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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.

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 date 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.

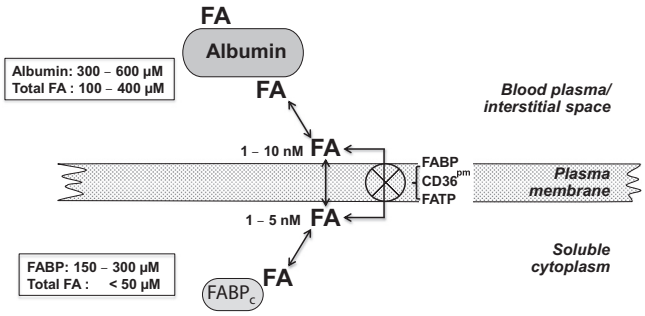

Fig. 1. Schematic presentation of the involvement of various lipid binding proteins in the cellular uptake of long-chain fatty acids. The concentrations of soluble binding proteins, i.e., albumin (68 kDa) in plasma (approximately 600 μM) or interstitial space (approximately 300 μM), and cytoplasmic FABP (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.

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 wherafter 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 FABPpm has been shown to facilitate cellular fatty acid uptake