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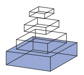

Phylogenetic analysis of the thylakoid ATP/ADP carrier reveals new insights into its function restricted to green plants

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ATP is the common energy currency of cellular metabolism in all living organisms. Most of them synthesize ATP in the cytosol or on the mitochondrial inner membrane, whereas land plants, algae, and cyanobacteria also produce it on the thylakoid membrane during the light-dependent reactions of photosynthesis. From the site of synthesis, ATP is transported to the site of utilization via intracellular membrane transporters. One major type of ATP transporters is represented by the mitochondrial ADP/ATP carrier family. Here we review a recently characterized member, namely the thylakoid ATP/ADP carrier from *Arabidopsis thaliana* (AtTAAC). Thus far, no orthologs of this carrier have been characterized in other organisms, although similar sequences can be recognized in many sequenced genomes. Protein Sequence database searches and phylogenetic analyses indicate the absence of TAAC in cyanobacteria and its appearance early in the evolution of photosynthetic eukaryotes. The TAAC clade is composed of carriers found in land plants and some green algae, but no proteins from other photosynthetic taxa, such as red algae, brown algae, and diatoms. This implies that TAAC-like sequences arose only once before the divergence of green algae and land plants. Based on these findings, it is proposed that TAAC may have evolved in response to the need of a new activity in higher photosynthetic eukaryotes. This activity may provide the energy to drive reactions during biogenesis and turnover of photosynthetic complexes, which are heterogeneously distributed in a thylakoid membrane system composed of appressed and non-appressed regions.

Keywords: green alga, chloroplast, plant, photosynthesis, ADP/ATP carrier, thylakoid, TAAC phylogeny

INTRODUCTION

Oxygenic photosynthesis is a biophysicochemical process that converts carbon dioxide into organic compounds using sunlight as a source of energy. It occurs in the chloroplasts of land plants and algae, and also in the cytoplasm of cyanobacteria, and uses water as a source of electrons, releasing oxygen as a waste product (for a recent review, see Hohmann-Marriott and Blankenship, 2011). The chloroplast in algae and plants has evolved from a cyanobacterial ancestor via endosymbiosis with a primitive eukaryotic host. It is a highly compartmentalized organelle, with three membrane systems (outer envelope, inner envelope, and thylakoid) and three soluble spaces (intermembrane space, stroma, and thylakoid lumen). A wide variety of solute and metabolite transporters reside within the different types of chloroplast membranes and mediate communication between the cytosol, stroma, and lumen. Several excellent reviews on the identification and functional characterization of these transporters have recently become available (Spetea and Schoefs, 2010; Breuers et al., 2011; Flügge et al., 2011; Weber and Linka, 2011).

Regarding their evolution, the majority of the inner envelope metabolite transporters have been shown to have a host origin, driven by the requirement to establish communication between the host cytosol and the cyanobiont (Facchinelli and Weber, 2011). There are so far no evolutionary studies dedicated to solute transporters from the outer envelope or thylakoid membranes, but it is believed that they originate from proteins in the ancestral cyanobacterial outer and thylakoid membranes, respectively.

Mitochondria and chloroplasts are the two organelles able to synthesize ATP, which is the universal energy currency of cellular metabolism in all living organisms. The difference between these organelles in this respect is that in all eukaryotes mitochondria produce ATP via oxidative phosphorylation on the inner membrane, to be used during cell metabolism. Chloroplasts and also cyanobacteria use sunlight as a source of energy to produce ATP (photophosphorylation) on the thylakoid membrane, which is consumed during CO_2 fixation in the stroma. In addition, ATP is used for energy-dependent reactions on the envelope and thylakoid membrane or inside the thylakoid lumen (Spetea and Thuswaldner, 2008).

ATP is the largest and most highly charged solute transported across organellar membranes. Two structurally and phylogenetically different types of ATP transporters are represented in chloroplasts, namely ATP/ADP antiporters (AAA, TC #2.1.12, according to Saier et al., 2009) and mitochondrial ADP/ATP carriers (AAC,

TC #2.A.29.1.1). There are two ATP/ADP antiporters (AATPs) in the inner envelope membrane of photosynthetic and heterotrophic plastids, supplying cytosolic ATP to the stroma (for recent reviews, see Haferkamp et al., 2011; Traba et al., 2011). The transport is electroneutral since the counter-ions for ATP^{4-} are ADP^{3-} together with $H_2PO_4^-$ (Trentmann et al., 2008). AATPs possess 12 putative transmembrane helices, and share a common origin with the ATP/ADP antiporters found in the parasite bacteria *Rickettsia prowazekii* and *Chlamydia psittaci* (Haferkamp et al., 2011).

The mitochondrial ADP/ATP carriers are the first and most studied members of the mitochondrial carrier (MC) family and are present only in eukaryotic cells (Haferkamp et al., 2011; Traba et al., 2011). Like the members of the AAA family, AACs are exchangers, but the transport is electrogenic (ATP^{4-}/ADP^{3-}) and proceeds in the opposite direction, since they transport matrix ATP through the intermembrane space out into the cytosol. Yet another functional difference from AAA is that AACs are sensitive to specific inhibitors, such as bongkrekic acid and carboxyatractyloside (Klingenberg, 2008). The 3D structure of the bovine AAC has been resolved at 2.2 Å resolution in a conformation stabilized with carboxyatractyloside (Pebay-Peyroula et al., 2003). The structure revealed six transmembrane helices and a selectivity filter for adenine nucleotides, whose sequence could be used to predict other AACs and even other MCs (Nury et al., 2010). From a total of 58 MC in *Arabidopsis thaliana*, three classical mitochondrial AACs have been characterized, with at least four more paralogous sequences awaiting validation (Palmieri et al., 2011). In addition to the mitochondrion, AAC members have also been found in peroxisomes, endoplasmic reticulum, amyloplasts, and chloroplasts (Haferkamp et al., 2011; Traba et al., 2011).

Using western blotting and activity inhibition with an antibody against the bovine AAC, the activity of an AAC was reported in the spinach thylakoid membrane (Spetea et al., 2004). BLAST searches with the bovine AAC against the *Arabidopsis* protein database combined with prediction of chloroplast transit peptides revealed one putative chloroplast AAC, encoded by the *At5g1500* gene. The corresponding protein was localized to the thylakoid membrane of *Arabidopsis* (Thuswaldner et al., 2007; Zybailov et al., 2008), and was annotated as the thylakoid ATP/ADP carrier (AtTAAC). Subfractionation as well as immunocytochemical experiments indicated the non-appressed regions as the precise location of TAAC within the thylakoids (Thuswaldner et al., 2007). Another chloroplast AAC is encoded by the *At3g51870* gene and was initially localized to the envelope using western blotting (Spetea, C., unpublished data) and mass-spectrometry based proteomics (Ferro et al., 2010).

The AtTAAC sequence contains 415 amino acids that include a predicted transit peptide of 60 amino acids. The sequence of the processed form is 80 residues longer than that of bovine AAC, explaining the observed difference between the two proteins in the reported size in SDS gels (Spetea et al., 2004). The extra 80 residues are distributed as 50 in the N-terminus and 30 in the C-terminus – regions containing many charged residues and a five-glycine repeat that could play a role in the regulation of TAAC activity. TAAC shares about 30% identity with bovine AAC, which is concentrated in the six putative transmembrane helices and to a lesser degree in the connecting loops (Thuswaldner et al., 2007). The selectivity filter for adenine nucleotides, represented by residues K-130, R-186, Y-282, and K-369, is fully conserved, indicating adenine nucleotides as the most likely substrates for the transport activity of TAAC.

Arabidopsis TAAC was characterized in *E. coli* as an ATP importer in exchange for cytosolic ADP (Thuswaldner et al., 2007), and its activity was found sensitive to bongkrekic acid (Thuswaldner, S., and Spetea, C., unpublished data). Pi is not a substrate for transport by TAAC (Thuswaldner et al., 2007), implying the requirement for a separate thylakoid Pi transporter. Indeed, such a protein has been identified in *Arabidopsis*, and functionally characterized in yeast and *E. coli* (Guo et al., 2008; Pavón et al., 2008). When assessed in thylakoid membranes, TAAC transports stromal ATP into the thylakoid lumen in exchange for ADP. The direction of TAAC-mediated transport determined in both *E. coli* and thylakoids is opposite to the direction of transport by mitochondrial AACs (Thuswaldner et al., 2007). Therefore, to distinguish it from the mitochondrial ADP/ATP carrier, the thylakoid protein has been named ATP/ADP carrier. Through adenine nucleotide exchange, TAAC was proposed to supply ATP for nucleotide-dependent reactions in the thylakoid lumen (Spetea et al., 2004). An extensive review on the structure, function, and evolution of the MC family has become recently available and provides insights into their roles in plants (Palmieri et al., 2011). This review focuses on the evolutionary origin of the TAAC subfamily of the mitochondrial AACs, which aids in elucidating its function in the thylakoid membrane.

WHEN AND WHERE IN THE TREE OF LIFE DID TAAC ORIGINATE?

We assembled a set of protein sequences with which to place TAAC in an evolutionary context. We extracted protein sequences from the curated gene families at ARAMEMNON (Schwacke et al., 2003)[1] and from search results to specific clades and genomes at NCBI[2] and PHYTOZOME (Goodstein et al., 2011)[3], respectively. We added the best BlastP matches to AtTAAC from each major eukaryotic division of life with an *E*-value $<10^{-55}$. We also added all 17 members of the *Arabidopsis* MC family (including AtTAAC) that were listed as protein sequences related to TAAC at ARAMEMNON. We also added the best BlastP hits to proteins from several green plant clades, including Bryophyta, Chlorophyta, Lycopodiophyta, and Pinophyta. An alignment of these sequences was made using MUSCLE (Edgar, 2004, implemented at http://www.ebi.ac.uk). From the alignment (not shown) we could see that only two copies in *Arabidopsis* (encoded by the *At5g01500* and *At3g51870* genes) and all other non-*Arabidopsis* land plant proteins in this sample possessed a partly conserved N-terminal motif, consisting of 19 amino acid residues directly upstream from the first transmembrane helix delimited by Thuswaldner et al. (2007).

For the first phylogenetic analysis we included amino acid positions 121–369 in TAAC (spanning the six transmembrane

[1]http://aramemnon.uni-koeln.de/
[2]http://blast.ncbi.nlm.nih.gov/
[3]http://www.phytozome.net/

domains), which resulted in 340 aligned positions. The analysis was carried out using a Bayesian approach. We used four parallel chains of a reverse model jump protein Bayesian analysis in MrBayes 3.1.2 (Huelsenbeck and Ronquist, 2001). Each chain was run for two million generations and sampled every 1,000 generations. The tree in **Figure 1** shows a well-supported [posterior probability (PP) = 1.0] N-terminal containing clade (the "TAAC clade") that includes land plants and some copies from Chlorophyta, but no proteins from other taxa. Sister to this clade with strong support (PP = 1.0) is a clade (also PP = 1.0) containing proteins from Chlorophyta that lack the N-terminal motif, including proteins from *Chlamydomonas*, *Chlorella*, and *Volvox*.

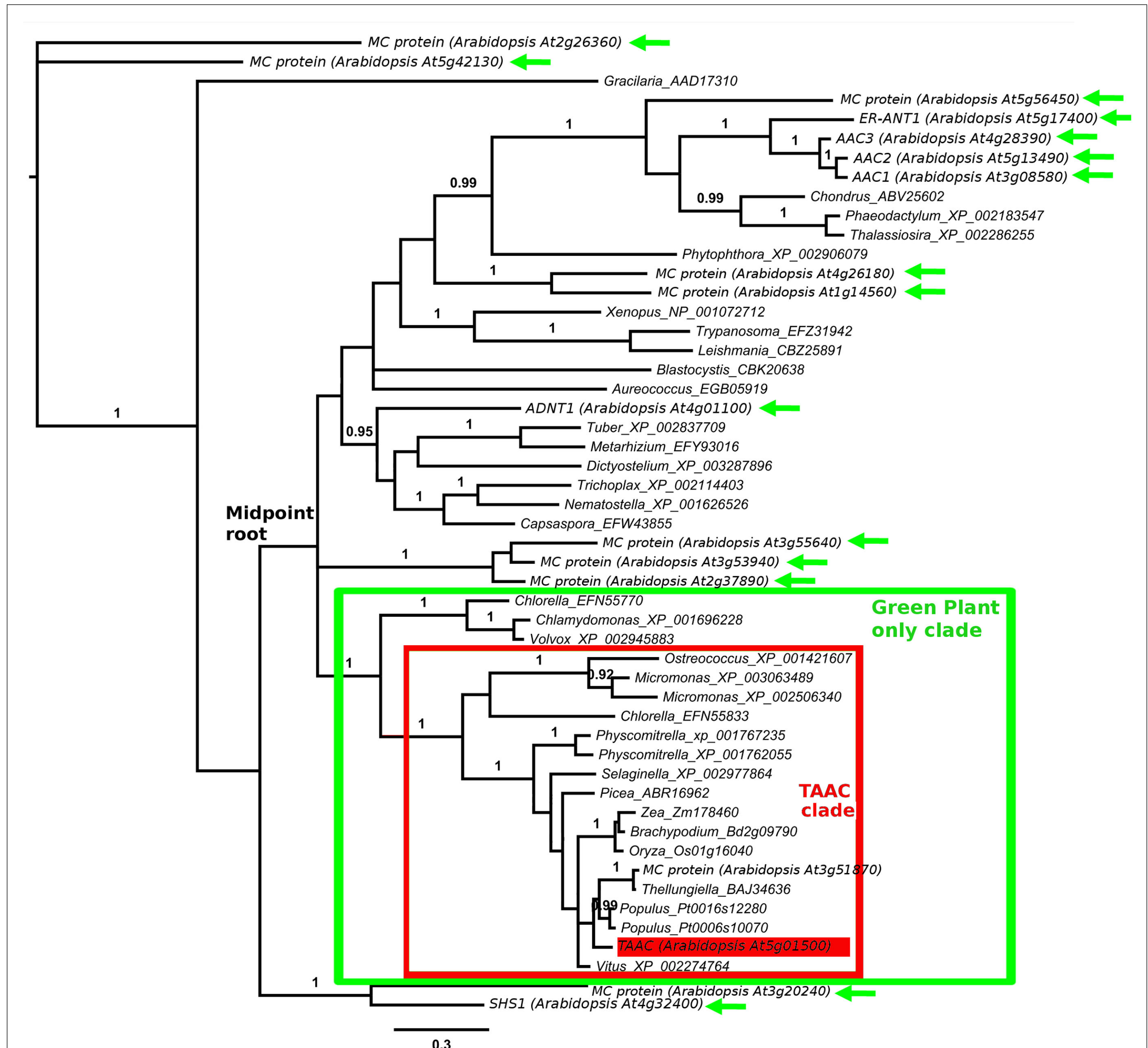

FIGURE 1 | Protein phylogeny of 340 Muscle aligned positions of selected members of the MC family. The analysis involved 51 protein sequences, including 17 from Arabidopsis. The root position shown is arbitrary. The mid-point root position is marked, as is the clade containing all TAAC-like sequences (boxed in red). The clade of Green Plants is marked in green. All plant sequences outside this clade are indicated by green arrows. Accession numbers follow the gene annotation (where available) and names of genera within which the proteins are found. The position of *Arabidopsis* TAAC is highlighted in red. The scale bar indicates substitutions per site. Posterior probabilities ≥0.90 of clades summarizing two million Markov chain Monte Carlo generations (of a reversible model jump protein Bayesian analysis in MrBayes 3.1.2) are shown above branches. The results discussed are robust to an alternative alignment (MAFFT, not shown).

The best BlastP matches to proteins from the following taxa did not contain the N-terminal motif, although they each possessed the conserved six transmembrane domain structure: Amoebozoa, Animalia, Euglenozoa, Fungi, Opisthokonta, Rhodophyta, and Stramenopiles – the latter includes brown algae and diatoms (nomenclature based on NCBI's taxonomy). All other eukaryote taxa at one hierarchical level below Eukaryota in NCBI's taxonomy were searched, but did not contain BlastP matches to AtTAAC with *E*-values $<10^{-55}$. Apart from TAAC, only one other protein from *Arabidopsis* is also a member of the TAAC clade and contains this motif, namely the one encoded by the *At3g51870* gene. The amino acid sequences of these two proteins are 67% identical.

The TAAC clade contains relatively short branches in relation to the remainder of the phylogeny, making it unlikely that the root resides within the clade. This is also consistent with mid-point rooting (marked in **Figure 1**) as well as the phylogenetic pattern expected among the plants that carry these proteins. Together, this indicates that the TAAC clade contains several proteins orthologous to AtTAAC. This clade also contains duplicated copies (paralogs) from several plant taxa (more are seen in our expanded sample in **Figure 2**, details below), but these are inferred to have arisen only after green plants diverged from other eukaryotes and are expected due to the action of recent gene and/or genome duplication (e.g., in *Arabidopsis*, Bowers et al., 2003; legumes, Pfeil et al., 2005; *Physcomitrella*, Rensing et al., 2007).

The position of the remaining 15 *Arabidopsis* MC proteins (**Figure 1**) indicates that the MC protein family was present very early in eukaryote evolution. Scattered across the tree are, for example, homologs from Metazoa (*Nematostella*), Fungi (*Tuber*), Amoebozoa (*Dictyostelium*), Stramenopiles (*Aureococcus*), Euglenozoa (*Leishmania*), and Rhodophyta (*Chondrus*). However, none of these homologs are part of the TAAC clade, which contains only proteins from Chlorophyta and Streptophyta. No matches within the BlastP cut-off used were found to other photosynthetic organisms, such as Bacillariophyta (diatoms), Cyanophyta (cyanobacteria), Glaucocystophyceae, Phaeophyceae (brown algae), or Rhodophyta (red algae).

Therefore, we conclude that TAAC-like sequences arose only a single time, after the clade including both Chlorophyta and Streptophyta (the latter including land plants) diverged from the other taxa in our sample, but earlier than the divergence of Chlorophyta and Streptophyta. The phylogenetic results are robust to an alternative alignment based on MAFFT (Katoh et al., 2002), although this is not shown here.

HOW DID THE TAAC COPIES IN *ARABIDOPSIS* AND OTHER EUDICOTS EVOLVE?

We increased the sample of TAAC-like proteins in a more focused phylogenetic inference in order to place the two *Arabidopsis* members of the TAAC subfamily into context. For this purpose, we sampled all copies from the species listed in **Table 1** that contain the N- and C-terminal motifs similar to TAAC and that were also part of the TAAC clade. We focused on eudicots, because preliminary analyses indicated that the two *Arabidopsis* TAAC subfamily members were placed in a clade containing proteins from eudicot species only.

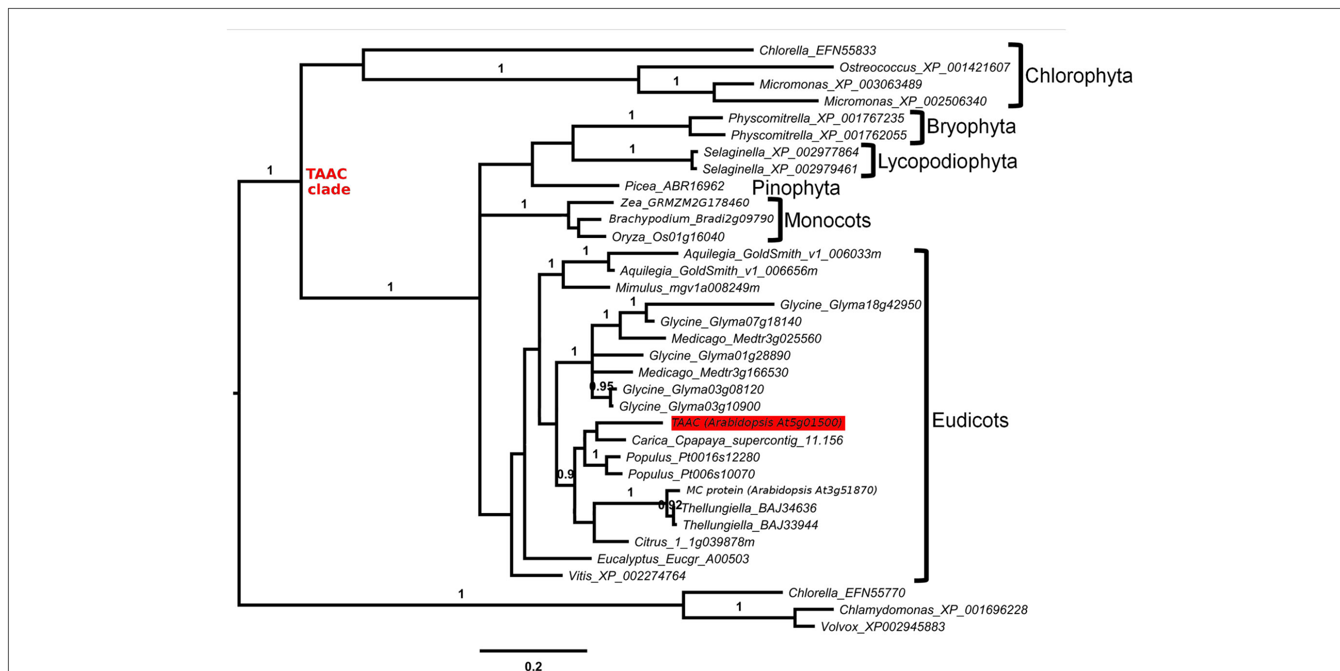

FIGURE 2 | Protein phylogeny of 379 Muscle aligned positions of selected members of the MC family, focusing on the TAAC clade (marked). The analysis involved 35 protein sequences, including two from *Arabidopsis*. The root position is based on **Figure 1**. Accession numbers follow the names of genera within which the proteins are found. The taxon to which each subclade belongs is indicated. The position of *Arabidopsis* TAAC is highlighted in red. The scale bar indicates substitutions per site. Posterior probabilities $\geq$0.90 of clades, analyzed as in **Figure 1**, are shown above branches. The results discussed are robust to an alternative alignment (MAFFT, not shown).

Table 1 | Copy number of TAAC-like proteins found in various eudicot plants.

Taxon	Group (NCBI taxonomy)	TAAC-like copies
Arabidopsis thaliana (L.) Heynh	Malvids	2
Thellungiella halophila O. E. Schulz	Malvids	2
Eucalyptus grandis W. Hill	Malvids	1
Carica papaya L.	Malvids	1
Citrus sinensis Osbeck	Malvids	1
Populus trichocarpa Torr and A. Gray	Fabids	2
Medicago truncatula Gaertn	Fabids	2
Glycine max (L.) Merr	Fabids	5
Vitis vinifera L.	Rosids incertae sedis	1
Mimulus guttatus DC	Asterids	1
Aquilegia caerulea E. James	Stem eudicots	2

We expanded our search for land plant sequences containing the N-terminal motif by using BlastP with AtTAAC as the query to specific genomes in Phytozome, as well as to *Thellungiella* (Brassicaceae), because in earlier BlastP searches a *Thellungiella* sequence closely related to TAAC was detected. We excluded possible allelic variants that differed by only a single amino acid from our enumeration. The alignment of this set of sequences was performed as before. From this alignment (Figure S1 in Supplementary Material), we used amino acids 107–482 in TAAC (corresponding to 375 aligned positions and including the N-terminal and C-terminal motifs) in our second phylogenetic analysis and also added the sister group of the TAAC clade (from **Figure 1**) as an outgroup. The phylogenetic analysis was performed as described for the data shown in **Figure 1**, with sample information summarized in **Table 2** and the results presented in **Figure 2**.

The copy number of TAAC-like proteins in the eudicots examined here appears to be rather conservative, ranging from one to five copies (**Table 1**). *Arabidopsis*, *Medicago*, and *Populus* each have only two copies, but these are perhaps the best-known eudicot genomes. Therefore, the copy number for the other species may be underestimated. The lack of support for some key nodes in the phylogeny (**Figure 2**) makes it difficult to pinpoint the timing of divergence of the two copies found in *Arabidopsis.* They almost certainly diverged sometime before this genus diverged from *Thellungiella* (perhaps 40–50 million years ago: Amtmann, 2009; Beilstein et al., 2010), but it is difficult to say how much earlier this divergence might have been.

Unlike the *Arabidopsis* copies, one of the copies found in *Aquilegia* differs from its closest relative by a long branch (**Figure 2**). In contrast, the rather recently diverged (in comparison to *Arabidopsis*) multiple copies found in *Selaginella* and *Physcomitrella* do not show this pattern. The long branch observed in *Aquilegia* may indicate functional shifts and positive selection may be involved, as has been shown in, e.g., monkey pancreatic ribonucleases (Zhang et al., 2002). These possibilities could be examined further and may lead to novel research questions. However, in the case of one *Glycine* sequence, poor assembly is a more likely explanation for the long branch observed in that taxon (NB: alignment positions 308–389 in Figure S1 in Supplementary Material), so caution needs to be taken in specific cases.

HOW DOES THE N-TERMINAL MOTIF VARY WITHIN THE TAAC SUBFAMILY?

The N-terminal motif may be helpful to identify potential members of the TAAC subfamily. Furthermore, this clade shows complete conservation of the ring of four positively charged residues (Figure S1 in Supplementary Material) proposed to act as a selectivity filter for adenine nucleotides (Thuswaldner et al., 2007), confirming that these aligned proteins are all AACs.

Potentially important is that significant variation in the N-terminal sequences (beyond just the 19 residue motif described earlier) occurs among the proteins sampled here. For example, several proteins contain many charged residues, including paired charged ones, and a five-glycine repeat (Figure S1 in Supplementary Material). These may be implicated in ligand (e.g., calcium) binding and large conformational changes that could regulate their activity, as in the case of Ca^{2+}-dependent members of the MC family (Weber et al., 1997). However, some of these proteins do not contain either of these features. For example, the *Selaginella* sequences have only 13 residues upstream of the more conserved N-terminal motif, few charged residues, and lack the five-glycine repeat. One *Micromonas* protein appears to lack the N-terminal motif altogether (Figure S1 in Supplementary Material). Variation in the N-terminal motif among the land plant TAAC-like proteins is smaller (**Table 2**), but so is the phylogenetic distance. It is tempting to speculate as to what the precise function of the N-terminal residues might be, moreover, interesting research questions can be formulated around these sequences. However, the sequences (especially those apparently lacking the N-terminal motif) should of course be verified before pursuing these lines of investigation, as technical problems (e.g., with the assembly), deposition of incomplete sequences, etc., need to be ruled out first.

WHAT ARE THE POSSIBLE FUNCTIONS OF TAAC IN LAND PLANTS AND GREEN ALGAE?

The phylogenetic analyses performed in this work indicate that TAAC is absent in cyanobacteria and that the most recent common ancestor of green plants (Streptophyta + Chlorophyta) was the earliest photosynthetic organism that we can identify to have carried a TAAC-like protein. Although TAAC is a thylakoid protein and the thylakoid membrane originated with the thylakoid membrane of an ancestral cyanobacterium, TAAC appears to be eukaryote-specific, as are all mitochondrial AACs (Palmieri et al., 2011). Nevertheless, in contrast to mitochondrial AACs, which are found in both photosynthetic and heterotrophic eukaryotes (Palmieri et al., 2011), only some photosynthetic eukaryotes, more specifically, Chlorophyta and Streptophyta, carry TAAC-like copies. Other photosynthetic eukaryotes (red algae, brown algae, and diatoms) and, interestingly, even some Chlorophyta (*Chlamydomonas* and *Volvox*) do not appear to have such a protein, i.e., not one with a similar N-terminus nor placed in the TAAC clade, whereas other Chlorophyta do (e.g., *Chlorella*; **Table 2**).

A potential answer to the question "why do not all photosynthetic organisms carry TAAC-like proteins?" could be that TAAC may fulfill specialized functions in the thylakoid membrane of

Table 2 | The presence (green) or absence (red) of TAAC-like proteins within the surveyed genomes is shown.

Clade	Species	Accessions used (Figure 2 only)	Annotation[1]	N-terminal[2] % AA identity to TAAC	Accession source
Eudicots	*Aquilegia caerulea*	AcoGoldSmith_v1.006656m	MC[3] protein	68	Phytozome
		AcoGoldSmith_v1.006033m	MC protein	58	Phytozome
	Arabidopsis thaliana	**At5g01500**	**Thylakoid ATP/ADP carrier (TAAC)**	**100**	Phytozome
		At3g51870	MC protein	68	Phytozome
	Carica papaya	evm.TU.supercontig_11.156	MC protein	58	Phytozome
	Citrus sinensis	orange1.1g039878m	MC protein	Not available	Phytozome
	Eucalyptus grandis	Eucgr.A00503	MC protein	53	Phytozome
	Glycine max	Glyma03g10900	MC protein	Not available	Phytozome
		Glyma03g08120	MC protein	58	Phytozome
		Glyma01g28890	MC protein	Not available	Phytozome
		Glyma07g18140	MC protein	53	Phytozome
		Glyma18g42950	MC protein	58	Phytozome
	Medicago truncatula	Medtr3g166530	MC protein	Not available	Phytozome
		Medtr3g025560	MC protein	58	Phytozome
	Mimulus guttatus	mgv1a008249m	MC protein	47	Phytozome
	Populus trichocarpa	Pt0006s10070	MC protein	68	Aramemnon
		Pt0016s12280	MC protein	63	Aramemnon
	Thellungiella halophila	BAJ33944	MC protein	68	NCBI
		BAJ34636	MC protein	68	NCBI
	Vitis vinifera	XP_002274764	MC protein	47	NCBI
Monocots	*Oryza sativa*	LOC_Os01g16040	MC protein	26	Phytozome
	Brachypodium distachyon	Bradi2g09790	MC protein	37	Phytozome
	Zea mays	GRMZM2G178460	MC protein	53	Phytozome
Pinophyta	*Picea sitchensis*	ABR16962	MC protein (NCBI)	42	NCBI
Lycopodiophyta	*Selaginella moellendorffii*	XP_002977864	Putative MC protein (NCBI)	42	NCBI
		XP_002979461	Putative MC protein (NCBI)	42	NCBI
Bryophyta	*Physcomitrella patens*	XP_001762055	Putative MC protein (NCBI)	37	NCBI
		XP_001767235	Putative MC protein (NCBI)	42	NCBI
Chlorophyta	*Micromonas* sp. *RCC299*	XP_002506340	Putative MC protein (NCBI)	15	NCBI
	Micromonas pusilla	XP_003063489	Amyloplast brittle-1 (BT1) protein homolog (NCBI)	Not available	NCBI
	Ostreococcus lucimarinus	XP_001421607	ADP/ATP transporter on adenylate translocase; provisional (NCBI)	26	NCBI
	Chlorella variabilis	EFN55833	As above	26	NCBI
		EFN55770	ADP/ATP transporter on adenylate translocase; provisional (NCBI)	Not available	NCBI
	Volvox carteri	XP_002945883	ADP/ATP transporter on adenylate translocase; provisional (NCBI)	Not present	NCBI
	Chlamydomonas reinhardtii	XP_001696228	ADP/ATP transporter on adenylate translocase; provisional (NCBI)	Not present	NCBI
Alveolata			No hits $<10^{-55}$		
Amoebozoa	*Dictyostelium purpureum*	XP_003287896	Putative MC protein (NCBI)	Not present	NCBI
Apusozoa			No hits $<10^{-55}$		
Centroheliozoa			No hits $<10^{-55}$		
Cryptophyta			No hits $<10^{-55}$		

(Continued)

Table 2 | Continued

Clade	Species	Accessions used (Figure 2 only)	Annotation[1]	N-terminal[2] % AA identity to TAAC	Accession source
Euglenozoa	*Leishmania mexicana*	CBZ25891	Putative MC protein (NCBI)	Not present	NCBI
Fornicata			No hits <10^{-55}		
Glaucocystophyceae			No hits <10^{-55}		
Haptophyceae			No hits <10^{-55}		
Jakobida			No hits <10^{-55}		
Katablepharidophyta			No hits <10^{-55}		
Malawimonadidae			No hits <10^{-55}		
Opisthokonta	*Capsaspora owczarzaki*	EFW43855	MC protein (NCBI)	Not present	NCBI
	Nematostella vectensis	XP_001626526	Putative MC protein (NCBI)	Not present	NCBI
	Trichoplax adhaerens	XP_002114403	Putative MC protein (NCBI)	Not present	NCBI
	Tuber melanosporum	XP_002837709	Putative MC protein (NCBI)	Not present	NCBI
	Xenopus tropicalis	NP_001072712	MC protein (NCBI)	Not present	NCBI
	Metarhizium acridum	EFY93016	Putative MC protein (NCBI)	Not present	NCBI
Oxymonadida			No hits <10^{-55}		
Parabasalia			No hits <10^{-55}		
Rhizaria			No hits <10^{-55}		
Rhodophyta	*Chondrus crispus*	ABV25602	Putative MC protein (NCBI)	Not present	NCBI
	Gracilaria gracilis	AAD17310	Putative MC protein (NCBI)	Not available	NCBI
Stramenopiles	*Phytophthora infestans*	XP_002906079	Putative MC protein (NCBI)	Not present	NCBI
	Bacillariophyta (diatoms)		No hits <10^{-55}		
	Phaeophyceae (brown algae)		No hits <10^{-55}		
Bacteria (including cyanobacteria)			No hits <10^{-55}		

The taxon, species of origin, accession numbers, annotation, and sequence identity of the N-terminus relative to the Arabidopsis TAAC are indicated. The information about Arabidopsis TAAC is highlighted in bold. The source of these data is given in the last column: Phytozome, ARAMEMNON, or NCBI. Not available, incomplete gene model (no start codon); not present, the sequence appears to be complete, but lacks anything resembling the 19 amino acid N-terminal motif common to most sequences in the TAAC clade. Green = taxa with genes in the TAAC clade. Red = taxa without genes in the TAAC clade. E-value for BlastP (http://blast.ncbi.nlm.nih.gov) against Arabidopsis thaliana TAAC. For clades where TAAC type sequences are not found, the best hit (September 2011) is recorded instead, down to a threshold of 10^{-55}. We assume that matches with E-value < 10^{-55} will not be closely related to the TAAC clade, given that many matches better than this are also not part of this clade. "Putative" annotations include "hypothetical" annotations and annotations based on conceptual translations. [1]Annotations come from Phytozome unless stated otherwise in the table. [2]N-terminal refers to the 19 residue N-terminal motif discussed in the text. [3]MC, mitochondrial carrier.

land plants and most green algae. These membranes are organized in highly stacked (appressed) regions interconnected by stroma-exposed (non-appressed) regions (**Figure 3**). Other photosynthetic organisms (cyanobacteria, red algae, brown algae, and diatoms) display unstacked or weakly stacked thylakoids (for details and references, see the legend to **Figure 3**). To explain the apparent difference within green algae, it is relevant to consider that *Chlamydomonas* has appressed thylakoids, but they do not form regular grana stacks (de Vitry and Vallon, 1999). To our knowledge, the thylakoid structure has not, thus far, been studied in green algae other than *Chlamydomonas*, but they are expected to have a similar organization to the land plant thylakoids. The thylakoid organization depends on the type and arrangement of light-harvesting antennae and on the distribution of photosynthetic complexes (**Figure 3**). It was held for a long time that the different macrocomplexes comprising the photosynthetic apparatus were organized linearly along thylakoid membranes. This view is no longer valid since it has been established that these complexes are laterally distributed, i.e., localized exclusively in the appressed membranes (photosystem II), exclusively in the stroma-exposed thylakoids (photosystem I, ATP synthase) or in both types of membranes (cytochrome b_6/f complex; Anderson, 2002). This heterogenous composition of thylakoids is restricted to the green algae and land plants (**Figure 3**).

The differences in thylakoid membrane organization among cyanobacteria, green algae, and land plants may have implications for biogenesis and turnover of photosynthetic complexes, such as photosystem II (PSII). The biosynthesis of complexes in cyanobacteria occurs at contact sites with the plasma membrane, whereas PSII repair takes place within thylakoid membranes (Zak et al., 2001). In green algae, the site of PSII assembly during *de novo* D1 synthesis is around a so-called pyrenoid, a specialized sub-compartment within the chloroplast for CO_2 fixation that is different from the site of PSII repair – the stroma-regions of the thylakoid membrane (Uniacke and Zerges, 2007). In land plants, the location of thylakoid membrane complex biosynthesis is uncertain. A widely accepted model is that PSII subunits assemble in the non-appressed region of the thylakoid membrane (Baena-González and Aro, 2002). The mechanism of PSII repair in plants has been studied in detail and shown to have important

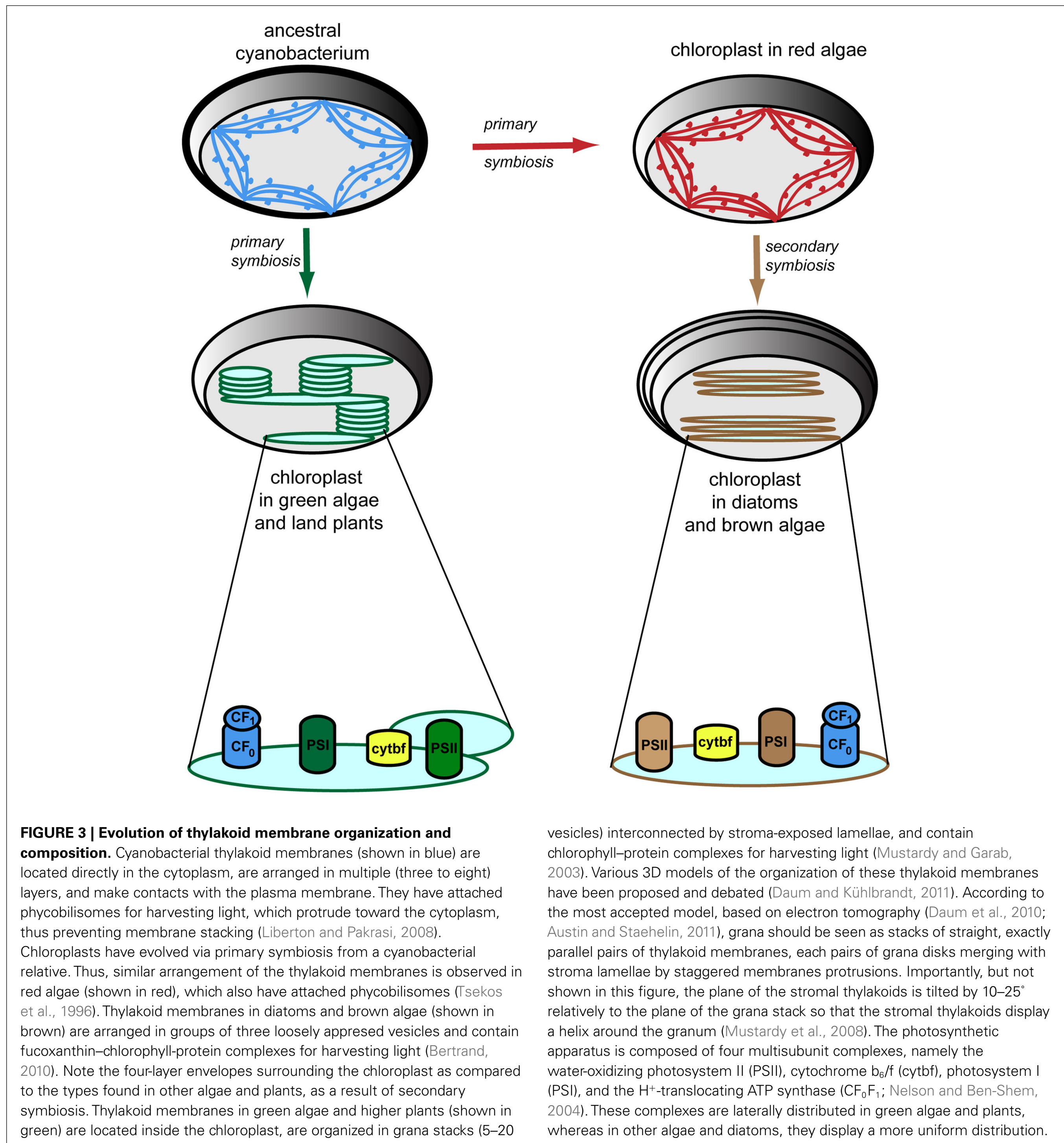

FIGURE 3 | Evolution of thylakoid membrane organization and composition. Cyanobacterial thylakoid membranes (shown in blue) are located directly in the cytoplasm, are arranged in multiple (three to eight) layers, and make contacts with the plasma membrane. They have attached phycobilisomes for harvesting light, which protrude toward the cytoplasm, thus preventing membrane stacking (Liberton and Pakrasi, 2008). Chloroplasts have evolved via primary symbiosis from a cyanobacterial relative. Thus, similar arrangement of the thylakoid membranes is observed in red algae (shown in red), which also have attached phycobilisomes (Tsekos et al., 1996). Thylakoid membranes in diatoms and brown algae (shown in brown) are arranged in groups of three loosely appresed vesicles and contain fucoxanthin–chlorophyll-protein complexes for harvesting light (Bertrand, 2010). Note the four-layer envelopes surrounding the chloroplast as compared to the types found in other algae and plants, as a result of secondary symbiosis. Thylakoid membranes in green algae and higher plants (shown in green) are located inside the chloroplast, are organized in grana stacks (5–20 vesicles) interconnected by stroma-exposed lamellae, and contain chlorophyll–protein complexes for harvesting light (Mustardy and Garab, 2003). Various 3D models of the organization of these thylakoid membranes have been proposed and debated (Daum and Kühlbrandt, 2011). According to the most accepted model, based on electron tomography (Daum et al., 2010; Austin and Staehelin, 2011), grana should be seen as stacks of straight, exactly parallel pairs of thylakoid membranes, each pairs of grana disks merging with stroma lamellae by staggered membranes protrusions. Importantly, but not shown in this figure, the plane of the stromal thylakoids is tilted by 10–25˚ relatively to the plane of the grana stack so that the stromal thylakoids display a helix around the granum (Mustardy et al., 2008). The photosynthetic apparatus is composed of four multisubunit complexes, namely the water-oxidizing photosystem II (PSII), cytochrome b_6/f (cytbf), photosystem I (PSI), and the H^+-translocating ATP synthase (CF_0F_1; Nelson and Ben-Shem, 2004). These complexes are laterally distributed in green algae and plants, whereas in other algae and diatoms, they display a more uniform distribution.

differences from that in cyanobacteria, such as the shuttling of PSII subcomplexes between the grana and stroma membranes, which is accompanied by changes in the oligomeric structure of the complex (Mulo et al., 2011).

The question arising is whether TAAC plays a role in the biogenesis and turnover of plant photosynthetic complexes. Its tissue expression pattern has been studied in detail, and supports this possibility, as described below. AtTAAC was found highly expressed in young photosynthetic organs, such as developing leaves, flower buds, and green siliques. Furthermore, it was found expressed in etiolated seedlings, similar to the thylakoid HCF136 protein, which was proven to be required for biogenesis of thylakoids and PSII assembly (Meurer et al., 1998; Plücken et al., 2002). TAAC expression is strongly upregulated in leaves

undergoing senescence or exposed to wounding, light stress, oxidative stress, salt stress, and desiccation, pointing to an additional role in supplying ATP for energy-dependent processes (e.g., proteolysis, folding) during turnover of photosynthetic complexes.

Thus far, no dedicated studies have been undertaken on the role of TAAC activity during thylakoid biogenesis. Nevertheless, its role during PSII repair has been studied in more detail by taking advantage of *taac* mutants. Remarkably, the mutants grew slower and were more sensitive to high light stress due to an inability to degrade the reaction center D1 protein (Yin et al., 2010). A model for its function during PSII repair cycle in plants under high light stress is presented in **Figure 4**. Briefly, ATP translocated by TAAC into the lumen is converted to GTP, which is then bound to the PsbO lumenal extrinsic subunit of the PSII dimeric complex (Spetea et al., 2004; Lundin et al., 2007a). The GTPase activity of this protein regulates the monomerization and partial disassembly of PSII, pre-requisite steps for the proteolytic degradation of the D1 protein (Lundin et al., 2007b). Replacement of the damaged D1 with a new copy requires coordination between its degradation, synthesis, insertion, and assembly of the new copy in the PSII complex. We propose that the novel mechanism of ATP transport and GTP signaling across thylakoid membranes, discussed above, may be a plant-specific feature for the following reasons: the D1 degradation is GTP dependent in plants but not in cyanobacterial thylakoids (Spetea et al., 1999); GTP binding to PsbO may be a plant-specific feature, since putative GTP binding sequence domains are not found conserved in cyanobacteria or the green alga *Chlamydomonas* PsbOs (Lundin et al., 2007a); TAAC belongs to the MC family, which is eukaryotic specific (Palmieri et al., 2011). Thus, we speculate that TAAC is associated with the need for highly controlled regulation of PSII repair in a highly stacked thylakoid membrane system requiring shuttling of complexes between the appressed and non-appressed regions.

CONCLUSION

Study of the adenine nucleotide carrier TAAC in chloroplast thylakoids is interesting because it has revealed similarities but also differences from classical mitochondrial AACs. Most MC (including AACs) are present in both phototrophic and heterotrophic eukaryotes, suggesting functions required for basic eukaryotic processes that take place inside the mitochondria and other organelles. On the other hand, TAAC-like proteins have been found only in green plants, indicating at the earliest an appearance after the endosymbiosis of a phototrophic prokaryote with the most recent common ancestor of land plants and green algae. Essentially, TAAC is an AAC with additional N (and C) motifs, apart from the chloroplast targeting sequence. The pathway by which TAAC arrived in the chloroplast and the precise function of the N-motif in TAAC activity remain to be investigated. Nevertheless, based on the phylogenetic study presented here, we propose that TAAC may fulfill functions that may be required in the context of the more complex organization of thylakoid membranes in green algae and land plants, such as biogenesis and repair of photosynthetic complexes. Some of the lumenal enzymes participating in the biogenesis/turnover processes may require ATP or other nucleotides resulting from inter-conversion, and therefore ATP must be translocated. This would not be unexpected, taking into consideration the increasing evidence for a complex role of the thylakoid lumen in photosynthetic regulation and plant cell signaling, expanding its function beyond an energetic perspective

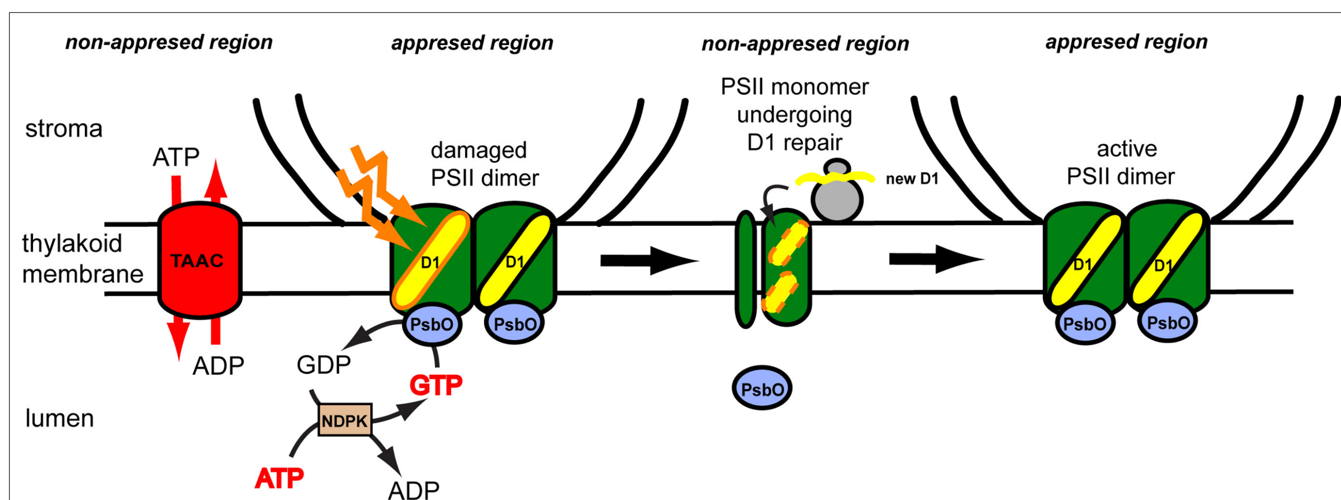

FIGURE 4 | Proposed model for role of the thylakoid ATP/ADP carrier (TAAC) during photosystem II (PSII) repair cycle in plants. The plant thylakoid membrane is organized in grana stacks (appressed region) and stroma-exposed (non-appressed region) lamellae. The composition of the thylakoid membrane is heterogenous, although its lumenal space is continuous. TAAC is located in the stroma lamellae and exchanges stromal ATP for lumenal ADP. ATP is inter-converted to GTP by the lumenal nucleoside diphosphate kinase (NDPK). The active PSII dimer is located in the grana regions and contains lumenal extrinsic PsbO proteins. During illumination with excess light, the reaction center D1 protein may be oxidatively damaged and needs to be replaced. The PsbO subunit of the damaged monomer binds and hydrolyzes GTP, leading to its dissociation and partial disassembly of the monomeric complex on the way to the stroma-exposed regions. Here the D1 protein is degraded and replaced with a new copy synthesized by the chloroplast ribosomes and co-translationally inserted in the membrane. Monomers assemble into the dimers and migrate to the grana regions.

(for a recent review, see Spetea, 2011). Thus, learning about TAAC evolution can be very important to understand its functional importance in green plants.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Plant_Physiology/10.3389/fpls.2011.00110/abstract

Figure S1 | MUSCLE alignment of TAAC subfamily of full-length amino acid sequences.

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