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Review

Acyl-CoA binding protein and epidermal barrier function ☆

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ABSTRACT

The acyl-CoA binding protein (ACBP) is a 10 kDa intracellular protein expressed in all eukaryotic species and mammalian tissues investigated. It binds acyl-CoA esters with high specificity and affinity and is thought to act as an intracellular transporter of acyl-CoA esters between different enzymatic systems; however, the precise function remains unknown. ACBP is expressed at relatively high levels in the epidermis, particularly in the suprabasal layers, which are highly active in lipid synthesis. Targeted disruption of the ACBP gene in mice leads to a pronounced skin and fur phenotype, which includes tousled and greasy fur, development of alopecia and scaling of the skin with age. Furthermore, epidermal barrier function is compromised causing a ~50% increase in transepidermal water loss relative to that of wild type mice. Lipidomic analyses indicate that this is due to significantly reduced levels of non-esterified very long chain fatty acids in the stratum corneum of ACBP$^{-/-}$ mice. Here we review the current knowledge of ACBP with special focus on the function of ACBP in the epidermal barrier. This article is part of a Special Issue entitled The Important Role of Lipids in the Epidermis and their Role in the Formation and Maintenance of the Cutaneous Barrier. Guest Editors: Kenneth R. Feingold and Peter Elias.

1. Identification and evolutionary conservation of ACBP

Acyl-CoA binding protein (ACBP)/diazepam-binding inhibitor (DBI) (hereafter named ACBP) was first identified in rat brain in 1983 as a diazepam-binding inhibitor [1]. In 1987 it was independently isolated from bovine liver as a 10 kDa acyl-CoA binding protein able to terminate fatty acid synthesis by goat mammary gland fatty acid synthetase in vitro [2].

ACBP is expressed in all eukaryotic cells analyzed to date and displays a high degree of sequence conservation between species [3,4]. Thus, species as diverse as yeast (*Saccharomyces cerevisiae*) and humans share 48% amino acid identity, while two closely related species, mouse and rat, show 97% amino acid identity. ACBP belongs to a family of proteins, which in addition to ACBP includes a number of ACBP domain-containing proteins (ACBD) [5,6] with an ACBP-like domain in the N-terminus of a larger multidomain protein [6]. The present review focuses on the generally expressed ACBP isoform, and in particular on its function in epidermal lipid metabolism and maintenance of the barrier function.

2. ACBP in vitro functions

ACBP binds medium and long chain acyl-CoA esters (C_{14}–C_{22}) with very high affinity (K_d ~ 1–10 nM, 1:1 stochiometry) [7,8] independent of acyl-chain saturation [7]. The affinity towards short chain acyl-CoA esters and free Coenzyme A is very low [9,10], and ACBP does not bind e.g. free fatty acids, palmitoyl-carnitine and cholesterol [7]. Based on in vitro studies, ACBP has been proposed to play important roles in regulating acyl-CoA transport and metabolism (Fig. 1). These include extraction of acyl-CoA esters from membrane bilayers [11] and delivery of acyl-CoA esters to phospholipid [12–14], glycerolipid [15] and cholesteryl ester synthesis [16]. Furthermore, by sequestering acyl-CoA esters, ACBP is able to prevent acyl-CoA-mediated inhibition of the fatty acid synthetase (FAS) [2], acetyl-CoA carboxylase (ACC) and long chain acyl-CoA synthetase enzymes [17].

3. Tissue distribution of ACBP

In mammals, ACBP is expressed in all tissues and cell types investigated [3,4]; however, the level of expression varies greatly between different cell types. Peripheral tissues with a highly active lipid metabolism, such as liver and adipose tissues, display the highest level of ACBP expression [10,18–21].

ACBP is also expressed at high levels in type C2 lung surfactant secreting cells [4], and in the steroid hormone synthesizing adrenal glands as well as the Leydig cells of the testis [22]. Intermediate levels of ACBP are found in the epithelium in the kidneys, in particular in the cells specialized in water/electrolyte transport and secretion including

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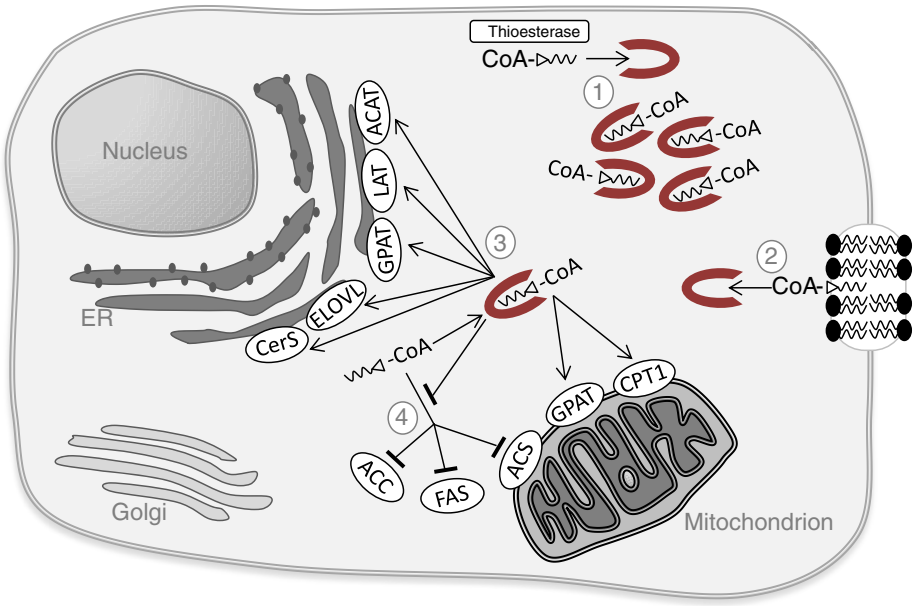

Fig. 1. Proposed functions of ACBP. By in vitro studies as well as studies in cell cultures and lower organisms, ACBP has been suggested to carry out a number of functions. ACBP (illustrated as a red bowl-like shape) is thought to act as an acyl-CoA pool former protecting acyl-CoA esters from hydrolysis (1), extract acyl-CoA esters from membranes (2), deliver acyl-CoA esters to phospholipid, glycerolipid and cholesteol ester and ceramide synthesis (CerS), to β-oxidation as well as fatty acid elongation (ELOVL) (3), and relieve acyl-CoA product inhibition of the enzymes FAS, ACC and ACS (4). Abbreviations: ACAT, acyl-CoA:cholesterol acyltransferase; ACC, acyl-CoA carboxylase; ACS, acyl-CoA synthetase; CerS, ceramide synthase; CPT1, carnitine palmitoyltransferase 1; ELOVL, elongation of very long chain fatty acids; FAS, fatty acid synthase; GPAT, glycerol-3-phosphat acyltransferase; LAT, lysophosphatidic acyltransferase.

brush border cells in the proximal tubules of the kidneys [23,24], in the epithelial cells of the gastrointestinal tract [25], and the salivary, lachrymal, sweat, sebaceous and prostate glands ([10,23,26–28] and our unpublished observations). The distribution of ACBP in the skin will be described below.

ACBP has been found in all cellular compartments [10,29,30]. Recently, fluorescently labeled bovine ACBP was shown to localize to the endoplasmic reticulum and Golgi apparatus after microinjection in HeLa and bovine mammary gland epithelial cells in a ligand dependent manner, and to accumulate around the Golgi apparatus in response to supplementation of exogenous fatty acids [31].

4. Regulation of ACBP expression

In mammals, ACBP is encoded by a ~10 kb gene organized in 4 exons [32]. Transcription of the gene is subject to activation by both peroxisome proliferator activated receptors (PPAR) and by sterol regulatory element binding proteins (SREBP) [21,33–35]. PPARγ is likely to be involved in induction of ACBP expression during adipocyte differentiation through binding to an intronic enhancer [35,36], whereas PPARα activates ACBP expression in the liver [33]. Moreover, both PPARs as well as SREBP-1 may play a role in induction of hepatic ACBP expression by high fat diet [37]. Androgens have been reported to induce ACBP expression in prostate epithelial cells, lacrimal glands, adrenals, and submandibular glands [38], possibly through a sterol regulatory element in the proximal promoter of the ACBP gene.

It remains unknown how ACBP expression is regulated in the epidermis. However, PPARs [39] as well as SREBPs [40,41] are involved in epidermal barrier formation and maintenance (reviewed elsewhere in this special issue by M. Schmuth et al.), and it is conceivable that these factors might be important regulators of ACBP expression in the epidermis.

5. Functional investigations of ACBP in simple model organisms and cell culture

5.1. Acyl-CoA binding protein in S. cerevisiae

Disruption of the gene encoding the ACBP homologue *ACB1* in *S. cerevisiae* results in reduced cellular growth [42–44]. Furthermore, *ACB1* deletion facilitates acyl-CoA chain elongation to C_{18}, and accumulation of $C_{18:0}$-CoA, concomitant with a decrease in unsaturated acyl-CoA species. Despite this change in acyl-CoA composition, the size of the total acyl-CoA pool remains unchanged. The most dramatic change in fatty acid composition is a 70% decrease in the presence of $C_{26:0}$ fatty acids in the yeast knockout strain, indicating that transport of $C_{16:0}$–$C_{18:0}$-CoA esters towards the fatty acid elongation system may be impaired. To this end, synthesis of ceramides and other sphingolipids is decreased by 50–70% in Acb1 depleted cells [43,44]. Cells depleted of Acb1 also show perturbed plasma membrane structure, accumulation of autophagocytotic vesicles, and fragmented vacuoles, which are unable to undergo homotypic vacuole fusion in vitro [43,44]. The latter is likely due to loss of SNARE proteins, which are required for vacuolar membrane fusion [44]. The abnormal morphology of vacuoles in Acb1-depleted yeast cells can be rescued by over-expression of yeast, human, mouse or insect ACBP and supplementation of exogenous fatty acids. Interestingly, Acb1 depletion sensitizes cells to osmotic changes, indicating that the perturbed plasma membrane structure impairs membrane permeability and ion homeostasis [43].

Depletion of Acb1 in yeast leads to increased expression of genes encoding proteins involved in fatty acid and phospholipid synthesis, glycolysis, glycerol metabolism as well as ion transport and uptake [45]. Although the exact mechanism underlying these changes remains to be elucidated, the expression of at least two of the target genes investigated (inositol-1-phosphate synthase, *INO1* and phospholipid methyltransferase, *OPI3*) could be normalized by exogenous supplementation with fatty acids or ectopic expression of FAS or ACC. Consistent with the above, over-expression of a mutant Acb1 unable to bind acyl-CoA