

Interactions between *Arabidopsis* acyl-CoA-binding proteins and their protein partners

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Abstract Protein–protein interactions are at the core of cellular interactomics and are essential for various biological functions. Since proteins commonly function as macromolecular complexes, it is important to identify their interacting partners to better understand their function and the significance in these interactions. The acyl-CoA-binding proteins (ACBPs) of eukaryotes show conservation in the presence of a lipid-binding acyl-CoA-binding domain. In *Arabidopsis thaliana*, four of six members from the AtACBP family possess ankyrin repeats (AtACBP1 and AtACBP2) or kelch motifs (AtACBP4 and AtACBP5), which can potentially mediate protein–protein interactions. Through yeast two-hybrid screens, a dozen putative protein partners interacting with AtACBPs have been isolated from an *Arabidopsis* cDNA library. Investigations in the past decade on the interaction between AtACBPs and their protein partners have revealed novel roles for AtACBPs, including functions in mediating oxidative stress responses, heavy metal tolerance and oxygen sensing. Recent progress and current questions on AtACBPs and their interactors are discussed in this review.

Keywords Ankyrin repeats · Lipid metabolism · Protein–protein interactions · Stress · Transcription factors

Abbreviations

ACBP Acyl-CoA-binding protein
ACB Acyl-CoA-binding domain
TF Transcription factor
ERF Ethylene response factor

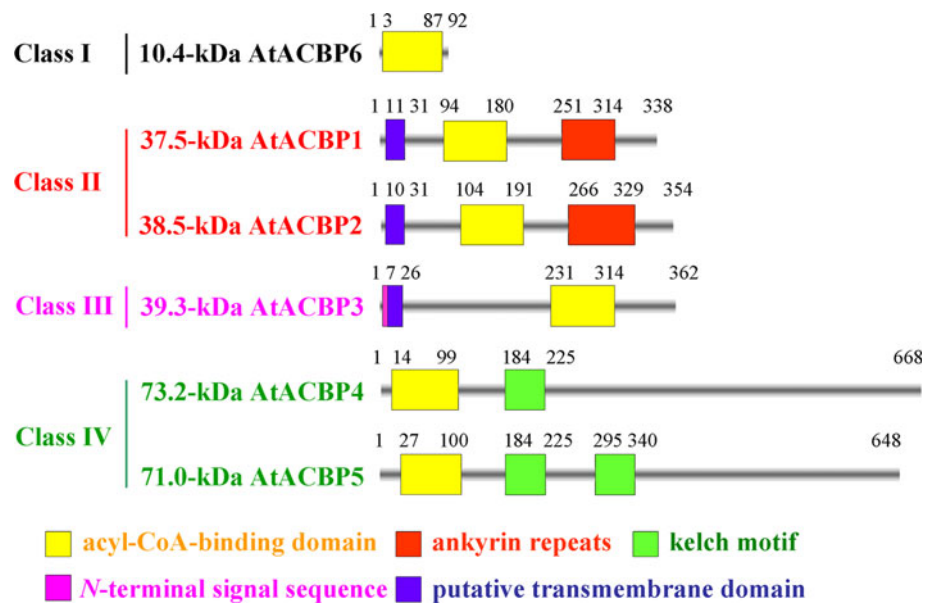
Introduction

Acyl-CoA-binding proteins (ACBPs) have been reported to bind long-chain acyl-CoA esters (C₁₂–C₂₂) through their acyl-CoA-binding domains with high specificities and affinities (Rasmussen et al. 1993; Chye 1998; Chye et al. 2000; Knudsen et al. 2000; Burton et al. 2005; Leung et al. 2004, 2006). The first identified ACBP was a neuropeptide (diazepam-binding inhibitor) from rat brain that inhibits benzodiazepine-binding (Guidotti et al. 1983). Subsequently, similar small cytosolic ACBPs were isolated from many eukaryotes and some prokaryotes (Burton et al. 2005; Xiao and Chye 2011a). These 10-kDa ACBPs were found to participate in acyl-CoA transport (Rasmussen et al. 1994; Schjerling et al. 1996) and in the maintenance of intracellular acyl-CoA pools (Knudsen et al. 1994; Gaigg et al. 2001; Huang et al. 2005), in membrane biosynthesis (Gaigg et al. 2001; Faergeman et al. 2004) and in the regulation of gene expression and enzyme activities related to lipid metabolism (Rasmussen et al. 1993; Mandrup et al. 1998; Kannan et al. 2003; Feddersen et al. 2007; Oikari et al. 2008).

In *Arabidopsis thaliana*, five larger ACBPs, AtACBP1 to AtACBP5, have been characterized besides the 10-kDa ACBP homologue, which has been designated as AtACBP6 (Xiao and Chye 2009, 2011a). Although *Arabidopsis* ACBPs are conserved at the acyl-CoA-binding domain, they show a range in size from 10.4 to 73.2 kDa (Fig. 1) (Xiao and Chye 2009, 2011a). AtACBP1 and its highly conserved homologue, AtACBP2, share 76.9 % amino acid identity and each has an N-terminal hydrophobic transmembrane domain and C-terminal ankyrin repeats (Fig. 1) (Chye 1998; Chye et al. 1999, 2000). *AtACBP1* and *AtACBP2* are expressed in siliques, stems, leaves, flowers and roots (Chye 1998; Chye et al. 2000). Previous studies have

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Fig. 1 Domain architecture of Arabidopsis ACBPs. The numbers indicate amino acid positions in each protein. Six members of Arabidopsis ACBPs (AtACBPs) are distributed across four classes, classes I–IV, as indicated (Meng et al. 2011)



confirmed that they are subcellularly localized to the plasma membrane (PM) and the endoplasmic reticulum (ER) (Chye 1998; Chye et al. 1999, 2000). AtACBP3 has an N-terminal signal peptide and a transmembrane domain, and is targeted to the extracellular space (Fig. 1) (Leung et al. 2006). Kelch-motif containing AtACBP4 and AtACBP5 share 81.4 % amino acid identity (Fig. 1) (Leung et al. 2004). They are subcellularly localized to the cytosol (Xiao et al. 2008), while AtACBP4 has also been detected at the periphery of nuclei (Li et al. 2008). The 10-kDa AtACBP6, consisting solely of an ACB domain, was experimentally verified to be a cytosolic protein (Fig. 1) (Chen et al. 2008).

In recent years, increasing evidence has revealed that AtACBPs are involved in many biological processes, such as plant development (Chen et al. 2010; Du et al. 2013a), leaf senescence (Xiao et al. 2010), pathogen resistance (Xiao and Chye 2011b) and response to environmental stresses (Chen et al. 2008; Du et al. 2010, 2013b) including oxidative and heavy metal stresses (Xiao et al. 2008; Gao et al. 2009, 2010). In addition, AtACBPs containing ankyrin repeats (AtACBP1 and AtACBP2) and kelch motifs (AtACBP4) have been observed to interact with protein partners, some of which have also turned out to be stress-responsive proteins (Li and Chye 2004; Li et al. 2008; Gao et al. 2009, 2010; Licausi et al. 2011; Du et al. 2013a).

AtACBPs interact with enzymes of lipid metabolism

Ankyrin repeats are one of the most common motifs that mediate protein–protein interactions and are found in AtACBP1 and AtACBP2 (Fig. 1) (Michaely and Bennett 1992; Sedgwick and Smerdon 1999; Li et al. 2006). AtACBP2 has

been reported to interact with LYSOPHOSPHOLIPASE2 (lysoPL2), which can detoxify lysophosphatidylcholine (lysoPC) (Gao et al. 2010). Lysophospholipids are generated by phospholipase A in response to stresses (Ryu 2004). Fluorescence resonance energy transfer (FRET) analysis using agroinfiltrated tobacco leaves revealed that the interaction between lysoPL2 and AtACBP2 occurs at the ER as well as the plasma membrane, via the ankyrin repeats of AtACBP2, consistent with the observations in yeast two-hybrid and co-immunoprecipitation assays (Gao et al. 2010). A mutant of AtACBP2 lacking the ankyrin repeat domain did not show interaction with lysoPL2 (Gao et al. 2010). The overexpression of lysoPL2 in transgenic Arabidopsis conferred enhanced tolerance to cadmium (Cd) and hydrogen peroxide (H_2O_2) treatments (Gao et al. 2010). Consistently, *lysoPL2* mutants were sensitive to zinc (Zn) and H_2O_2 , suggesting a positive role for lysoPL2 in oxidative stress (Gao et al. 2010). Subsequently, recombinant lysoPL2 was demonstrated to degrade toxic lysoPC in vitro (Gao et al. 2010). Considering that AtACBP2 binds lysoPC through its ACB domain and interacts with lysoPL2 via its ankyrin repeats, these partners likely promote lysoPC degradation (Fig. 2a).

Another ankyrin repeat-containing AtACBP, AtACBP1, has been recently reported to interact with PHOSPHOLIPASE D α 1 (PLD α 1) at the plasma membrane by bimolecular fluorescence complementation (BiFC) and yeast two-hybrid assays (Du et al. 2013a). PLD α 1 is a membrane phospholipase, producing phosphatidic acid (PA) (Fan et al. 1999), and its activity can be stimulated by abscisic acid (ABA) (Zhang et al. 2004). It has been shown that AtACBP1 overexpression in Arabidopsis enhances *PLD α 1* expression in response to ABA treatment (Du et al. 2013a).

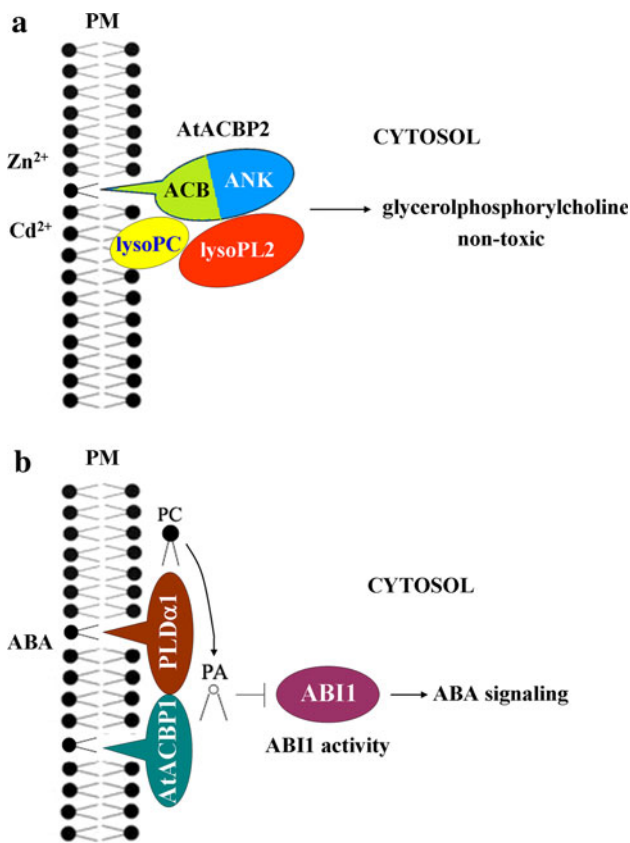


Fig. 2 Arabidopsis ACBPs interact with enzymes involved in lipid metabolism. **a** AtACBP2 binds both lysoPL2 and lysoPC. AtACBP2 recruits lysoPL2 to degrade toxic lysoPC resulting from Zn or Cd-induced stress, **b** AtACBP1 binds PLDα1 and PA. The membrane-associated PA likely inhibits ABI1 activity to promote ABA signaling. PA, phosphatidic acid; PC, phosphatidylcholine; PM, plasma membrane; lysoPC, lysophosphatidylcholine; ACB, acyl-CoA-binding domain; ANK, ankyrin repeats

Given that recombinant AtACBP1 binds PA and phosphatidylcholine (PC) in vitro (Chen et al. 2010; Du et al. 2010, 2013a) and that AtACBP1 interacts with PLDα1 at the plasma membrane (Du et al. 2013a), AtACBP1 possibly promotes hydrolysis of PC to PA as a result of an increase in *PLDα1* expression (Fig. 2b). Similar PC/PA changes occur in freezing stress; upregulation of AtACBP1 enhances *PLDα1* expression in response to freezing stress and AtACBP1-overexpressors produce more PA but less PC than the wild type and the *acbp1* mutant (Du et al. 2010). PLDα1-derived PA directly binds to ABSCISIC ACID-INSENSITIVE1 (ABI1), a principal negative regulator of ABA responses (Gosti et al. 1999; Merlot et al. 2001), leading to the suppression of ABI1 activity and thereby promotion of ABA signaling (Fig. 2b) (Zhang et al. 2004; Li et al. 2009). This model can explain the increase in ABA sensitivity of AtACBP1-overexpressors during seed germination and seedling development (Fig. 2b) (Du et al. 2013a).

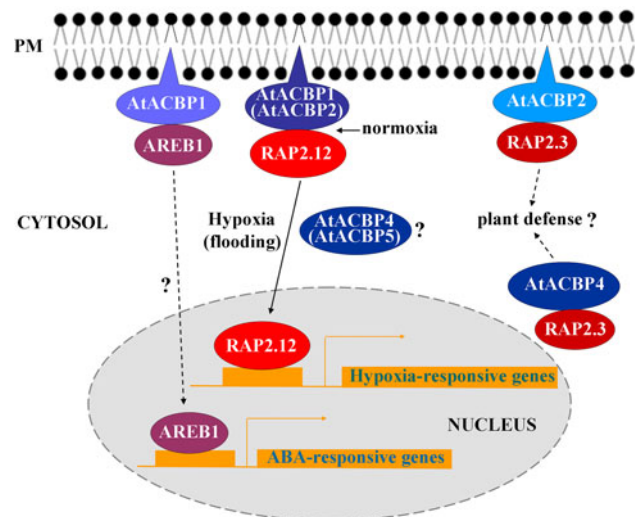


Fig. 3 Arabidopsis ACBPs interact with transcriptional factors. AtACBP2 and AtACBP4 may be involved in plant defense responses by their interactions with RAP2.3 at the plasma membrane and the cytosol, respectively (Li and Chye 2004; Li et al. 2008). AtACBP1 and AtACBP2 participate in oxygen sensing via interactions with RAP2.12 at the plasma membrane (Licausi et al. 2011). Under normoxia, RAP2.12 is sequestered by AtACBP1 or AtACBP2 at the plasma membrane (Licausi et al. 2011), and is thereby protected against degradation by the *N*-end rule pathway (Gibbs et al. 2011; Licausi et al. 2011). Upon hypoxia, RAP2.12 moves into the nucleus to activate the expression of hypoxia-responsive genes (Licausi et al. 2011). AtACBP1 also interacts with AREB1 via a yet unknown mechanism (Tse 2005)

AtACBPs interact with transcriptional factors

Besides enzymes in lipid metabolism, AtACBPs have been also noted to interact with transcriptional factors (TFs), including members from the ethylene response factor (ERF) family (Li and Chye 2004; Li et al. 2008; Licausi et al. 2011). Using yeast two-hybrid screening with an Arabidopsis cDNA library, AtACBP2 was first observed to interact with an ethylene-responsive element-binding protein, AtEBP, also named RELATED TO APETALA2.3 (RAP2.3) (Li and Chye 2004). Their interaction was further confirmed by co-immunoprecipitation assays and colocalization analysis by confocal microscopy, which revealed their interaction at the plasma membrane (Fig. 3) (Li and Chye 2004). This represented the first report suggesting that an AtACBP which is targeted to the ER and plasma membrane interacts with a TF (Li and Chye 2004).

Subsequently, another AtACBP, the cytosolic AtACBP4, was reported to interact with the same ERF, RAP2.3, in the cytosol (Fig. 3) (Li et al. 2008). This interaction, initially detected using yeast two-hybrid screens, was further confirmed by co-immunoprecipitation assays and FRET analysis (Li et al. 2008). It is interesting that both AtACBP2 and AtACBP4 interact with RAP2.3. Further investigations showed that it is the ankyrin repeats

of AtACBP2 that facilitate the interaction between AtACBP2 and RAP2.3, because a deletion mutant of AtACBP2 lacking the ankyrin repeats failed to interact with RAP2.3 (Li and Chye 2004). In contrast, the interacting sites on AtACBP4 and RAP2.3 are still unclear (Li et al 2008). However, as shown in Fig. 1, AtACBP4 possesses kelch motifs which are known to mediate protein–protein interactions (Adams et al. 2000; Andrade et al. 2001). Thus, it has been predicted that AtACBP4 could interact with RAP2.3 via these motifs (Li et al. 2008). Given that the expression of *RAP2.3* and *AtACBP4* are induced by *Botrytis cinerea* infection, as well as by compounds that are essential in defense responses to *B. cinerea*, the ethylene precursor 1-aminocyclopropane-1-carboxylic acid and methyl jasmonate, RAP2.3 and AtACBP2/AtACBP4 may participate in plant defense responses through ethylene and/or jasmonate signaling (Fig. 3) (Li et al. 2008). Subsequently, interaction between RAP2.12 (which also belongs to the ERF family) and AtACBP1/AtACBP2 were reported using BiFC and yeast two-hybrid assays (Licausi et al. 2011).

The Arabidopsis ERF family includes over 100 members phylogenetically parsed into ten clades, while both RAP2.12 and RAP2.3 belong to the group VII ERFs (Nakano et al. 2006). There are five members in this group, RAP2.12, RAP2.2, RAP2.3, HYPOXIA RESPONSIVE1 (HRE1) and HRE2, which are characterized by a conserved *N*-terminal motif (MCGGAIL) (Nakano et al. 2006; Bailey-Serres et al. 2012). Four members of this group (except RAP2.3) have been reported to be associated with responses to submergence (flooding) and hypoxia (Papdi et al. 2008; Hinz et al. 2010; Licausi et al. 2010). Two recent studies have demonstrated that all five members in group VII ERFs could be degraded by the *N*-end rule pathway via a conserved *N*-terminal motif initiating with Met-Cys (Gibbs et al. 2011; Licausi et al. 2011). This represents a new mechanism of plant oxygen sensing regulated by the *N*-end rule pathway (Gibbs et al. 2011; Licausi et al. 2011). AtACBP1 and AtACBP2 were shown to participate in oxygen sensing through their interactions with RAP2.12 at the plasma membrane (Licausi et al. 2011). Under aerobic conditions, RAP2.12 was observed to be localized to the plasma membrane as indicated by fluorescent signals of the RAP2.12::GFP fusion (Licausi et al. 2011). Given the absence of a hydrophobic domain in RAP2.12, its membrane association suggests that there could be binding partners that sequester RAP2.12 at the plasma membrane. Considering the previous findings that AtACBP2 and AtACBP4 bind RAP2.3, two plasma membrane localized AtACBPs, AtACBP1 and AtACBP2 were checked whether they were the potential binding partners of RAP2.12 using BiFC and yeast two-hybrid assays (Licausi et al. 2011). Using a deletion mutant of

RAP2.12, their results showed that RAP2.12 interacts with AtACBP1/AtACBP2 at the RAYD motif of RAP2.12 (Licausi et al. 2011), a domain that has been previously reported to mediate protein–protein interactions (Okamoto et al. 1997). These interactions between AtACBP1/AtACBP2 and RAP2.12 are important because their binding forms a membrane-bound complex as indicated by BiFC assays, thereby limiting the access of RAP2.12 to the nucleus (Licausi et al. 2011) and protecting RAP2.12 from degradation by the *N*-end rule pathway (Fig. 3) (Gibbs et al. 2011; Licausi et al. 2011). Interestingly, upon hypoxic conditions (i.e. flooding), membrane-bound RAP2.12 disappeared and RAP2.12 was observed in the nucleus to function in the activation of hypoxia-responsive gene expression (Fig. 3) (Licausi et al. 2011). During reoxygenation, RAP2.12 is degraded rapidly (within one hour) by proteolysis to deactivate the hypoxic response (Fig. 3) (Licausi et al. 2011).

According to the results from yeast two-hybrid screening, AtACBP1 also interacts with another TF, ABA-RESPONSIVE ELEMENT BINDING PROTEIN1 (AREB1) (Tse 2005), which is a transcriptional activator regulating ABA signaling in seed germination, seedling development and drought stress (Fujita et al. 2005; Yoshida et al. 2010). The expression of *AREB1* was observed to be up-regulated in AtACBP1-overexpressors in response to ABA treatment (Du et al. 2013a), suggesting a positive role of AtACBP1 in ABA signaling.

Conclusion and perspective

Over a dozen protein partners of AtACBPs have been isolated the past decade (Li and Chye 2004; Li et al. 2008; Tse 2005; Gao 2009; Gao et al. 2009, 2010; Licausi et al. 2011; Du et al. 2013a). Investigations on these interactors have revealed novel roles of AtACBPs in development and stress responses. The interactions between AtACBP1/AtACBP2 and TFs were unexpected given their final protein destinations. However, this is a good model on how TFs can be sequestered from entering the nucleus to participate in the regulation of gene expression (Licausi et al. 2011). Although the newly identified mechanism of oxygen sensing in plants is significant and AtACBPs have been shown to play important roles in this process (Licausi et al. 2011; Bailey-Serres et al. 2012), a number of questions remain. The interaction between AtACBP1/AtACBP2 and RAP2.12 could be crucial in the hypoxic response (Licausi et al. 2011). Thus, it would be interesting to test whether the anoxia response and flooding tolerance fluctuate according to differential levels in AtACBP1/AtACBP2 expression. Membrane association of RAP2.12 was observed under normoxia but disappeared upon hypoxia

(Licausi et al. 2011). Are the interactions between AtACBP1/AtACBP2 and RAP2.12 affected by oxygen levels? Is RAP2.12 released from membrane-bound AtACBP1/AtACBP2 upon hypoxia? Does RAP2.12 migrate from the plasma membrane (or cytosol) to the nucleus upon hypoxia? Are the cytosolic AtACBP4/AtACBP5 involved in the TF transfer given that AtACBP4 binds RAP2.3 (Li et al. 2008)? Does the binding of RAP2.12 to AtACBP1/AtACBP2 (also RAP2.3 to AtACBP2/AtACBP4) actually prevent degradation by the *N*-end rule pathway? If it does, would it affect E3 ligase recognition? Besides RAP2.12 and RAP2.3, do the other members in the group VII ERFs interact with AtACBPs at the plasma membrane? Previous studies have shown that AtACBP2 and AtACBP4 interact with RAP2.3 at the plasma membrane and cytosol, respectively (Li and Chye 2004; Li et al. 2008). AtACBP4 was observed to be localized to the periphery of nucleus likely arising from its interaction with RAP2.3 (Li et al. 2008). Considering that RAP2.3 can be degraded by the *N*-end rule pathway (Gibbs et al. 2011), does RAP2.3 also participate in the hypoxia response mimicking the oxygen-sensing mechanism of RAP2.12?

AtACBP1 has been observed to interact with AREB1 (Tse 2005) to promote ABA signaling in germination and vegetative growth (Du et al. 2013a). However, the mechanism of the AtACBP1 and AREB1 interaction is still unclear. AtACBP2 is involved in Cd(II) and H₂O₂ tolerance by the interaction with FARNESYLATED PROTEIN6 (AtFP6) (Gao et al. 2009), which is also known as the HEAVY METAL ASSOCIATED ISOPRENYLATED PLANT PROTEIN26 (HIP26) (Barth et al. 2009). Although GFP::AtFP6 was co-localized with DsRed::AtACBP2 to the plasma membrane (Gao et al. 2009), AtFP6/HIP26 was detected in the nucleus and found to interact with the stress-related ZINC FINGER HOMEODOMAIN TRANSCRIPTION FACTOR ATHB29 (Barth et al. 2009), indicating an indirect association between AtACBP2 and ATHB29. Furthermore, the results of yeast two-hybrid screens show a number of uncharacterized interactors of AtACBP1/AtACBP2 (Tse 2005; Gao 2009). The current knowledge on AtACBP interactors provides a good basis for further investigations to better understand the function of Arabidopsis ACBPs and their interactors.

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