The BBX subfamily IV
Additional cogs and sprockets to fine-tune light-dependent development

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Keywords: Arabidopsis, B-box zinc finger proteins, light signaling, STO, STH, COP1, HY5, transcriptional activator

Plants depend on light during all phases of its life cycle, and have evolved a complex signaling network to constantly monitor its surroundings. Photomorphogenesis, a process during which the plant reprograms itself in order to dwell life in presence of light is one of the most studied phenomena in plants. Recent mutant analyses using model plant Arabidopsis thaliana and protein interaction assays have unraveled a new set of players, an 8-member subfamily of B-box proteins, known as BBX subfamily IV. For the members of this subfamily, positive (BBX21, BBX22) as well as negative (BBX24) functions have been described for its members, showing a strong association to two major players of the photomorphogenic cascade, HY5 and COP1. The roles of these new BBX regulators are not restricted to photomorphogenesis, but also have functions in other facets of light-dependent development. Therefore this newly identified set of regulators has opened up new insights into the understanding of the fine-tuning of this complex process.

Introduction

Plants, as autotrophs, depend on light for their survival. Light influences seed germination, gravitropism, seedling de-etiolation, circadian rhythms and flowering time.1 One of the most important processes during plant development is photomorphogenesis, which involves transition from a heterotrophic darkness-dwelling state (skotomorphogenesis) to an autotrophic light-dwelling state (photomorphogenesis). The morphological changes accompanying this transition include the inhibition of hypocotyl elongation, opening of cotyledons and chlorophyll and anthocyanin biosynthesis.2 In Arabidopsis, this process is governed by the interplay of the different photoreceptors. These receptors include the red/far-red absorbing phytochromes (PhyA-PhyE), the blue/UV-A absorbing cryptochromes (Cry1, Cry2, Cry3), phototropins (Phot1, Phot2), and the recently identified UV-B photoreceptors (UVR8).3 Phytochromes A and B regulate the major responses to red and far red light such as seedling de-etiolation, root and hypocotyl growth, entrainment of the circadian clock, repression of flowering and regulation of shade avoidance, among many others.4-11 PHYA is the predominant photochrome in etiolated seedlings, and it is rapidly degraded upon PHYA photoconversion.12 PHYB is the predominant photoreceptor during prolonged red light responses in plants.5,13-14 The cryptochrome photoreceptors Cry1 and Cry2 dominate general de-etiolation responses under blue light; similarly, they are involved in flowering control, and the resetting of the circadian clock is partially dependent on the activity of this protein family.15-17 In darkness, the photomorphogenic process is negatively regulated by the COP/DET/FUS repressors.18,19 The most remarkable characteristic of the COP/DET/FUS-mutants is the display of photomorphogenic development in the dark. The group can be divided into three main complexes, according to their interactions: the COP10-DDB1-DET1 (CDD) complex, the COP9 signalosome (CSN) and the COP1 complex.20-23

Research efforts have been made to identify the signaling networks downstream the initial perception of the light stimulus.24-30 The photomorphogenic process is regulated by a multi-member gene network, in which the joint action of individual photoreceptors triggers the responses of the seedling to light adaptation. This process occurs at most levels of gene regulation, from chromatin conformational changes to protein modification and regulation.24,30,32 Among the signaling regulators described, special attention has been drawn to the transcriptional regulators. The main downstream effectors of the photomorphogenesis cascade can be grouped in bZIP,33-35 bHLH,26,36 MYB,37 Mutator-like transposases38 and the recently described B-box Zinc-finger proteins, named the BBX protein family.39,40

The B-box zinc finger protein family (BBX family40) has been implicated in the regulation of light-influenced processes, such as photomorphogenesis, shade avoidance, circadian rhythm and flowering. Its most well-known member, CONSTANS (CO, BBX1) is an important regulator of flowering in the photoperiod pathway.41,42 BBX proteins present a modular arrangement of one or two B-box zinc finger motifs in its N-terminal region. The family was organized into five sub-families. This review will document the described functional roles and mechanisms of regulation for each member of the BBX subfamily IV and give some
insights on the probable relation of the members to the major regulators of photomorphogenesis and light signaling.

**BBX Protein Classification**

The BBX protein family is divided into five main clades according to its protein sequence. Sub-family I consists of six members (including CO; BBX1-6); sub-family II has seven members (BBX7-13). Both sub-families share the same structure: two B-box zinc finger motifs at the N-terminus and a CCT (CONSTANS CONSTANS-LIKE TOC1) domain at the C-terminus (BBX1-13) (Fig. 1). Sub-family III is formed by four members (BBX14-17) that share one B-box motif and also a CCT domain. Sub-family IV has eight members and carries only two B-box zinc fingers (motifs) (BBX18-25), and the final group (Sub-family V) has one B-box motif and is composed of seven members (BBX26-32).

The C-terminal CCT (CO-COL-TOC1) domain is believed to modulate protein and DNA binding. The B-box domains in the whole family are thought to mediate protein-protein interactions, but confirmation of these interactions is described only in few individuals. Functional description of other members of this family have uncovered roles in circadian rhythm regulation for COL1, red light photomorphogenic signaling for COL3, flowering control for COL5 and COL9, and negative control of light-induced genes in the dark for BBX32.

Sub-family IV is composed of eight members (Fig. 1). Protein alignments show around 20% amino acid identity among the members, but close homologs are observed in BBX18-BBX19 and BBX24-BBX25 protein pairs with 70% of amino acid identity for each pair. As noted before, all members share around 55% amino acid identity in the B-box domains.

**Function and Regulation**

BBX24 and BBX25. SALT TOLERANCE (STO/BBX24) was the first member of the sub-family which was linked to light signaling. BBX24 was initially described as a protein which could complement the salt sensitive phenotype of yeast mutants. Nagaoka and Takano (2003) showed that Arabidopsis plants overexpressing BBX24 had an enhanced tolerance to salicylic media.

BBX24 interacts in yeast-two-hybrid assays with the hormone and abiotic stress regulator CLONE EIGHTY-ONE/RADICAL INDUCED CELL DEATH1 (CEO/RCD1) and with COP1, a negative regulator of photomorphogenesis. Holm and colleagues (2001) described a conserved amino-acid motif shared by BBX24, BBX25 and HY5 (V-P-E/D-Φ-G; Φ = hydrophobic residue) which is needed for a correct interaction with the WD40 domain of COP1.

BBX24 was linked to the photomorphogenic signaling cascade as a putative negative regulator (Table 1). BBX24 gain- and loss-of-function mutants displayed contrasting hypocotyl elongation and reciprocal cotyledon expansion when grown under different qualities of monochromatic light. Furthermore, Indorf and collaborators showed that the BBX24 protein is nuclear-localized, co-localizes with COP1 in the nucleus, and is degraded by a COP1-dependent mechanism. Most interesting, BBX24 accumulation in planta presented light-dependent stabilization, which makes of BBX24 a negative regulator of photomorphogenesis during the light stimulus.

Yan et al. reported that interaction with COP1 is required for proper function and protein turnover of BBX24 in light. Interestingly, transgenic plants overexpressing BBX24 with a mutation in the COP1-interacting motif (bbx24<sup>COP1</sup>) did not accumulate the protein in darkness, where COP1 is supposed to be active. Genetic analyses suggest that although COP1 needs to be present, no direct interaction with COP1 is required for protein degradation in darkness. Protein analyses in yeast demonstrated that this mutation did not provoke structural defects in the protein. An interesting observation described by Yan et al. is the BBX24-mediated transcriptional activation when fused to a DNA-Binding domain in yeast two-hybrid experiments. This result hints a role of BBX24 in transcriptional activation. A recent report links BBX24 to UV-B dependent signaling pathways. The authors demonstrate that the bbx24 mutant displays a hypersensitive phenotype under low intensity UV-B. Furthermore, BBX24 interacts with COP1 upon UV-B induction and antagonizes HY5 UV-B induced inhibition of hypocotyl elongation by suppression of its transcriptional activity.

The homolog of BBX24, BBX25, has been reported to function as a negative regulator of hypocotyl elongation under red and far-red light. The phenotype described for bbx25 mutants is weak,
when compared with *bbx24* alleles. Given the homology presented between this protein pair, it can be argued that the presence of a functional BBX24 protein in the *bbx25* mutant background can conceal a stronger effect probably due to redundancy, as observed already for protein homologs in the light signaling cascade.\(^{35,63,64}\) Both homologs might have related but independent functions during photomorphogenesis, being BBX24 the major player of the pair, and BBX25 having a minor role during photomorphogenesis (unpublished results, F. Sarmiento). The report by Jiang and colleagues (2012) of BBX24 involved in UV-B signaling opens another functional window for possible functions of BBX25 in this developmental cascade.

**BBX18 and BBX19.** BBX18 and BBX19 protein pair were initially characterized as putative negative regulators of photomorphogenesis (Table 1).\(^{39}\) The expression of both transcripts is regulated by the circadian rhythm, and 35S:*BBX18* and 35S:*BBX19* overexpression plants display hyposensitivity to red and far-red light. Experiments by Wang and colleagues\(^{69}\) demonstrated that BBX18 is a nuclear-localized protein. Light fluence-response analyses of BBX18 gain-and-loss-of-function lines proved that this gene is involved in blue light-dependent hypocotyl elongation as a negative regulator, and its phenotype is related to gibberellin signaling pathways.\(^{65}\) Further experiments have proved that BBX18 is involved as a negative regulator of basal and acquired thermotolerance.\(^{66}\) In addition, BBX18 has been shown to influence flowering.\(^{67}\)

**BBX21 and BBX22.** *STH2/BBX21* and *STH3/LZF1/BBX22*, even though they are not close homologs (Fig. 1),\(^{40}\) have striking functional similarities. Both proteins interact in yeast and plants with HY5.\(^{44,45}\) The *B-box* motifs of both proteins are important for the interaction with HY5 and have been characterized as positive regulators of light signaling.\(^{44,45,52}\) BBX22 interacts with HY5 HOMOLOG (HYH)\(^{44}\) and its expression in light depends on a functional HY5.\(^{52}\) Knockout T-DNA alleles of *STH2/BBX21* and *STH3/LZF1/BBX22* (*sh2-1, lzf1-1*) display a hyposensitive phenotype under different light qualities, reduced anthocyanin level, and are involved in HY5-dependent and independent signaling.\(^{44,45,52}\)

Furthermore the genetic interaction with COPI also depicted similarities between BBX21 and BBX22. Allele-specific complementation of *cop1* mutation effects (hypocotyl growth, anthocyanin accumulation) was observed in genetic interactions of *bbx22-1* with *cop1-4* and *cop1-6*.\(^{44}\) On the other hand, the absence of BBX21 in the *cop1-4* and *cop1-6* alleles partially suppressed hypocotyl reduction and anthocyanin accumulation displayed by these mutants.\(^{39}\) The joint effect of *bbx21-1* and *lzf1-1/sth3* in the *cop1-4* and *cop1-6* backgrounds strongly suppressed hypocotyl inhibition of the *cop1* alleles and reduced anthocyanin accumulation in the *cop1-4* and *cop1-6* alleles, respectively.\(^{44}\) This suggests that the misregulation of these BBX proteins is an important event for the phenotypes displayed by the *cop1* alleles.\(^{44}\)

Despite these described genetic interactions, there was no physical interaction detected between COPI and BBX21 or BBX22 in plant cells, although co-localization to the same sub-nuclear bodies was observed.\(^{44,45}\) In vitro ubiquitination of BBX22 in the presence of COPI was also reported.

The similarity in the phenotypes of the loss-of-function mutants and the genetic interaction with HY5 implies that these two proteins act redundantly in the regulation of photomorphogenesis. Indeed, phenotypic characterization of the *sth2-1/sth3/lef1-1* double mutant demonstrated the enhanced phenotypes observed in hypocotyl growth and anthocyanin accumulation.\(^{44}\) Transcription activation assays in protoplasts demonstrated that BBX21 and BBX22 were able to activate the transcription of chlorophyll *a/b* binding protein (CAB) and chalcone isomerase (CHI).\(^{44,52}\) The joint action of both proteins greatly increased transcription efficiency of the luciferase gene fused to the promoters of CAB and CHI.\(^{44,52}\) Mutations in the proposed G-box of the tested promoters or in the B-boxes diminished the transcriptional activation ability. Interestingly, these experiments also uncovered a higher affinity of BBX21 for the CHI promoter and BBX22 for the CAB promoter.

The reports by Datta and colleagues\(^{44,45}\) and Chang et al.\(^{52}\) also described specific roles for each of the studied BBX proteins (Table 1). A close examination of the *sth2-1/bbx21-1* allele revealed an increased number of emerged lateral roots compared with the WT when the plants were grown in short days (SD). Genetic interaction analyses in this condition uncovered that the *hy5-215* allele was epistatic to *bbx21-1*.\(^{45}\) Additionally the *lzf1-1/(...
bbx22-1 mutant displayed a lower amount of chlorophyll and a delay in the formation of chloroplasts in etiolated plants treated with white light.\textsuperscript{52}

Chang and colleagues\textsuperscript{46} demonstrated that BBX22, as previously described for BBX24, is tightly regulated at a post-translational level, and this control is mediated by HY5 and COP1. BBX22-GFP Protein analyses in the hy5-1 and cop1-4 mutants revealed that COP1 is required for protein degradation of BBX22 in the dark, while HY5 has a role in the degradation of BBX22 in light.\textsuperscript{68} Consistent with these observations, phenotypic analyses of 35S:BBX22-GFPox-cop1 lines proved that the overexpression of BBX22-GFP enhanced the cop1 phenotype during skotomorphogenesis and photomorphogenesis. In addition, growth rate experiments for the bbx22 line showed that under short days the mutant displayed an increased growth rate compared with WT during the dark phase in day 4 after germination. This suggests a more prominent role for BBX22 in SD adaptive processes, by possibly transmitting the signal for attenuated hypocotyl elongation during the night.\textsuperscript{68}

A recent report links the BBX protein sub-family IV to the shade avoidance syndrome (SAS).\textsuperscript{69} A T-DNA mutant screening for seedlings with longer hypocotyls under simulated shade, but with WT phenotype under white light and dark conditions, isolated a new bbx21-101 allele which displayed a longer hypocotyl than the WT when grown under shade. The mutant alleles bbx19, bbx21 and bbx22 displayed an enhanced hypocotyl elongation, while bbx18 and bbx24 exhibited the opposite phenotype under shade, hinting a function during the shade avoidance response. In contrast, no phenotype was observed for the bbx25 allele.\textsuperscript{69} The authors conclude that BBX21 is a negative regulator of SAS in conjunction with specific hormone-mediated signaling cascades. BBX21 promotes the expression of genes early responding to simulated shade, and represses some genes under long-term canopy shade. Furthermore, genetic and expression analyses suggest that BBX21 and BBX22 are involved in COP1-mediated regulation of the shade avoidance response.\textsuperscript{69}

**BBX20 and BBX23.** BBX20 and BBX23 seem to be elusive members of this sub-family (Table 1). Expression analyses were performed under continuous light by Kumagai and colleagues,\textsuperscript{39} but the transcripts of these two genes were not detected. A report describing transcriptional responses to karrikins, a germination stimulant identified in the smoke of wildfires, characterized BBX20/STH7 as an early response transcript.\textsuperscript{70} The transcriptional response of BBX20/STH7 to karrikins during germination was independent of light, gibberellins and light regulator HY5. However, it is still not known if BBX20 has a role in karrikin-dependent germination responses. Fan et al.\textsuperscript{71} described the function of BBX20 as a negative regulator of brassinosteroid (BR) signaling, but a positive regulator of photomorphogenesis. The authors found that BBX20 is regulated transcriptionally via BR signaling (by BZR1), and posttranscriptionally by means of a COP1-dependent mechanism,\textsuperscript{72} similarly to GATA2 regulation.\textsuperscript{72} Confocal microscopy analyses localize BBX20:YFP in the nucleolus and cytoplasm, making this feature unique for this protein in sub-family IV.\textsuperscript{71} Much less is known for BBX23. Genevestigator transcriptomic data mining showed that the condition under which the BBX23 transcript is upregulated is darkness.\textsuperscript{73}

### The Role of Subfamily IV BBX Proteins

Most of the data here presented point to the fact that the BBX sub-family IV might be transcriptional regulators strongly linked to the light signaling cascade, especially associated with COP1 and HY5 regulators, and probably cross-talk with other networks, such as different hormonal pathways.\textsuperscript{65,71} Independent experiments demonstrate that BBX21, BBX22 and BBX24 have trans-activating capacity in transcriptional systems.\textsuperscript{44,45,51,60} Although no DNA binding ability has been described. The proposed mechanism of action uses the interaction with other transcription factors that bind to DNA, such as HY5 and HYH (Fig. 2).\textsuperscript{44,51} It has been documented that HY5 is able to bind to promoters of genes that apparently are not directly activated by this transcription factor;\textsuperscript{74} therefore it is probable that HY5 acts in combination with other transcriptional activators, such as the BBX proteins, as was previously proposed.\textsuperscript{49} Given that there are positive and negative regulators of photomorphogenesis in this group, a fine tuning of photomorphogenesis by differential binding of these BBX proteins to HY5 and maybe other transcriptional activators might occur (Fig. 2). Although interaction with HY5 has been described in yeast 2-hybrid assays, there is only indirect evidence for the HY5-BBX complexes in plants. Datta and colleagues,\textsuperscript{45} were unable to detect the complex formation in-vitro, probably due to lack of other co-factors.

Holtan et al.\textsuperscript{51} described the formation of heterodimers between BBX21 and BBX32, and probably homodimers of BBX21, by means of its B-box motifs. The authors suggest a mechanism of regulation in which BBX32 binds to BBX21 to modulate its action in plants. It might be possible, that besides a possible differential binding to HY5, there might be also co-regulation of these factors by heterodimer formation. Efforts must be set into the analysis of these interactions. Up to date, there are no reports on the interactions among members of this BBX sub-family, except for the similar roles of BBX21 and BBX22, and there are members still with unknown function (BBX23). Construction of higher order mutants, protein interaction assays, co-immune precipitations and transcriptional activation assays could elucidate the mode of action, similarities and differences of the members of the BBX sub-family IV proteins.

A close relationship has been proposed between these BBX proteins and signaling regulator COP1. The main function of COP1 is targeting positive regulators of photomorphogenesis and regulation of flowering in the photoperiod pathway.\textsuperscript{75-77} All functions related to its E-3 ubiquitin-ligase activity in the dark. The latest reports have attributed roles for COP1 in light, during the first hours of de-etiolation,\textsuperscript{60,78} and a recent model explains the protein kinetics of two known COP1 targets during de-etiolation as part of a molecular switch involving two ubiquitin-ligase complexes.\textsuperscript{79} COP1 is probably targeting the BBX proteins for degradation as it does for CO/BBX1 (Fig. 2).\textsuperscript{76,77} This theory was tested by Yan et al.,\textsuperscript{60} and their experiments suggest that the
previously described interaction of BBX24 with COP1 is needed for the correct protein turnover of BBX24 and also for the function of BBX24 in plants.

Even though ubiquitination of BBX22 by COP1 was described in vitro, no direct interaction was observed in vivo.\(^4\) Direct interaction with COP1 is not needed for COP1-mediated protein regulation, as was reported for GIGANTEA protein degradation.\(^7\) In this line of thought, it is possible that BBX22 and also other BBX proteins are targeted for COP1-mediated protein degradation by means of adaptor proteins. Evidence on BBX24 and BBX22 points out that post-translational regulation might be the most important regulatory step for the BBX proteins. Saijo et al.\(^10\) detected mono-ubiquitinated phyA in in vitro assays, suggesting that COP1-mediated ubiquitination might not only serve to target proteins for degradation. Whether COP1 or other ubiquitination machinery is in charge of controlling the action of any of these proteins still has to be elucidated.

Since the first report on STO/BBX24\(^4\) there have been advances in the description of this subfamily; a radical shift was made from a possible function in salt stress to a role in light signaling. Reports on the other members of this subfamily have uncovered various light-related functions and have linked these proteins to important regulators of light signaling such as COP1 and HY5 and to hormone pathways. Further research is needed to define how the BBX proteins interact with each other and with common partners in order to fine-tune light-related responses.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

I wish to thank Alejandra Sarmiento for the help provided with the diagrams, and Mauricio Quimbaya, Cornelia Bär, Jacobo Arango, Teresa Mosquera and the members of the Neuhaus lab at the University of Freiburg for all the useful discussions and comments before and during the completion of this manuscript.

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