD36 localization from the endosomes to the sarcolemma leading to enhanced fatty acid uptake, fatty acids becoming the predominant substrate for metabolic energy production (ATP), excessive storage of fatty acids into triacylglycerols (TAG), and subsequent inhibition of insulin signaling by fatty acid metabolites such as diacylglycerols and ceramides. Subsequently, translocation of GLUT4 from endosomes to the sarcolemma is inhibited (*right panel, curved dashed arrow*), resulting in lowered glucose uptake and decreased incorporation into glycogen. At that stage, the muscle has become insulin resistant.

governed by hormonal (insulin) and mechanical (muscle contraction) stimuli, while its facilitatory action on cellular fatty acid uptake is regulated a.o. by post-translational modifications including glycosylation, palmitoylation and ubiquitination of the protein. Adding to the complexity is the fact that the various ligands of CD36 (thrombospondin, oxidized LDL, and various long-chain fatty acid species) may compete for the same extracellular hydrophobic binding pocket of the protein [5]. Once more insight has been obtained in these additional aspects it will be possible to design therapies to selectively modulate the actions of lipid binding proteins. As outlined above, a number of recent studies already indicate the feasibility of applying small molecule inhibitors directed against specific lipid binding proteins to rectify aberrant lipid metabolism and inflammation occurring in chronic disease.

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