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The binding versatility of plant acyl-CoA-binding proteins and their significance in lipid metabolism☆

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ABSTRACT

Acyl-CoA esters are the activated form of fatty acids and play important roles in lipid metabolism and the regulation of cell functions. They are bound and transported by nonenzymic proteins such as the acyl-CoA-binding proteins (ACBPs). Although plant ACBPs were so named by virtue of amino acid homology to existing yeast and mammalian counterparts, recent studies revealed that ligand specificities of plant ACBPs are not restricted to acyl-CoA esters. *Arabidopsis* and rice ACBPs also interact with phospholipids, and their affinities to different acyl-CoA species and phospholipid classes vary amongst isoforms. Their ligands also include heavy metals. Interactors of plant ACBPs are further diversified due to the evolution of protein–protein interacting domains. This review summarizes our current understanding of plant ACBPs with a focus on their binding versatility. Their broad ligand range is of paramount significance in serving a multitude of functions during development and stress responses as discussed herein. This article is part of a Special Issue entitled: Plant Lipid Biology edited by Kent D. Chapman and Ivo Feussner.

1. Introduction

In eukaryotes, acyl-CoA synthetase activates long-chain fatty acids (FAs) by the attachment of coenzyme A (CoA) *via* a thioester linkage [1]. The resulting acyl-CoA esters are crucial for the transport and intermediary metabolism of FAs such as complex lipid assembly, β-oxidative degradation, protein acylation and derivation into very-long-chain (VLC) variants [2–4]. Together with their involvement in regulating enzyme activities [5–7], vesicular trafficking [8,9], gene expression [10–12] and intracellular signaling [13,14], the abundance of acyl-CoA esters is tightly controlled and they scarcely exist in free, unbound form [15,16]. Despite an estimation of cellular acyl-CoA concentration at several hundred μM, free molecules in the cytosol are maintained at <10 nM due to their association with membrane lipids and binding proteins [15,17]. Although acyl-CoA esters are non-specific ligands of ubiquitous nonenzymic proteins such as FA-binding proteins [18–20], sterol carrier protein-2 [21,22] and lipid-transfer proteins (LTPs) [23,24], their higher affinity to acyl-CoA-binding proteins (ACBPs) support these as the predominant carriers [20].

Initially, the first ACBP was reported as a neuromodulator that inhibits binding of an anxiolytic agent, diazepam, to its receptors on synaptic membranes in rat brain [25,26]. Some mammalian ACBPs were co-recognized as cell growth modulators [27], steroidogenesis stimulators [28] and insulin secretion inhibitors [29]. The discovery of acyl-CoA-binding (ACB) functions of ACBPs [30,31] prompted sequence homology searches in other genomes, yielding orthologs from virtually all eukaryotes and some pathogenic eubacteria [32,33]. Multiple isoforms exist in most eukaryotes examined except fungi [33,34]. Despite the classical definition as a small (ca. 10-kDa) protein, widely regarded as the prototypic form, ACBPs can also appear as large multi-domain proteins [16,33–35]. In mammals, ACBPs are grouped by tissue specificities into (i) the commonly expressed ACBP/diazepam-binding inhibitor (DBI)/endozepine which was first identified in bovine liver (L-ACBP); (ii) testis-specific endozepine-like protein (T-ACBP); and (iii) brain-specific DBI from duck and frog brains (B-ACBP) [32–34,36]. In contrast, classification of plant ACBPs is based on their molecular mass and domain architecture [37–40] (Fig. 1). Each of the four classes (namely small, ankyrin-repeat, large and kelch ACBPs) is well represented, for instance, by at least one member in 12 of the 13 higher plant species investigated [37,41]. Apparently, this classification scheme may not be applicable to non-plant ACBPs which exhibit considerable diversity and flexibility in protein domain architecture [16]. Besides the four distinct domains (i.e. Golgi dynamics, Herpes DNAp, ankyrin and enoyl-CoA hydratase) present in human ACBPs, other mammalian forms also contain haemolytic-, microcephalin-, GVQW- and homeo-domains with further diversity in the animal phyla [16].

Apart from classification, plant ACBPs differ from non-plant counterparts in ligand-binding specificities. In animals, although the identity of the major contributing proteins for binding acyl-CoA esters had been a subject of debate, a consensus was reached on the high-affinity binding

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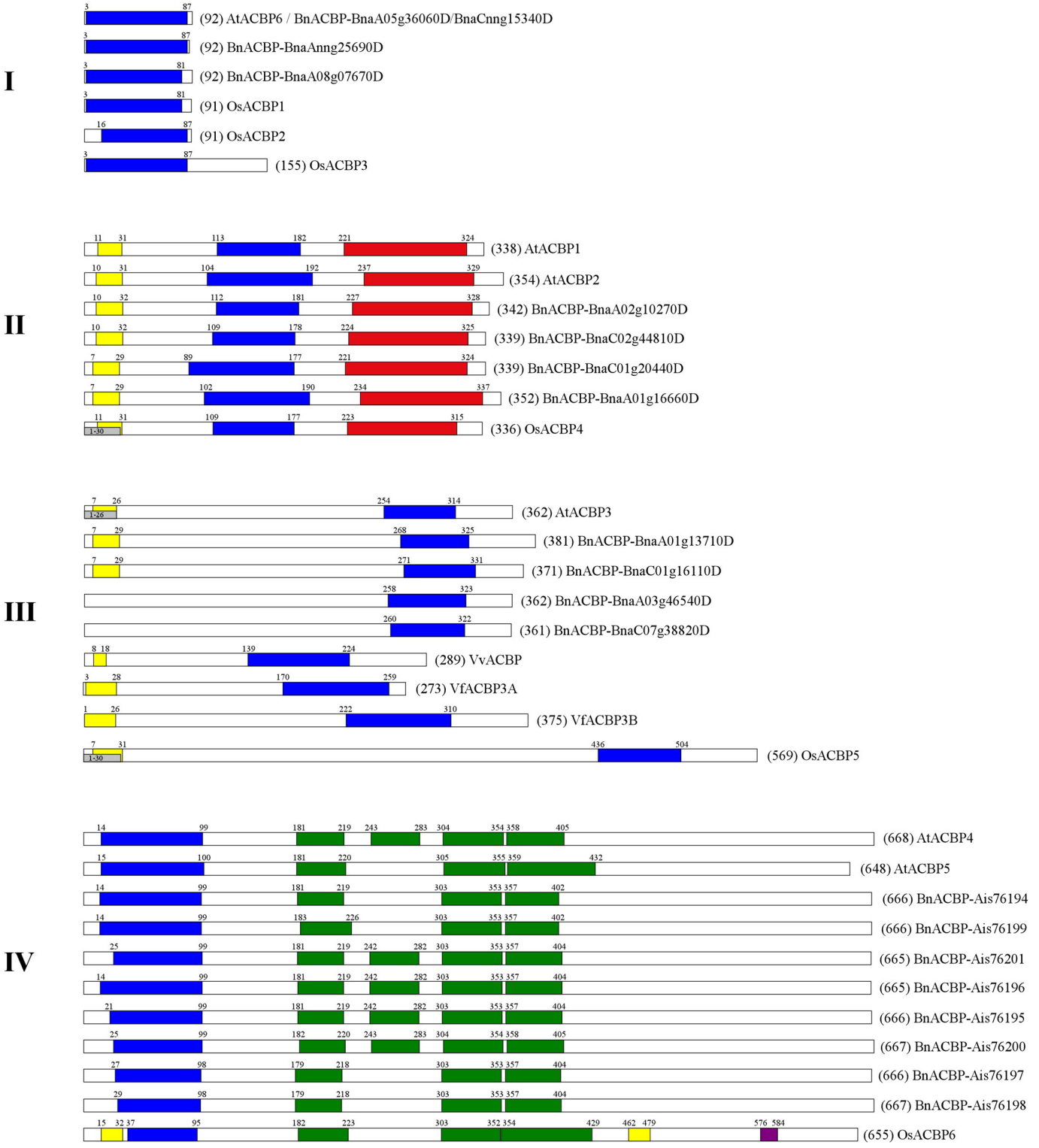

Fig. 1. Domain architecture of Classes I–IV ACBPs from various higher plant species. For alignment with the Conserved Domain Database (CDD) collection, ACBP sequences from *A. thaliana*, *B. napus*, *V. vinifera*, *V. fordii* and *O. sativa* were submitted to the NCBI protein BLAST search at http://blast.ncbi.nlm.nih.gov/Blast.cgi/. The identified domains and motifs include acyl-CoA-binding domain (cd00435) as annotated in blue, ankyrin-repeat domain (cd00204) in red, and kelch motif (pfam01344, 07646, 13415, 13418 and 13854) in green, and the predicted transmembrane domains are shown in yellow. Sorting sequences include signal peptides (in grey) and a peroxisomal-targeting signal (in purple). The total amino acid numbers are indicated in parentheses. The protein sequences are retrievable under the GenBank accession numbers as indicated for BnACBPs or as follows: AtACBP1 (AED96361), AtACBP2 (AEE85391), AtACBP3 (AEE84874), AtACBP4 (AEE74237), AtACBP5 (AED93708), AtACBP6 (AEE31396), VvACBP (ADK56449), VfACBP3A (AFZ62128), VfACBP3B(AFZ62129), OsACBP1 (BAG86980), OsACBP2 (BAG86809), OsACBP3 (ABF97253), OsACBP4 (BAF16206), OsACBP5 (BAG93201) and OsACBP6 (ABF99748).

of animal ACBPs exclusively to long-chain acyl-CoA esters (but not to FAs, phospholipids, lysophosphatidylcholine (lysoPC), cholesterol or other ligands tested), distinguishing this protein family from other non-specific binding proteins [15,23,30,33,42,43]. On the contrary, the past decade has seen the emergence of a broader ligand range of plant ACBPs, from diverse species of acyl-CoA esters, phospholipids to heavy metals. The evolution of protein–protein interacting domains in some subclasses further diversifies the nature of plant ACBP interactants. In

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