The Assembly of the CAAT-box Binding Complex at a Photosynthesis Gene Promoter Is Regulated by Light, Cytokinin, and the Stage of the Plastids*

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Victor Kusnetsov†‡§, Martin Landsberger†, Jörg Meurer‡, and Ralf Oelmüller†¶

From the †Timiriazev Institute of Plant Physiology, Russian Academy of Sciences, Moscow 127276, Russia and ‡Institut für Allgemeine Botanik, Lehrstuhl Pflanzenphysiologie, Friedrich-Schiller-Universität Jena, D-07743 Jena, Germany

A functionally important region in the promoter of the spinach photosynthesis gene AtpC, which encodes the subunit γ of the chloroplast ATP synthase, is located immediately upstream of the CAAT-box. A single nucleotide exchange in this region (AAAATTCAT → AAGATCAAT) uncouples the expression of an AtpC promoter::uidA gene fusion from the regulation by light, cytokinin, and functional plastids and results in a high constitutive expression in etiolated and photobleached material is caused by an inhibitory effect. The structure/low level of expression in etiolated and photobleached seedlings treated with cytokinin. Binding to the uidA mutant sequence, which directs constitutive high level expression in vivo, is significantly stronger than to the wild-type sequence. The data are consistent with the idea that the assembly of CBF at the AtpC promoter is regulated in response to light and cytokinin and that the low level of expression in etiolated and photobleached material is caused by an inhibitory effect. The structure/function relationships of the Arabidopsis CBFs are discussed in relation to their regulatory function in AtpC gene expression.

The plastid ATP synthase consists of nine different subunits; three of them are encoded by the nuclear genes AtpC, AtpD, and AtpG (gene products: the subunits γ and δ of the CF₁ moiety and CF₂,II (1)). Expression of these genes is strongly regulated in response to cell-internal and -external factors such as light, phytohormones, diurnal light changes, functional plastids, or factors determining organ and tissue specificity (cf. Refs. 2–6). Expression analysis of promoter::reporter gene fusions in transgenic tobacco seedlings suggested that these regulators influence transcription and defined cis-acting elements, which are involved in these processes (3). In contrast to many photosynthesis genes, essential cis-elements determining the regulated expression of AtpC are positioned in close vicinity of the respective transcription start sites (3), and crucial nucleotides for the light-regulated, plastid-dependent, and organ-specific expression appear to be located within a segment, which might also be involved in the assembly of the CAAT-box binding complex. Here we describe the isolation of cDNAs encoding the subunit C of the CAAT-box binding factor CBF³ (7), a plant homolog of the previously characterized CBF from metazoa (8, 9), we demonstrate that CBF-C is part of a complex that binds to the CAAT-box of AtpC, and we provide evidence that the binding activity is regulated in response to the above-mentioned regulators. In addition, binding of CBF-C to various mutant sequences in vitro corresponds to the promoter activities in vivo. This suggests that expression of AtpC is regulated by the assembly of CBF and that low levels of expression result from the repression of CBF assembly. At least eight homologs of CBF-C are present in the Arabidopsis genome, and one of them exhibits striking similarities to the human DRAP1, a general inhibitor of transcription initiation by RNA polymerase II.

EXPERIMENTAL PROCEDURES

Plant Growth, Generation of Promoter::uidA Gene Constructs, Transformation of Tobacco, and Analysis of uidA Gene Expression in Transgenic F₁ Seeds—Tobacco seeds were surface-sterilized, planted on one-half strength Murashige and Skoog medium supplemented with 2% sucrose in the presence or absence of Norflurazon (10⁻⁴ M) and kept in the cold room in darkness for 2 days to synchronize germination. Seedlings were either kept in darkness for 10 days at 22 °C or they were transferred to white light 20 h before harvest in the absence (L) or presence (L/NF) of Norflurazon. To test the effect of cytokinin on Atp gene expression, etiolated seedlings were transferred to cytokinin-containing plates (N°-benzylaminopurine, 10⁻⁴ M) in darkness 20 h before harvest. 36 h before phytohormone application, the seedlings were illuminated with red light (7 Wattmeter⁻²) for 12 h. In herbicide-treated seedlings, the red light treatment severely affected plastid development; the untreated material served as a control.

The transgenic lines with AtpC and AtpD promoter::uidA gene fusions have been described (3). A spontaneous mutation of the AtpC region –73/+173 was obtained in which a single A nucleotide was exchanged to G (AAAATTCAT → AAGATCAAT). The mutant promoter segment was excised from pBSC as an 5′-SalI-BamHI-3′ frag-

1 The abbreviation used is: CBF, CAAT-box binding factor.
ment and cloned into pBI 101.1. The plasmid was transferred into tobacco (*Nicotiana tabacum* Samsun var.) by leaf disc transformation. 15 plants were regenerated, and their seeds were harvested individually. The β-glucuronidase assay has been described (3). The cotyledons and the upper part of the hypocotyls were harvested for the enzyme assay.

For Northern analysis RNA was isolated from approximately 150 seedlings with the RNeasy extraction kit (Qiagen, Hilden, Germany). An equal amount of RNA (3 µg) was loaded per lane, and the filter was hybridized to AtPC, AtpD, and AtpG genes from *Arabidopsis*.

After digestion of the plasmids with *Bam*HI and *Sma*I and Caution: Whole cell Extracts from *Arabidopsis*, Southern western Hybridization—Oligonucleotides for wild-type and mutant sequences were annealed (10) and cloned into the SmalI site of pBSC (Stratagene, San Diego) before sequencing. Plasmids were chosen in which the 5′-end of the promoter fragment was oriented toward the *Bam*HI site of pBSC+. Thus all promoter fragments had the following 5′- and 3′-extensions:

5′-GATCCCCC [Insert] GGCTGCA-3′
3′-GGGG [Insert] CCGC-5′

**SEQUENCE 1**

After digestion of the plasmids with *Pst*I and *Bam*HI, the *Bam*HI site was filled-in with all four radiolabeled nucleotides and the Klenow enzyme, and the fragments were gel-purified on agarose gels. For the analysis of the electrophoretic mobility of the DNA fragments on polyacrylamide gels (15%), see Fig. 6, the insertions were excised with *Bam*HI and *Pst*I and run either at 22 °C or 60 °C in a temperature-controlled growth chamber.

For Southwestern analysis, nuclear protein extracts were isolated from 6-week-old spinach or tobacco plants grown in the greenhouse. The cauliflower was obtained from the local market. For physiological studies, nuclear extracts were prepared from the cotyledons of 2-week-old spinach seedlings, which were either kept in light or darkness, or etiolated seedlings were treated with cytokinin 48 h before harvest. The nuclear protein fraction was prepared as described (11).

Approximately 150,000 phages of an *Arabidopsis thaliana* cDNA library were screened with the radiolabeled AtpC promoter region (~68/39) in the presence of nuclear extracts (1 µg/ml buffer). 4 positive plaques were plaque-purified, and pBSC+ was excised according to the manufacturer's instruction (Stratagene) before sequencing and in vitro transcription and translation.

Southwest hybridization was performed at 4 °C. The filters were first blocked with blocking buffer by gentle shaking for 3 h (50 µl SW buffer (25 mM HEPES-NaOH, pH 7.6, 50 mM NaCl, 5 mM MgCl2, 1 mM EDTA, 5% v/v glycerol, 1% dithiothreitol), 1% bovine serum albumin, and 1.5 mg/ml denatured salmon sperm DNA). After 3 washing steps (10 min each) with HS buffer (SW buffer, 1 µg/ml denatured salmon sperm DNA), the filters were incubated overnight with SW buffer in the presence of the radioactive DNA fragments. When indicated, 1 µg of nuclear extract from tobacco, spinach, or cauliflower/ml of hybridization medium was added. After washing with SW buffer, the filters were exposed to an x-ray film.

**Results**

*Light and Cytokinin Stimulate the Expression of Nuclear-encoded Atp genes and Promoter:*uidA Gene Fusions in Tissue with Functional Plastids; Analysis of an AtpC Promoter Mutant—Fig. 1 demonstrates that two factors, light and cytokinin, stimulate the expression of AtpC, AtpD, and AtpG in 10-day-old tobacco seedlings. The stimulatory effect of both inducers is substantially reduced if plastid development is impaired by treatments with the bleaching herbicide Norflurazon. Regulation of *Atp* gene expression appears to reflect differences in transcription rates, since four promoter:uidA gene fusions with 5′-flanking sequences of the spinach *AtpC* and *AtpD* genes exhibit similar regulatory features in transgenic tobacco (Table I). Thus, light and cytokinin stimulate *Atp* gene expression, and this regulation requires functional plastids.

The shortest *AtpC* promoter:uidA gene construct (~73/173) still exhibits proper regulation in response to light, cytokinin, and the stage of the plastids (Table I). A single A → G nucleotide exchange immediately upstream of the putative CAAT-box (AAAATTCAAT → AAGATCAAT; construct: *AtpC-M*) results in a significant increase in *uidA* gene expression in etiolated material and in material with photobleached plastids. As a consequence, the β-glucuronidase levels directed by the mutant sequence in etiolated and photobleached seedlings do not differ significantly from those observed in light and after cytokinin treatment (Table I). This indicates that the low expression in etiolated and photobleached wild-type material is caused by an inhibitory effect that is not operative under inductive conditions (light, cytokinin) and in seedlings harboring the mutant promoter sequence (cf. see “Discussion”).

The *AtpC* Promoter Region Contains a Binding Site for CBF—A double-stranded oligonucleotide from the −69/−39 *AtpC* Region (5′-TTTACTCTCCAAAAATTCAATGGCCAAAATC-T′3′) harboring the AAAAT (bold) and CAAT (italics) motifs was used to screen an expression library from *Arabidopsis*. Positive signals were only obtained when the screen was performed in the presence of 1 µg/ml nuclear extract from spinach or tobacco, and four positive plaques with identical inserts were isolated (Fig. 2). Positive signals were also obtained with cauliflower nuclear extracts, suggesting that the missing factor(s) is neither organism-specific nor related to photosynthesis. Signals with whole cell extracts from *Arabidopsis* were significantly weaker, presumably because of the dilution of the nuclear protein fraction (data not shown). Binding in the presence of spinach extract could also be detected to the mutant oligonucleotide with the A → G nucleotide exchange (AAAAT mutant), but not to an oligonucleotide, in which the CAAT-containing region CAATGG was replaced by CTAT (Ref. 3; cf. see below). DNA sequence analysis revealed that the insertions encode a protein with high homology to the human, yeast, and *Aspergillus nidulans* CBF-C (Fig. 3; Refs. 8 and 9). A data bank search revealed that at least eight genes with striking homologies are present in the *Arabidopsis* genome; the two with the highest similarities are included in Fig. 3 (Ara IA, Ara VA). The middle part of the proteins, which displays similarities to hist-

**Fig. 1.** Northern analysis for tobacco *AtpC, AtpD,* and *AtpG.* Seedlings were either grown in darkness (D, D+) or they were transferred to light (L) 20 h before harvest or they were transferred to cytokinin-containing media in darkness (Cyt) 20 h before harvest, *NP* (growth in the presence of Norflurazon); *, seedlings received a 12-h red light pretreatment 24 h before cytokinin application to destroy the plastids. Equal RNA loading (3 µg per lane) was confirmed by the Image Master ID Prime software from Amersham Pharmacia Biotech. For hybridization, *Arabidopsis* expressed sequence tags were used.

**RESULTS**

*Light and Cytokinin Stimulate the Expression of Nuclear-encoded Atp genes and Promoter:*uidA Gene Fusions in Tissue with Functional Plastids; Analysis of an AtpC Promoter Mutant—Fig. 1 demonstrates that two factors, light and cytokinin, stimulate the expression of AtpC, AtpD, and AtpG in 10-day-old tobacco seedlings. The stimulatory effect of both inducers is substantially reduced if plastid development is impaired by
and a

either in the absence (A. thaliana expression library. As controls, two mutant fragments, AAAAT → AAGAT and CAAT → GTTA, were hybridized in the presence of spinach nuclear extract.

tone-fold motifs of the histones H2B and H2A and resembles the DNA binding region (cf. see “Discussion”), is highly conserved not only among the three Arabidopsis proteins, but also among human, yeast, and A. nidulans, whereas both the N- and C-terminal regions differ substantially with respect to their lengths and amino acid sequences. The histone-fold motif, which consists of the short α-helix I followed by a loop and a β-stranded segment LI, a longer α-helix II, a second short loop and a β-stranded segment LII, and a short α-helix III (Fig. 3), is also present in the subunit A of the Arabidopsis CBF (data bank accession number Y13723) and appears to be crucial for dimer formation (cf. see “Discussion”).

Fig. 2 compares the middle parts of the Arabidopsis CBF-C homologs. Two of them are encoded on chromosome I (IA and IB), the residual six genes on chromosome V (VA-VF). Interestingly, three of the genes on chromosome V, VB-VD, are organized in a cluster. Besides the high degree of similarities among the Arabidopsis proteins, they also exhibit homologies to the human DRAP1 and its yeast homolog NCB-1. This is particularly striking for VF (Fig. 4). In human, DRAP1 forms a heterodimer with Dr1 and functions as a global repressor for transcription (Refs. 13–15, cf. see “Discussion”).

| TABLE I |
| --- |
| β-Glucuronidase activity in 10-day-old tobacco seedlings with 5'-flanking sequences of the spinach AtpC and AtpD genes, or as well as with the 5'-flanking sequences of the 35 S RNA (CaMV) transcription unit (–1583/+3) fused to the uidA reporter gene. Seedlings were either grown in darkness (D, D*) (as indicated in the table) transferred to light (L) 20 h before harvest, or transferred to cytokinin-containing media in darkness (Cyt) 20 h before harvest. AtpC (M), a mutant AtpC promoter sequence (–173/+173) with an A to G exchange immediately upstream of the CAAT-box (see text). NF, growth in the presence of Norflurazon (10–6 M); *, seedlings received a 12-h red light pretreatment 24 h before cytokinin application to destroy the plastids. For each experiment, seeds from 12 independently transformed plants were analyzed separately. |
| β-Glucuronidase activity | D | L | L/NF |
| --- | --- | --- | --- |
| AtpD (–1137/+62) | 17.5 ± 2.7 | 61.3 ± 11.7 | 18.4 ± 3.3 |
| AtpD (–185/+62) | 1.3 ± 0.2 | 4.3 ± 0.9 | 1.1 ± 0.2 |
| AtpC (–1874/+173) | 7.5 ± 1.3 | 13.3 ± 2.2 | 6.8 ± 1.2 |
| AtpC (–73/+173) | 1.3 ± 0.2 | 8.8 ± 1.3 | 1.0 ± 0.1 |
| AtpC (M) | 6.1 ± 0.7 | 6.9 ± 1.1 | 6.0 ± 1.0 |
| 35 S RNA CaMV | 124 ± 19 | 112 ± 22 | 141 ± 16 |
| D* | | | |
| D/Cyt | | | |
| NF | | | |
| AtpC (–1137/+62) | 22.9 ± 4.4 | 45.3 ± 6.5 | 25.1 ± 3.3 |
| AtpD (–185/+62) | 2.0 ± 0.3 | 4.4 ± 0.7 | 1.8 ± 0.4 |
| AtpC (–173/+173) | 10.9 ± 0.9 | 15.5 ± 2.1 | 9.1 ± 0.8 |
| AtpC (–73/+173) | 1.8 ± 0.3 | 6.1 ± 0.7 | 1.4 ± 0.1 |
| AtpC (M) | 6.0 ± 0.4 | 6.4 ± 0.5 | 5.6 ± 0.3 |
| 35 S RNA CaMV | 119 ± 23 | 134 ± 12 | 144 ± 29 |

Assembly of CBF at the AtpC Promoter

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Binding of CBF-C to the AtpC Promoter in Vitro Correlates with the Promoter Activity in Vivo—In metazoa, the CBF complex is characterized by its requirement for a high degree of conservation both within the CAAT-box sequence and flanking sequences (cf. see Ref. 7). In contrast to the typical metazoa CCAAT-boxes, the spinach AtpC CAAT motif lacks one C, and the nucleotides surrounding this motif appear to differ from the consensus sequence determined by Bi et al. (16) for metazoa. To test the sequence requirement for the formation of the CBF-DNA complex at the AtpC promoter, a series of mutant sequences were tested for their ability to bind CBF-C in the presence of nuclear extracts from spinach.

Fig. 5 demonstrates that mutation of the CAAT motif completely abolishes the binding activity (lane 6) and that the binding activity to the oligonucleotide with the A → G exchange increases relative to the wild-type sequence (compare lanes 2 and 3). Introduction of a second C at the 5'-end of the CAAT motif did not affect the binding activity significantly (compare lanes 2, 4, and 5). This confirms that CBF-C is a CAXbox binding factor and that the binding activity of CBF at the AtpC promoter is influenced by nucleotides located 5' to the CAAT motif.

The wild-type sequence (AAAATTCGAAT) as well as the CAXbox mutant (AAAATTGTAAT) migrated faster on polyacrylamide gels at 22 °C when compared with the A → G mutant (AAGATTCAAT). An intermediate migration was observed for the fragment with the CAAT motif (AAAATTCCAAT, Fig. 6, 22 °C). However, at 60 °C (Fig. 6, 60 °C), most of the DNA molecules exhibit a slow electrophoretic mobility similar to that observed for the A → G mutant. This indicates that the wild-type sequence has the potential to form a secondary structure at room temperature and that both the central A (replaced by G) and the 3'-flanking T (replaced by C) contribute to this behavior (cf. see “Discussion”).

A correlation of the promoter activity in vivo (Table I) and its capability to bind CBF-C in the presence of nuclear extract from spinach is presented in Fig. 7. Four representative nuclear extracts from dark-adapted seedlings (Fig. 7A, D extract, 1–4) showed little binding activity to the radiolabeled CBF-C if the wild-type oligonucleotide was used for the gel shift assays. Consistent with the higher gene expression level, directed by the mutant sequence, a stronger retardation signal can be detected in gel mobility shift assays. Two representative nuclear extracts from light-grown seedlings (Fig. 7A, WL extract, 1–2) showed substantially stronger retardation signals irrespective of whether the wild-type or the mutant sequence was analyzed. The same appears to be true for cytokinin treatments (Fig. 7B), whereas herbicide treatments significantly reduced the binding activity with both extracts from light-grown seedlings and etiolated seedlings treated with cytokinin. This suggests that the assembly of CBF at the AtpC promoter is crucial for the regulated expression of AtpC.

Discussion

In many eukaryotic class II promoters, CCAAT motifs are often found between 50 and 100 nucleotides upstream of the transcription start site (17–20), and these motifs are recognized by different classes of CCAAT-binding proteins, one of which is CBF. CBF consists of three different subunits, A, B, and C, and all of them are essential for DNA binding. CBF-A and CBF-C interact with each other to form a stable heterodimer, and...
CBF-B can only interact with the dimer to form a heterotrimERIC complex which then binds DNA (cf. see Ref. 7). In meta-
zoa, the CBF-DNA complex is characterized by its requirement
for a high degree of conservation within the binding motif
CCAAT (7, 21, 22), and sequences surrounding the pentameric
motif contribute to the binding specificity (Ref. 16 and refer-
ences therein). The complex that assembles at the spinach
AtpC promoter differs from those described for metazoa in two
respects: first, the putative CAAT-box in the
AtpC promoter lacks one of the two C residues, and introduction of an addi-
tional C does not affect significantly the binding activity (Fig.
3). Second, the surrounding nucleotides do not match to the
consensus sequence determined by Bi
et al.
(16). In contrast to
many animal CCAAT motifs, the majority of the plant se-

![Fig. 3. Comparison of the CBF-C se-
quences. The deduced amino acid se-
quences of two genomic Arabidopsis se-
quences from the chromosomes I and V,
respectively (Ara IA, Ara VA), are com-
pared with that of the isolated cDNA (Ara
cDNA, identical to the GenBank acces-
sion number Y13725.1) as well as with the
amino acid sequences of CBF-C from
human, yeast, and Aspergillus (AS-
PERG). Asterisks, identical amino acids;
dots, homologous amino acids; dashes,
gaps to optimize the alignment. Helix I,
II, III, the three helical regions I, II, and
III, are separated by the loops I and II (LI,
LII). The initiator methionines are in
bold.](image)

![Fig. 4. Alignment of the middle parts of CBF-C and the CBF-C-related amino acid sequences from Arabidopsis with the human
DRAPl repressor and its yeast homolog NCBI. The Arabidopsis amino acid sequences are deduced from the cDNA or the eight genomic genes
IA-IB and VA-VF. Amino acids identical to those of the Arabidopsis cDNA are underlined in gray and identical to those of DRAPl are underlined
in black. The three boxes represent regions with high amino acid conservations in all polypeptides. Asterisks, identical amino acids; periods,
homologous amino acids; dashes, gaps to optimize the alignment. Ara IA/B: the amino acid sequences of these two polypeptides are identical in this
region.](image)

AtpC promoter differs from those described for metazoan in two
respects: first, the putative CAAT-box in the AtpC promoter
lacks one of the two C residues, and introduction of an addi-
tional C does not affect significantly the binding activity (Fig.
5). Second, the surrounding nucleotides do not match to the
consensus sequence determined by Bi
et al.
(16). In contrast to
many animal CCAAT motifs, the majority of the plant se-
sequences contain only one C or lack a CAAT-box completely. On the other hand, the AtpC promoter is relatively weak, which could be caused by an imperfect CBF binding site.

The CAAAT-box sequences, which are believed to influence the frequency of transcriptional initiation, can also be the target site for regulation. Maity and de Crombrugghe (7) define three classes of CBFB binding promoters in mammals: (i) those in which a mutation in the CAAT motif decreases transcription in the absence of stimulatory influences (21–27), (ii) those by which transcription is altered in response to inducing agents (28–32), and (iii) those by which transcription is altered during cell growth (33–37). It is also interesting to note that the cDNA initially isolated in our screen lacks most of the 5'-end and starts immediately upstream of the region that encodes the histone-fold motif. This suggests that formation of the heterodimer between A and C, association of B with the dimer, and ultimately DNA binding do not require the N-terminal part of CBF-C.

There is increasing evidence that etiolation is caused by repressors active in darkness rather than stimulatory processes functional in light (cf. see Ref. 39). Here we demonstrate that transcription of a light-regulated gene is repressed in darkness and under photodamaging conditions. The nature of the postulated binding factor is unknown at present; however, because of the AT-rich sequence, one might speculate that it is involved in DNA bending or recognition of bent DNA regions (cf. see Ref. 40). It is also interesting that light and cytokinin do not only control AtpC gene expression via the same cis-element in the promoter but operate also in a comparable fashion, most likely by regulating the same trans-acting factors (Table I).

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