Molecular Plant
Review Article

CellPress
PARTNER JOURNAL

The Multifaceted Roles of HY5 in Plant Growth and Development

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http://dx.doi.org/10.1016/j.molp.2016.07.002

ABSTRACT

ELONGATED HYPOCOTYL5 (HY5), a member of the bZIP transcription factor family, inhibits hypocotyl growth and lateral root development, and promotes pigment accumulation in a light-dependent manner in *Arabidopsis*. Recent research on its role in different processes such as hormone, nutrient, abiotic stress (abscisic acid, salt, cold), and reactive oxygen species signaling pathways clearly places HY5 at the center of a transcriptional network hub. HY5 regulates the transcription of a large number of genes by directly binding to *cis*-regulatory elements. Recently, HY5 has also been shown to activate its own expression under both visible and UV-B light. Moreover, HY5 acts as a signal that moves from shoot to root to promote nitrate uptake and root growth. Here, we review recent advances on HY5 research in diverse aspects of plant development and highlight still open questions that need to be addressed in the near future for a complete understanding of its function in plant signaling and beyond.

Key words: HY5, HY5-orthologs, transcriptional regulation, hormonal cross-talk, photomorphogenesis, growth and development

Gangappa S.N. and Botto J.F. (2016). The Multifaceted Roles of HY5 in Plant Growth and Development. Mol. Plant. **9**, 1353–1365.

INTRODUCTION

Light is arguably one of the most important environmental factors that determine plant developmental processes such as seed germination, seedling de-etiolation, organ development, flowering, and seed development. Absorption of light by different photoreceptors leads to modulation of core signaling networks, which further orchestrates specific hormone and metabolic signaling pathways to adjust plant growth and development (Quail, 2002; Lau and Deng, 2012). Light is known to cause massive transcriptional reprogramming of nearly 35% of the total *Arabidopsis* genome (Tepperman et al., 2004). The perception of light by photoreceptors activates many intermediary transcription factors that belong to diverse families such as bZIP, bHLH, MYB, Zinc-finger, GATA, GT1, etc., which bind to light-responsive elements (LREs) such as G, Z, GT1, GATA, and MYB recognition elements to modulate transcription. Several transcription factors that act downstream to either single or multiple photoreceptors have been functionally characterized (Quail, 2002; Jiao et al., 2007; Leivar and Quail, 2011; Gangappa et al., 2013a, Gangappa and Botto, 2014). Among these, HY5 emerges as a central regulator of seedling development (Jiao et al., 2007; Heijde and Ulm, 2012; Lau and Deng, 2012; Gangappa and Botto, 2014). HY5 regulates fundamental developmental processes such as cell elongation, cell proliferation, chloroplast development, pigment accumulation, and nutrient assimilation (Koornneef et al., 1980; Oyama et al., 1997; Jing et al., 2013). HY5 promotes photomorphogenesis downstream to phytochromes, cryptochromes, and UV-B photoreceptors, and *hy5* mutant seedlings exhibit very long hypocotyl under red (R), blue (B), far-red (FR), and UV-B light (Koornneef et al., 1980; Oyama et al., 1997; Ang et al., 1998; Chattopadhyay et al., 1998; Oravecz et al., 2006; Brown and Jenkins, 2008; Heijde and Ulm, 2012; Li et al., 2013). In recent years, the role of HY5 in other signaling cascades such as hormonal, nutritional, terpene synthesis, defens, and temperature response pathways has started to be uncovered. Therefore, this review summarizes recent research advances on HY5, highlights the relevance of HY5 in plant growth and development, and discusses its emerging role in other signaling pathways.

HY5, A MASTER REGULATOR OF TRANSCRIPTION

HY5 is a member of the basic leucine zipper (bZIP) family of transcription factors (Jakoby et al., 2002), but crystallographic

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Signaling processes	Key genes targeted by HY5		Mode of regulation	Binding sequence	Reference
Light signaling	*HY5*	*Elongated Hypocotyl5*	Induction	*CACGTT*	Abbas et al., 2014; Binkert et al., 2014
	BBX22	*B-Box domain protein 22*	Induction	*G-box*	Chang et al., 2008
	COP1	*Constitutive photomorphogeneic 1*	Induction	*ACGT*	Huang et al., 2012
	FHY1	*Far-red Elongated Hypocotyl 1*	Induction	*ACGT*	Li et al., 2010
	FHL	*FHY1-LIKE*	Induction	*ACGT*	Li et al., 2010
	HYH	*HY5 Homolog*	Induction	*G-box*	Lee et al., 2007; Ciolfi et al., 2013
	HFR1	*Long Hypocotyl in Far-red 1*	Induction	*G-box*	Lee et al., 2007
	ELIP2	*Early Light Induced Protein 2*	Induction	*GGCCACGCCA*	Hayami et al., 2015
	RBCS-1A	*Ribulose bisphosphate carboxylase small chain 1A*	Induction	*G-box*	Chattopadhyay et al., 1998
	GLK2	*Golden Like 2*	Induction	*G-box*	Kobayashi et al., 2012
Circadian clock	*ELF4*	*Early Flowering 4*	Induction	*ACE*	Li et al., 2011a, 2011b; Lee et al., 2007
	CCA1	*Circadian Clock Associated1*	Induction		Andronis et al., 2008; Lee et al., 2007
	LHY	*Late Elongated Hypocotyl*	Induction		Lee et al., 2007
	TOC1	*Timing of CAB1*	Induction	*G-box*	Andronis et al., 2008; Lee et al., 2007
Anthocyanin biosynthesis	*CHS*	*Chalcone synthase*	Induction	*G-box, ACE*	Ang et al., 1998; Shin et al., 2007
	CHI	*Chalcone isomerase*	Induction	*ACE*	Shin et al., 2007
	FLS	*Flavonol synthase*	Induction	*ACE*	Shin et al., 2007
	MYB12	*MYB domain protein 12*	Induction	*ACE*	Stracke et al., 2010
	MYB111	*MYB domain protein 111*	Induction	*ACE*	Stracke et al., 2010
	PAP1	*Production of anthocyanin pigment1*	Induction	*ACE*	Shin et al., 2013
	MYBD	*MYB-like Domain*	Induction	*ACE*	Nguyen et al., 2015
Chlorophyll biosynthesis	*CAB1/ LHCB1.3*	*Light-Harvesting chlorophyll A/B 1.3*	Induction	*ATACGGT (Z-box)*	Catalá et al., 2011; Andronis et al., 2008
	PSY	*Phytoene synthase*	Induction	*G-box*	Toledo-Ortiz et al., 2014; Chen et al., 2016
	LHCA4	*Photosystem I light harvesting complex gene 4*	Induction	*G-box*	Toledo-Ortiz et al., 2014
	PORC	*Protochlorphyllide oxidoreductase C*	Induction	*G-box*	Toledo-Ortiz et al., 2014
	GUN5	*Genome Uncoupled 5*	Induction	*G-box*	Toledo-Ortiz et al., 2014
Cell elongation	*IAA19*	*Indole-3-acetic acid inducible 19*	Repression	*G-box*	Jing et al., 2013
	EXP2	*Expansin2*	Repression	*G-box*	Jing et al., 2013
	XTH5	*Xyloglucan endotransglucosylase/ Hydrolase 5*	Repression		Xu et al., 2016a, 2016b
	XTH21	*Xyloglucan endotransglucosylase/ Hydrolase 21*	Repression		
Hormone signaling					
Auxin	*SLR/IAA14*	*Solitary root/Indole acetic acid 14*	Induction	*G-box*	Cluis et al., 2004
	AXR2/IAA7	*Auxin resistant 2/Indole acetic acid 7*	Induction	*G-box*	Cluis et al., 2004
Ethylene	*ERF11*	*Ethylene Response Factor 11*	Induction	*G-box*	Li et al., 2011a, 2011b

Table 1. Key Genes Regulated by HY5 Across Diverse Signaling Pathways.

(Continued on next page)

Signaling processes	Key genes targeted by HY5		Mode of regulation	Binding sequence	Reference
Brassinosteroid	*MSBP1*	*Membrane Steroid Binding Protein 1*	Induction	*GATGATA*	Shi et al., 2011
Abscisic acid	*ABI5*	*Abscisic acid insensitive 5*	Induction	*G-box*	Chen et al., 2008
Nutrient signaling	NRT2.1	*Nitrate transporter 2.1*	Induction	*G-box*	Chen et al., 2016
	NIA2	*Nitrate reductase*	Induction		Jonassen et al., 2008
	NIR1	*Nitrite reductase*	Induction		Huang et al., 2015
	NRT1.2	*Nitrate transporter 1.2*	Repression		Huang et al., 2015
	AMT1.2	*Ammonium transporter1.2*	Repression		Huang et al., 2015
	APR	*Adenosine 5'-phosphosulfate reductase 1*	Induction		Lee et al., 2011
	APR	*Adenosine 5'-phosphosulfate reductase 2*	Induction		Lee et al., 2011
	SULTR1.2	*Sulfate transporter 1.2*	Induction		Lee et al., 2011
	MIR408	*MicroRNA 408*	Induction	*G-box*	Zhang et al., 2014
Sucrose metabolism	TPS1	*Trehalose-6-phosphate synthase 1*	Induction	*G-box*	Chen et al., 2016
	SWEET11	*Sucrose transporter 11*	Induction	*G-box*	Chen et al., 2016
	SWEET12	*Sucrose transporter 12*	Induction	*G-box*	Chen et al., 2016
Terpene synthesis	*QH6*	*Monoterpene β-pinene synthase*	Induction	*TGA CACGTGGCA*	Zhou et al., 2015
Defense signaling	*EDS1*	*Enhanced disease susceptibility 1*	Induction	*G-Box*	Chai et al., 2015
ROS signaling	*APX2*	*Ascorbate peroxidase 2*	Induction	*G-box*	Chen et al., 2013
	SIB1	*Sigma factor binding protein 1*	Induction	*G-box*	Chen et al., 2013
	ERF4	*Ethylene responsive element binding factor 4*	Induction	*G-box*	Chen et al., 2013
	SIB1	*Sigma factor binding protein 4*	Induction	*G-box*	Chen et al., 2013
	NDB2	*NAD(P)H dehydrogenase B2*	Induction	*G-box*	Chen et al., 2013

Table 1. ***Continued***

analysis of LZ (leucine zipper) suggests that its structure is significantly different from other bZIP proteins of *Arabidopsis* (Yoon et al., 2007). Therefore, one needs to be cautious when generalizing the structural and functional relationships of HY5 with other bZIP proteins. HY5 was originally shown to regulate the transcription of light-inducible genes such as *RIBULOSE BISPHOSPHATE CARBOXYLASE SMALL CHAIN 1A* (*RBCS-1A*) and *CHALCONE SYNTHASE* (*CHS*) by directly binding to the G-box LRE present in their minimal promoters (Ang et al., 1998; Chattopadhyay et al., 1998; Lee et al., 2007). In recent years, HY5 has been also shown to regulate the expression of numerous genes belonging to diverse hormone and metabolic pathways. Interestingly, genome-wide ChIP-chip experiments demonstrated that HY5 regulates the expression of nearly one-third of genes in *Arabidopsis*, and ~3000 of them are directly controlled by HY5 binding (Lee et al., 2007; Zhang et al., 2011a). In addition to G-box, HY5 has been shown to bind T/G-box (*CACGTT*), E-box (*CAATTG*), GATA-box (*GATGATA*), ACE-box (*ACGT*), Z-box (*ATACGGT*), C-box (*GTCANN*), and hybrid C/G- (G) and C/A-boxes present in promoters of many genes (Table 1 and references therein). HY5 targets include light-signaling components such as *CONSTITUITIVE PHOTOMORPHOGENIC 1* (*COP1*), *FAR-RED ELONGATED HYPOCOTYL 1* (*FHY1*), *FHY1-LIKE* (*FHL*), *CHLOROPHYLL A/B BINDING PROTEIN 1* (*CAB1*), *HY5 HOMOLOG* (*HYH*), *LONG HYPOCOTYL IN FAR-RED* (*HFR1*), *B-BOX22* (*BBX22*), and *PHYTOCHROME KINASE SUBSTRATE 1* (*PKS1*); flowering time components such as *SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1* (*SOC1*) and *GIGANTEA* (*GI*); and circadian clock regulatory genes such as *EARLY FLOWERING 4* (*ELF4*), *TIMING OF CAB EXPRESSION 1* (*TOC1*), *LATE ELONGATED HYPOCOTYL* (*LHY*), *CIRCADIAN CLOCK ASSOCIATED 1* (*CCA1*) (Table 1). HY5 and its homolog, HYH, together directly bind to ACGT-containing elements or G-box (*CACGTG*) present in the promoters of cell elongation genes to repress their expression (Table 1). Very recently, HY5 has been shown to negatively feed back to control the expression of COP1 in etiolated seedlings (Xu et al., 2016a).

HY5 also regulates the expression of the carotenoid biosynthetic gene, *PHYTOENE SYNTHASE* (*PSY*), and a subset of chlorophyll biosynthesis genes such as *LIGHT-HARVESTING COMPLEX 4 (LHCA4)*, *PROTOCHLOROPHYLLIDE OXIDOREDUCTASE C (PORC)*, and *GENOMES UNCOUPLED 5 (GUN5)* by directly binding on their promoters (Toledo-Ortiz et al., 2014). Further, HY5 has been shown to bind a hitherto unreported *cis*-element (known as Element B: *GGCCACGCCA*) present in the *Early Light Induced Protein 2* (*ELIP2*) promoter inducing its transcription under UV-B and high irradiation (Hayami et al.,

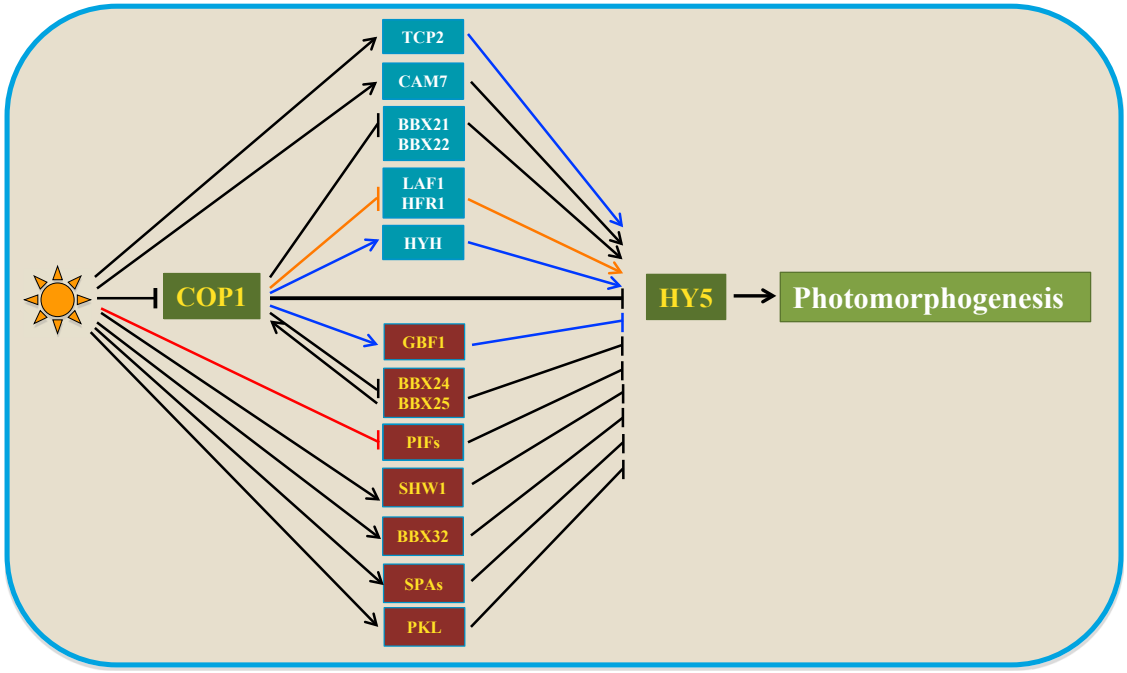

Figure 1. HY5 Forms a Central Hub of Photomorphogenesis.
HY5 is the central hub of the transcriptional network that regulates photomorphogenesis. A large number of proteins act to regulate HY5 function, including photoreceptors and downstream signaling components. Photoreceptors transduce the signals to HY5 through suppression of COP1 activity, a potent inhibitor of HY5 function. Proteins such as CAM7, TCP2, LAF1, HFR1, BBX21, and BBX22 act to enhance photomorphogenesis mediated by HY5, whereas SPAs (SPA1-4), BBX24-25, BBX32, PIFs (PIF1, PIF3-5), and GBF1 act to suppress it. Blue lines indicate specific function in blue light; orange lines indicate specific function in far-red light; black lines indicate function irrespective of the wavelength of light.

2015). Because ELIP2 has a photoprotective function in plants, these results suggest that HY5 can prevent damage caused by stressful light conditions (Hayami et al., 2015).

In addition, HY5 regulates the expression of eight *miRNAs* by directly binding to their promoters (Zhang et al., 2011a). In turn, these *miRNAs* control the expression of a large number of genes that are involved in diverse physiological process. These results indicate that HY5 regulates gene expression at both the transcription and post-transcription levels. HY5 and HYH have also been shown to be required for the expression of *HUA ENHANCER1* (*HEN1*), a methyltransferase that stabilizes small RNAs (Li et al., 2005; Tsai et al., 2014). Interestingly, HEN1 promotes biogenesis of *miRNA* such as *miR157d*, which in turn targets the 5′-UTR of *HY5* transcripts for cleavage, suggesting a post-transcriptional silencing mechanism for *HY5* regulation (Tsai et al., 2014).

Furthermore, HY5 induces its expression in all light conditions by directly binding to its own promoter (Abbas et al., 2014; Binkert et al., 2014). HY5, in combination with CAM7, binds to the T/G-box and E-box of the *HY5* promoter, inducing its expression in visible light (Abbas et al., 2014), whereas HY5, together with HYH, is required for the proper expression of *HY5* under UV-B light (Binkert et al., 2014). These findings suggest that the auto-regulation expression of *HY5* is critical for the control of HY5 activity. Very recently, a member of the TEOSINTE-LIKE1, CYCLOIDEA, and PROLIFERATING CELL FACTOR (TCP) transcription factor family, TCP2, has been shown to promote photomorphogenesis through activation of *HY5* and *HYH* expression, suggesting that TCP2 is an upstream activator of HY5 (He et al., 2016).

HY5 INTERACTS WITH OTHER PROTEINS

HY5 activity is achieved by physical interactions with signaling intermediates including both regulatory proteins and transcription factors (Figure 1). COP1 is a central negative regulator of photomorphogenesis that interacts physically with HY5 (Ang et al., 1998). HY5 interacts with COP1 through its N terminus leading to ubiquitination followed by degradation, suggesting one of the mechanisms through which HY5 activity is controlled in etiolated seedlings (Osterlund et al., 2000). Similarly, a group of negative COP1 co-regulators, SUPPRESSOR OF PHYA-105 (SPA) proteins have also been shown to interact with HY5 (Saijo et al., 2003; Zhu et al., 2008). SPA proteins, through interaction with COP1, enhance HY5 degradation in dark-grown seedlings (Saijo et al., 2003; Zhu et al., 2008). Among the transcription factors, HY5 forms heterodimers with many different classes of transcription factors such as, bZIP, bHLH, MYB, calmodulin, etc. Most importantly, HYH has been shown to have HY5 overlapping functions and acts redundantly for the regulation of hypocotyl growth, lateral root growth, pigment accumulation, and the expression of light-inducible genes (Oyama et al., 1997; Chattopadhyay et al., 1998; Holm et al., 2002; Sibout et al., 2006). Moreover, HYH has been shown to form heterodimers with HY5 at the G-box LRE and helps in transcriptional activation (Holm et al., 2002). Contrary to HYH, another bZIP protein, G-BOX BINDING FACTOR1 (GBF1), physically interacts with HY5 and interferes with the transcription expression of *RBCS-1A* (Singh

et al., 2012). Moreover, HY5 and GBF1 have been shown to bind on the same promoter elements as revealed from genome-wide ChIP-seq analysis suggesting complex regulatory mechanisms for the fine-tuning of gene expression (Ram et al., 2014).

In phyA-mediated photomorphogenesis, HY5 physically interacts with HFR1, a bHLH protein, and LONG AFTER FAR-RED LIGHT 1, LAF1, an MYB protein (Jang et al., 2013). The heterodimerization of HY5 with HFR1 and LAF1 might prevent them from protein degradation leading to increased stability of both transcription factors (Jang et al., 2013). Interestingly, HY5 physically interacts with two transposase-derived transcription factors, FAR-RED ELONGATED HYPOCOTYL 3 (FHY3) and FAR-RED IMPAIRED RESPONSE 1 (FAR1) to interfere with their transcriptional activity (Lin et al., 2007). In fact, FHY3 and FAR1 are required for the expression of *FHY1* and its homolog *FHL* (Li et al., 2010). Both FHY1 and FHL are essential for the nuclear import of phyA in a far-red-light-dependent manner (Hiltbrunner et al., 2005). Therefore, the negative regulation of FHY3 and FAR1 by HY5 is crucial for phyA-mediated signaling homeostasis in seedling development.

Furthermore, HY5 physically interacts with another important protein known as CALMODULIN 7 (CAM7) in the nucleus, and both bind to E-box and T/G-box *cis*-acting elements, respectively, for the regulation of *HY5* expression (Abbas et al., 2014). Consistent with this, CAM7 redundantly enhances the function of HY5 for the promotion of photomorphogenesis under different light conditions (Kushwaha et al., 2008).

HY5 has also been shown to functionally interact with B-box-containing proteins such as BBX21-BBX22 and BBX24-BBX25 (Datta et al., 2007, 2008; Gangappa et al., 2013a, 2013b, 2013c). BBX21 and BBX22 enhance, whereas BBX24 and BBX25 suppress HY5 function in promoting photomorphogenesis through a direct physical interaction (Datta et al., 2007, 2008; Gangappa et al., 2013b, 2013c). These results suggest that BBX proteins serve as co-regulators of HY5 for the fine-tuning of seedling photomorphogenesis. Moreover, a recent report has shown that BBX21 can bind to the T/G-box and directly activates the expression of *HY5*, suggesting that BBX proteins might regulate transcription directly (Xu et al., 2016a, 2016b). Similarly, BBX21-22 and BBX24-25 physically interact with HYH suggesting that BBX proteins could also act as potential co-regulators of HYH (Datta et al., 2007, 2008; Gangappa et al., 2013b, 2013c).

HY5 and HYH have also been shown to interact with PHYTOCHROME INTERACTING FACTOR (PIF1 and PIF3) and antagonistically regulate the expression of reactive oxygen species (ROS) signaling genes (Chen et al., 2013), thereby regulating excessive seedling damage from light during the de-etiolation process. Also, HY5 has been shown to suppress cell elongation by inhibiting the activity of chromatin remodeling protein, PICKLE (PKL). PKL in turn negatively regulates HY5 by repressing the deposition of H3K27me3 histone marks at the target loci involved in cell elongation (Jing et al., 2013).

REGULATION OF HY5 IS DYNAMIC

HY5 genetically and physically interacts with a large number of signaling components, which can function either as promoters or suppressors of photomorphogenesis (Figure 1). The most important and better-known partner of HY5 is COP1, a key suppressor of photomorphogenesis. COP1 targets HY5 and many other positive factors such as HYH, LAF1, HFR1, BBX22, ELF3, and SPA2 for degradation in darkness (Holm et al., 2002; Chang et al., 2011; Chen et al., 2015; Wang et al., 2015; Xu et al., 2015). HY5 physically interacts with COP1 through its N-terminal domain (N25 to N60 amino acids), is ubiquitinated, and further degraded by 26S proteasome (Ang et al., 1998; Osterlund et al., 2000). HY5 exists in two isoforms, phosphorylated and unphosphorylated; the unphosphorylated form is the active physiological form with higher affinity to target promoters and the strongest interaction with COP1 (Hardtke et al., 2000). Therefore, the phosphorylated form of HY5 maintained in the dark could serve as a reserve pool to be unphosphorylated quickly during the transition to light for seedling photomorphogenesis. In addition to COP1, SPA1–4 promote degradation of HY5 through COP1 (Saijo et al., 2003; Zhu et al., 2008). Another negative regulator of photomorphogenesis, SHORT HYPOCOTYL UNDER BLUE 1 (SHW1) also enhances HY5 degradation in a COP1-dependent manner (Srivastava et al., 2015).

Interestingly and contrary to the observation in darkness, SPA1 was found to promote HY5 stability indirectly in blue light by dissociating with COP1 and associating with CRY1. Therefore, dissociation of SPA1 from COP1 in a blue-light-dependent manner suppresses COP1-mediated degradation of HY5 and thereby promotes photomorphogenesis (Lian et al., 2011; Liu et al., 2011). Opposite to visible light, both COP1 and SPA1 are required to maintain HY5 stability in UV-B light (Huang et al., 2013).

HY5 stability is also directly proportional increased light intensity (Osterlund et al., 2000), suggesting that plants acquired a mechanism to dynamically regulate the level of HY5 protein in an intensity-dependent manner to modulate seedling elongation. In addition, a histone acetylation mark, such as H3K9ac, has been shown to play an important role in light-mediated induction of *HY5* and *HYH* expression. Many of the HY5 target genes are also enriched for H3K9ac marks, suggesting that acetylation might be a common epigenetic mechanism for the proper expression of HY5 targets during seedling de-etiolation (Charron et al., 2009).

Moreover, environmental factors also regulate HY5 activity dynamically. Two-week-old *hy5-1 Arabidopsis* plants exhibited lower freezing tolerance than wild-type after 1 week of cold acclimation at 4°C, because low temperature stabilizes HY5 protein even in darkness by reducing the nuclear accumulation of COP1 (Catalá et al., 2011). Similarly, a short heat shock treatment at 37°C in *Arabidopsis* seedlings stabilizes HY5 by reducing the nuclear abundance of COP1 (Karayekov et al., 2013). Recently, it has been shown that *Arabidopsis* seedlings cultivated in darkness at 17°C produce higher HY5 transcript and protein levels after a red light pulse than those grown at 27°C, and this correlates well with a higher production of carotenoid and chlorophyll pigment synthesis (Toledo-Ortiz et al., 2014).

HY5 INTEGRATES LIGHT AND HORMONE-SIGNALING PATHWAYS

HY5 promotes photomorphogenesis through a coordinated regulation of various hormonal signaling pathways (Figure 2).

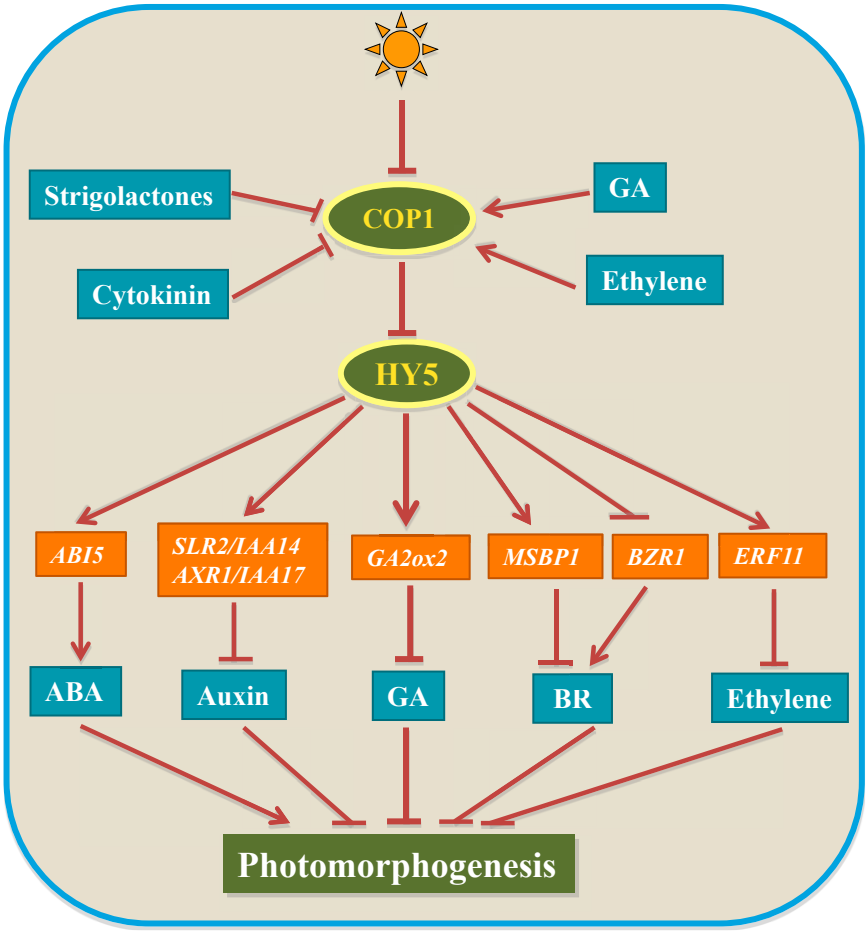

Figure 2. HY5 Promotes Photomorphogenesis through Modulation of Different Hormone Signaling Pathways.
Light-mediated activation of HY5 directly suppresses hormonal pathways (auxin, GA, BR, and ethylene) through the activation of key negative regulators; in the case of BR signaling, HY5 also inhibits the activity of BZR1 transcription factor. HY5 promotes photomorphogenesis through the ABA signaling pathway mediated by ABI5. Hormones such as cytokinin and strigolactones enhance HY5 activity indirectly by the negative regulation of COP1 activity, thereby promoting photomorphogenesis.

Hormones such as gibberellin (GA), brassinosteroid (BR), ethylene, and auxin promote skotomorphogenesis, whereas cytokinin, abscisic acid (ABA), and strigolactones promote photomorphogenesis (Chen et al., 2008; Feng et al., 2008; de Lucas et al., 2008; Shi et al., 2011; Rasmussen et al., 2012; Yu et al., 2013; Xu et al., 2014). HY5 negatively regulates hypocotyl elongation by suppressing auxin signaling (Cluis et al., 2004; Sibout et al., 2006). In fact, HY5 negatively regulates the auxin signaling pathway because HY5 promotes the expression of auxin signaling inhibitors such as INDOLE ACETIC ACID 14 (SLR/IAA14) and INDOLE ACETIC ACID 7 (AXR2/IAA7), and *hy5*, *hyh, hy5hyh* mutants show constitutive upregulation of auxin signaling genes (Sibout et al., 2006). Light suppresses GA signaling by decreasing GA biosynthesis and increasing DELLA activity (Achard et al., 2007; Alabadi and Blazquez, 2009). Interestingly, HY5 has been shown to target many of the GA metabolism genes as revealed from ChIP-seq analysis (Lee et al., 2007). In pea, the HY5 ortholog, LONG1, negatively regulates GA levels by inducing *GA2ox2* expression, a key GA catabolic gene (Weller et al., 2009). Furthermore, GA2ox2 enzyme inactivates most active GAs leading to increased DELLA activity and reduced PIF4 transcriptional activity (Feng et al., 2008; de Lucas et al., 2008). Light is also known to inhibit BR signaling at least partly mediated by HY5 and HYH, which directly induce the expression of *MEMBRANE STEROID BINDING PROTEIN 1*, *MSBP1* (Shi et al., 2011). MSBP1 negatively regulates BR signaling by physically interacting with BRI1-ASSOCIATED RECEPTOR KINASE (BRAK1), which further results in enhanced BAK1 endocytosis. Contrary to MSBP1, HY5 interferes with BZR1 transcriptional activity and protein stability (Li and He, 2015). HY5 also suppresses ethylene signaling by promoting the expression of *ERF DOMAIN PROTEIN 11* (*AtERF11*), which is a transcriptional repressor. AtERF11 protein then targets the promoter of ethylene biosynthetic genes, *1-AMINOCYCLOPROPANE-1-CARBOXYLATE SYNTHASE (ACS2* and *ACS5*) and suppresses their transcription (Li et al., 2011b). Interestingly, ethylene also counteracts HY5 action indirectly by enhancing HY5 degradation through increased COP1 accumulation in the nucleus (Yu et al., 2013).

As opposed to ethylene, cytokinin and strigolactones promote photomorphogenesis indirectly by reducing the nuclear accumulation of COP1, which further leads to the stabilization of HY5 protein (Vandenbussche et al., 2007; Tsuchiya et al., 2010; Jia et al., 2014). Genetic interactions between HY5 with strigolactone and karrikins signaling elements, *MORE AUXILLARY GROWTH 2* (*MAX2*) and *KARRIKIN-INSENSITIVE 2 (KAI2*), respectively, suggest that both components act additively through parallel pathways (Waters and Smith, 2013). Strigolactones also induce seed germination through HY5 activity at high temperatures (Toh et al., 2012). Moreover, HY5 integrates signals from light and ABA, inhibiting seed germination through the promotion of *ABSCISIC ACID 5* (*ABI5*) expression, a positive transcription factor of ABA signaling (Chen et al., 2008). Interestingly, the overexpression of ABI5 in *hy5* mutant seeds restores ABA sensitivity (Chen et al., 2008). In opposition, BBX21 inhibits *ABI5* expression indirectly by interfering with HY5 transcriptional activity (Xu et al., 2014).

EMERGING RESPONSES MEDIATED BY HY5

Circadian Clock

Photoreceptors have been shown to directly regulate the transcription of several clock genes, demonstrating that light is an

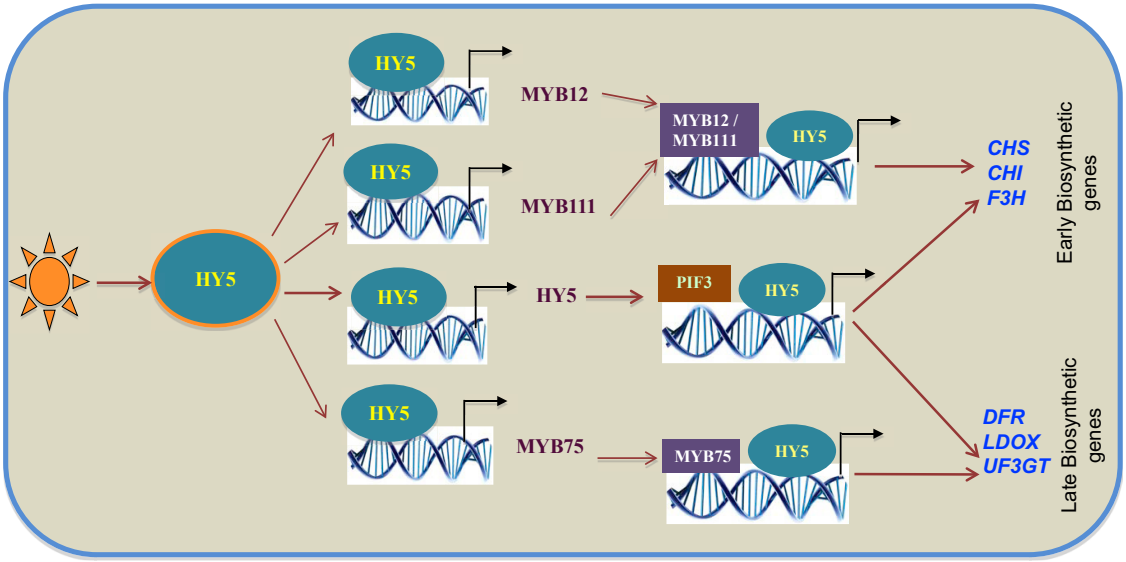

Figure 3. HY5 Promotes Anthocyanin Biosynthesis through Combinatorial Action of MYB and bHLH Transcription Factors.
Light-mediated activation of HY5 induces the expression of MYB transcription factors such as MYB12, MYB111, and MYB75. Further, HY5 in combination with MYB transcription factors bind to the promoter of anthocyanin biosynthetic genes in a sequence-specific manner and promote their expression. Similarly, HY5 in combination with PIF3 transcription factor binds to the promoters of anthocyanin biosynthetic genes independently in a sequence-specific manner and promotes their expression. MYB binds to MYB recognition element (MRE), HY5 binds to ACE-box, and PIF3 binds to G-box.

important factor that drives the rhythmic behavior of the clock. HY5 binds to the promoters of at least four central clock oscillator elements such as *TOC1*, *ELF4*, *CCA1*, and *LHY* to regulate their expression (Lee et al., 2007). Circadian clocks are mainly maintained by transcriptional feedback loops (Lim and Allada, 2013). In *Arabidopsis*, this involves two types of key clock oscillators such as *CCA1* and *LHY* at dawn and *TOC1* and *ELF4* at dusk (Andronis et al., 2008; Li et al., 2011a, 2011b). Whereas *CCA1* represses the expression of *ELF4*, HY5 directly binds to the promoter of *ELF4* through the ACE-box and promotes its expression (Li et al., 2011a, 2011b). Furthermore, physical interaction between HY5 and CCA1 abolishes *ELF4* activation suggesting the involvement of HY5 in the fine-tuning of *ELF4* expression and hence clock maintenance (Andronis et al., 2008; Li et al., 2011a, 2011b).

Pigment Accumulation

HY5 is the central transcription factor that promotes flavonoid accumulation by inducing the expression of flavonoid biosynthetic genes under both visible and UV-B light (Oyama et al., 1997; Holm et al., 2002; Shin et al., 2007; Song et al., 2008; Stracke et al., 2010). HY5 directly binds to either G-box or ACE-box of MYB transcription factors, such as *PRODUCTION OF FLAVONOL GLYCOSIDES (MYB12/PFG1* and *MYB111/PGF3*), *PRODUCTION OF ANTHOCYANIN PIGMENT1*, (*MYB75/PAP1*), and *MYB-like Domain* (*MYBD*) to promote their expression (Stracke et al., 2010; Shin et al., 2013; Nguyen et al., 2015). MYB12 and MYB111 further bind to the promoters of early flavonoids biosynthetic genes such as *CHS*, *CHALCONE ISOMERASE* (*CHI*), *FLAVANONE 3-HYDROXYLASE* (*F3H*), whereas MYB75 binds to the promoters of late flavonoids biosynthetic genes such as *DFR, LDOX*, and *UF3GT* (Dare et al., 2008; Stracke et al., 2010; Shin et al., 2013). In addition to MYB factors, HY5 has been shown to cooperatively function with PIF3 for the promotion of anthocyanin accumulation (Shin et al., 2007). PIF3 and HY5 co-regulate the expression of anthocyanin biosynthetic genes by binding to G-box and ACE-box elements, respectively, in their promoters (Shin et al., 2007). These results suggest that HY5 regulates anthocyanin biosynthesis in two steps; first, it directly binds and induces the expression of some MYB transcription factors genes, and second, together with other MYB factors, it induces the expression of biosynthetic enzymes genes in association with PIF3 activity (Figure 3).

Similarly, HY5 is the key factor required for the accumulation of chlorophyll and other photo-pigments such as carotenoids in a light-dependent manner (Toledo-Ortiz et al., 2014). HY5 regulates the expression of chlorophyll biosynthesis genes such as *PORC*, which converts protochlorophyllide to chlorophyllide, *GUN5*, which converts ChlH to Mg-chelatase; and components of the light-harvesting complex of the photosystem II, such as *LHCB1.3/CAB1*, *LHCB1.1/CAB2,* and *LHCA4/CAB4* (Lee et al., 2007; Toledo-Ortiz et al., 2014). Many of the constitutive photomorphogenic mutants such as *cop1* and *det1* produce green roots due to higher expression and protein accumulation of HY5 (Oyama et al., 1997). This observation suggests that greening of roots is also dependent on HY5. In fact, HY5 promotes the expression of *GOLDEN LIKE2* (*GLK2*) and both directly regulate the expression of genes involved in root greening by binding to *cis*-elements such as ACE (*CACGTG*) and *CCAATC*, respectively (Kobayashi et al., 2012). In addition, HY5 is involved in chloroplast biogenesis through the promotion of *DIGALACTOSYLDIACYLGLYCEROL SYNTHASE 1* (*DGD1*) for the biogenesis of thylakoids (Kobayashi et al., 2014; Afitlhile et al., 2015). Interestingly, *DGD1* expression is regulated by GLK1 and GLK2 transcription factors, which are

also involved in chlorophyll synthesis and chloroplast biogenesis (Kobayashi et al., 2014).

Shade Avoidance

Phytochromes, cryptochromes, and many downstream components involved in shade avoidance responses have been thoroughly discussed in a recent review (Casal, 2013). Recently, HY5 has been shown to be required for hypocotyl and petiole elongation under shade (Nozue et al., 2015). A genome-wide analysis in *Arabidopsis* seedlings exposed to short and prolonged shade demonstrated that *HY5* and *HYH* transcripts are late induced by low R/FR ratios (Ciolfi et al., 2013). Furthermore, kinetic analysis shows that upregulation of the *HYH* gene induced after 8 h of shade light depends on the action of HY5 through phyA signaling, and suggests that HY5 is essential for the adaptation of plants to long-term shade conditions (Ciolfi et al., 2013). HY5 together with HYH has been shown to terminate shade signaling in response to daily sunflecks, which are unfiltered light gaps that occur in the canopies (Sellaro et al., 2011). A gating experiment exposing *Arabidopsis* seedlings to sunflecks during the photoperiod showed that inhibition of hypocotyl growth is more efficient in the afternoon compared with the morning, a phytochrome-mediated response well correlated with the increase in HY5 abundance (Sellaro et al., 2011).

Terpenoid Biosynthesis

Light is known to regulate plant terpenoid metabolic pathways (Lichtenthaler, 1999; Rodríguez-Concepción et al., 2004). ChIP-chip experiments suggest that HY5 binds to a number of genes involved in the terpene biosynthetic pathway (Lee et al., 2007; Zhang et al., 2011a, 2011b). In fact, the promoters of two terpene synthases genes, *GERANYLGERANYL PYROPHOSPHATE SYNTHASE* (*ATSSU/GGPPS12*) and *2C-METHYL-D-ERYTHRITOL 2,4-CYCLODIPHOSPHATE SYNTHASE* (*MECPS*), contain HY5 binding sites. Moreover, a recent report reveals that HY5 regulates the expression of *QH6,* which encodes for a monoterpene β-pinene synthase in *Artemisia annua* L (Zhou et al., 2015). Indeed, yeast one-hybrid and electrophoretic mobility shift assays (EMSA) suggest that HY5 binds directly on the G-box (TGACACGTGGCA) of the *QH6* promoter gene. Interestingly, promoter-reporter transgenic analysis in wild-type and *hy5* mutant *Arabidopsis* plants suggests that HY5 controls the circadian regulation of *QH6* expression (Zhou et al., 2015).

Cold Acclimation

Cold temperature positively regulates the expression of HY5 both at the transcription and post-translation level (Catalá et al., 2011; Toledo-Ortiz et al., 2014). HY5 protein is stable at 4°C even in the dark as result of nuclear depletion of COP1 (Catalá et al., 2011). In addition, HY5 positively regulates the cold responses through activation of *Z*-box-containing genes such as *CAB1*; cold-responsive genes such as *RELATED TO AP2.1* (*RAP2.1*) and *LATE EMBRYOGENESIS ABUNDANT 18* (*LEA18*); and anthocyanin biosynthetic genes such as *CHI*, *CHS*, and *FLAVONOL SYNTHASE* (*FLS*) (Catalá et al., 2011). Moreover, HY5 promotes the expression of ROS-responsive genes such as *ASCORBATE PEROXIDASE2* (*APX2*), *SIGMA FACTOR BINDING PROTEIN1* (*SIB1*), and *ETHYLENE RESPONSIVE TRANSCRIPTION FACTOR4* (*ERF4*) during seedling de-etiolation (Table 1). Interestingly, HY5 negatively regulates ROS accumulation at low temperature to protect photosystems from the photoinhibition (Catalá et al., 2011). Accumulation of ROS was found to be higher in *hy5* mutant compared with wild-type when *Arabidopsis* seedlings were cultivated at 4°C, suggesting that HY5 is also required to suppress excessive ROS accumulation during plant acclimation to low temperature.

Plant Cell Death

Plant cell death is triggered at the end of the life cycle but also when plants are exposed to biotic and abiotic stresses. In fact, red light positively regulates ROS accumulation and cell death during seedling de-etiolation, a response mediated by HY5 (Gechev et al., 2006; Chen et al., 2013; Chai et al., 2015). HY5 also activates defense responses in red light by directly promoting the expression of *ENHANCED DISEASE SUSCEPTIBILITY 1* (*EDS1)* key activator. Interestingly, HY5 also binds to the promoters of many WRKY genes that encode for transcription factors involved in defense responses (Lee et al., 2007; Rushton et al., 2010), suggesting that HY5 could play a role in mediating light-dependent defense activation.

Nutrient Assimilation

Light is known to regulate several nutrient-signaling pathways associated with the increasing demand of metabolites such as nucleic acids, proteins, hormones, and fatty acids during plant growth. Nitrogen, phosphorus, sulfur, and copper are the most important essential nutrients regulated by light, and HY5 promotes these signaling pathways (Figure 4). HY5 along with HYH positively regulates the expression of two key genes of nitrogen signaling: *NITRATE REDUCTASE 2* (*NIA2*) encodes for nitrate reductase, which reduces nitrate to nitrite in the cytosol, and *NITRITE REDUCTASE 1* (*NIR1*) encodes for nitrite reductase, which converts nitrite to ammonium (Lillo, 2008; Jonassen et al., 2008; Yanagisawa, 2014; Huang et al., 2015). Contrary to *NIA2* and *NIR1,* HY5 negatively regulates the expression of nitrate uptake genes such as *NITRATE TRANSPORTER 1.1* (*NRT1.1*) and *AMMONIUM TRANSPORTER 1;2* (*AMT1;2*) (Jonassen et al., 2009a, 2009b; Yanagisawa, 2014; Huang et al., 2015). Very recently, it has been demonstrated that shoot-derived HY5 moves to the roots and activates its own expression to promote nitrate uptake through the activation of nitrate transporter *NRT2.1* gene expression, whereas in the shoot it promotes carbon assimilation and translocation (Chen et al., 2016). These novel results suggest that HY5 is involved in adjustment of the carbon-nitrogen balance in *Arabidopsis* plants exposed to fluctuating light conditions. In addition, HY5 regulates sulfate assimilation in a light-dependent manner by inducing the expression of two key enzymes *ADENOSINE 5′-PHOSPHOSULFATE REDUCTASE 1* (*APR1* and *APR2*) through directly binding to their promoters (Lee et al., 2011). Also, HY5 coordinates nitrogen and sulfur assimilation, as it has been observed that nitrogen starvation affects sulfate uptake and assimilation in wild-type but not in *hy5* mutants (Lee et al., 2011). Under limited nitrogen concentration, HY5 also regulates the expression of *SULFATE TRANSPORTER 1;2* (*SULTR1;2*) in a positive manner by directly binding to its promoter as revealed from ChIP analysis (Lee et al., 2011). Moreover, a recent study suggests that light and copper signaling are

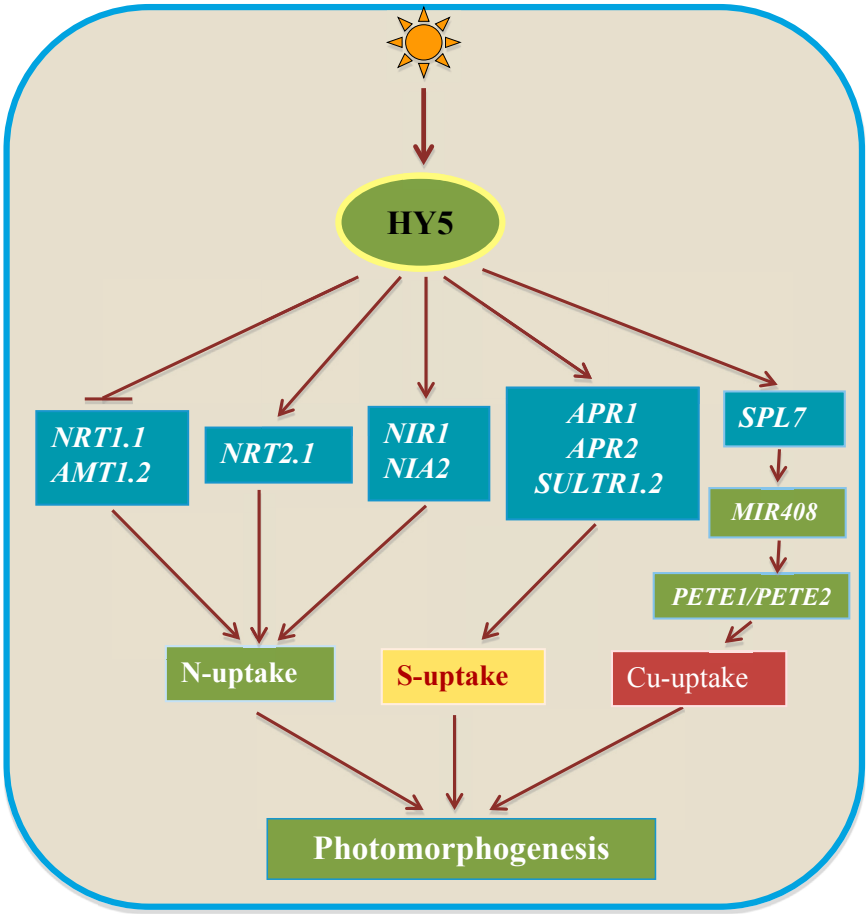

Figure 4. HY5 Promotes Photomorphogenesis through Regulation of Nutrient Signaling.

Light-mediated activation of HY5 leads to induction of genes involved in the uptake and/or transport of nitrogen, sulfur, and copper. However, HY5 inhibits the expression of *NRT1.1* and *AMT1.2* nitrate and ammonium transporters, respectively, suggesting that HY5 balances homeostasis of the nitrogen signaling pathway depending on plant-nitrogen requirements. HY5 promotes sulfur uptake by inducing the expression of two key enzymes, *APR1* and *APR2*. HY5 promotes sulfate transporter under low nitrogen conditions, suggesting that HY5 also coordinates nitrogen-sulfur assimilation. HY5 regulates copper signaling through SPL7. First, HY5 induces the expression of *SPL7* in a light-dependent manner, and then both HY5 and SPL7 induce the expression of *MIR408,* which is required to regulate the expression of *PETE1* and *PETE2* in the chloroplast.

connected through the action of HY5 and SQUAMOSA PROMOTER BINDING PROTEIN-LIKE 7 (SPL7). SPL7 and HY5 co-regulate many genes involved in photosynthesis and anthocyanin accumulation (Zhang et al., 2014). Also, SPL7 and HY5 promote the expression of *MIR408* by simultaneously binding to its promoter, which further increases the plastocyanin levels in the chloroplast by the regulation of two paralogous genes *PLASOCYANIN 1* (*PETE1*) and *PETE2* (Zhang et al., 2014).

HY5 FUNCTION IS CONSERVED IN PLANTS

HY5 functions are conserved across plant species. Several HY5 orthologs have been reported such as LONG1 from garden peas (*Pisum sativum*), LeHY5 from tomato, STF1 from soybean (*Glycine max*), *VfBZIPZF* from *Vicia faba*, and BZF/ASTRAY from *Lotus japonicus* (Cheong et al., 1998; Nishimura et al., 2002). LONG1 differs from HY5 by the presence of an extra N-terminal RING-type Zn-finger domain, which is similar to one present in cellulose synthase A subunit. LONG1 promotes photomorphogenesis in blue, red, and far-red light and inhibits GA biosynthesis in garden pea plants (Weller et al., 2009). LONG1 acts downstream of photoreceptors and LIP1, a COP1 ortholog of *Arabidopsis*, suggesting that light signaling mechanisms are conserved in *Arabidopsis* and pea species (Weller et al., 2009). Similarly, LeHY5 has also been shown to promote photomorphogenesis (Liu et al., 2004). Tomato plants with reduced expression of LeHY5 show defects in light responses such as longer hypocotyls, less accumulation of chlorophyll and carotenoids, and loss of thylakoid organization (Liu et al., 2004). Similar to *Arabidopsis*, tomato has also a COP1 ortholog, LeCOP1LIKE, which is a negative regulator of photomorphogenesis. LeCOP1LIKE-deficient transgenic lines exhibit short hypocotyls in light and dark and produce more carotenoids and chlorophyll (Liu et al., 2004). STF1, the HY5 ortholog in soybean, is functionally equivalent to HY5, as STF1 overexpression can fully complement *hy5* phenotype for hypocotyl length, root gravitropic response, and chlorophyll and anthocyanin content (Cheong et al., 1998; Song et al., 2008). In addition, STF1 and HY5 have been shown to have similar DNA binding properties as revealed from EMSA and random binding site selection assays (Song et al., 2008). Both HY5 and STF1 have strong binding affinity to ACGT-containing elements with a consensus sequence of 5′-(G/A)(G/A)TGACGT(C/G/A)(A/T/G)-3′. HY5 and STF1 bind to CG-box, CA-box, and CG hybrid-box with equal affinity, suggesting that they have similar functions and may regulate similar downstream genes (Song et al., 2008).

Similar to vascular plants, HY5 orthologs are also present in mosses such as *Physcometrella patens*, a basal species in the lineage of land plants. *P. patens* has two HY5 orthologs, *Pp*HY5a and *Pp*HY5b, and overexpression of *PpHY5aΔN* in *Arabidopsis* lead to a short hypocotyl phenotype (Yamawaki et al., 2011) in a similar manner to HY5ΔN in *Arabidopsis* (Ang et al., 1998), suggesting that they are functionally related with a conserved N terminus function. *Pp*HY5a and *Pp*HY5b are also involved in gametophyte development, as the *Pphy5a Pphy5b* double mutant is defective in this developmental program in light and dark conditions (Yamawaki et al., 2011). Collectively, these results suggest that HY5 functions are conserved from

ancestral plant lineages and plays a central in the adaptation of vascular land plants.

CONCLUSION AND FUTURE PERSPECTIVES

In addition to the role of HY5 in photomorphogenesis, the recent research findings discussed in this review suggest that HY5 functions goes beyond photomorphogenesis and seedling growth. The involvement of HY5 in nutrient signaling, abiotic (ABA, cold, ROS) and biotic stress responses indicate that HY5 has highly versatile functions. Furthermore, there is increasing evidence showing that HY5 promotes photomorphogenesis, integrating several hormone-signaling pathways. Although HY5 hormonal interaction signaling networks have been established to some extent, its connection with cytokinin is not clearly known except for the fact that cytokinin stabilizes HY5 protein. Therefore, future research addressing its interaction with key regulators of cytokinin signaling will shed light on the mechanism of HY5-cytokinin crosstalk for promoting photomorphogenesis. HY5 inhibits hypocotyl elongation in light and promotes plant growth, inducing nutrient uptake and/or the expression of key enzymes or proteins associated with nitrogen, sulfur, and copper signaling pathways, which are required for the overall growth of plants. Magnesium and manganese are also essential elements for photosynthesis, and it is probable that HY5 could be involved in these nutrients signaling pathways. Therefore, further efforts are required to have a complete understanding of HY5 functions on light-mediated plant growth. Finally, it is extremely important to extend the knowledge of HY5 acquired using the *Arabidopsis* model plant to crops. Better comprehension of HY5 functions and signaling in other species could be highly useful in improving agronomic traits such as nitrogen use efficiency and manipulation of root traits to produce high-quality crops.

FUNDING

J.F.B. thanks Prestamo (grant nos. BID PICT2013-0172 and PICT2014-1074) for funding.

ACKNOWLEDGMENTS

We thank anonymous reviewers for useful suggestions. We apologize to our colleagues whose work could not be cited due to space constraints. S.N.G. acknowledges the Carl Triggers Foundation for a postdoctoral fellowship. No conflict of interest declared.

Received: June 27, 2016
Revised: June 27, 2016
Accepted: July 8, 2016
Published: July 16, 2016

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