

# The Photomorphogenic Central Repressor COP1: Conservation and Functional Diversification during Evolution

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## ABSTRACT

Green plants on the earth have evolved intricate mechanisms to acclimatize to and utilize sunlight. In *Arabidopsis*, light signals are perceived by photoreceptors and transmitted through divergent but overlapping signaling networks to modulate plant photomorphogenic development. COP1 (CONSTITUTIVE PHOTOMORPHOGENIC 1) was first cloned as a central repressor of photomorphogenesis in higher plants and has been extensively studied for over 30 years. It acts as a RING E3 ubiquitin ligase downstream of multiple photoreceptors to target key light-signaling regulators for degradation, primarily as part of large protein complexes. The mammalian counterpart of COP1 is a pluripotent regulator of tumorigenesis and metabolism. A great deal of information on COP1 has been derived from whole-genome sequencing and functional studies in lower green plants, which enables us to illustrate its evolutionary history. Here, we review the current understanding about COP1, with a focus on the conservation and functional diversification of COP1 and its signaling partners in different taxonomic clades.

**Key words:** COP1, E3 ubiquitin ligase, photomorphogenesis, gravitropism, light protection, evolution

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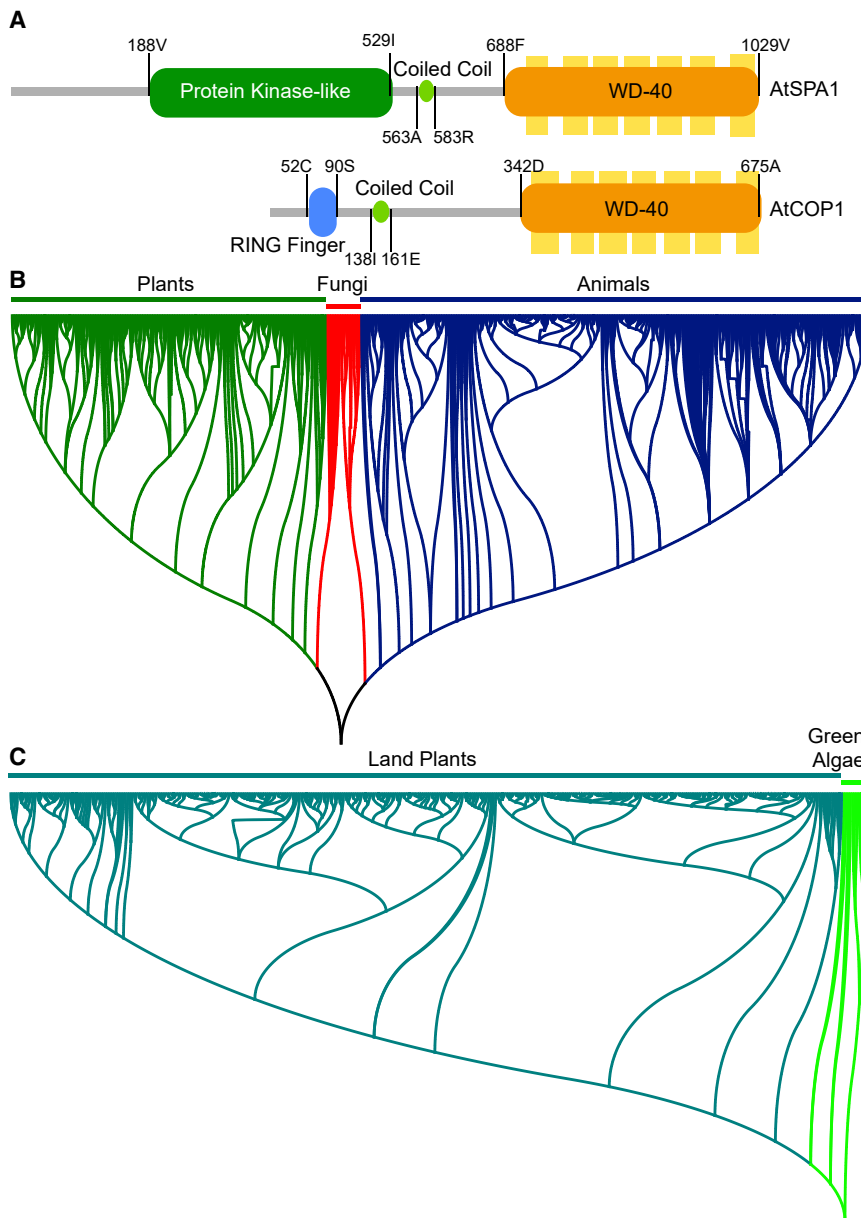
## INTRODUCTION

Light is one of the most important environmental factors for photosynthetic plants, not only as an energy source but also as an informational signal to modulate various developmental processes (McNellis and Deng, 1995; Wei and Deng, 1996). In *Arabidopsis*, light modulates plant growth and development throughout the whole life cycle, which is most dramatically illustrated by seedling morphogenesis (Kendrick and Kronenberg, 1994; von Arnim and Deng, 1996; Jiao et al., 2007). The developmental pattern in light conditions, termed photomorphogenesis, allows seedling morphology to be optimally developed for photosynthesis (von Arnim and Deng, 1996). A class of *Arabidopsis* mutants, *cop/det/fus* (constitutive photomorphogenic/de-etiolated/fusca), was initially identified in genetic screens as displaying constitutively photomorphogenic phenotypes in darkness (Schwechheimer and Deng, 2000; Lau and Deng, 2012). Among a total of nine COP1/DET/FUS loci characterized later (Chory et al., 1989; Deng et al., 1991; Wei and Deng, 1992; Miséra et al., 1994; Wei et al., 1994; Kwok et al., 1996), COP1 is the most extensively studied repressor of

plant photomorphogenesis (Ma et al., 2002; Yi and Deng, 2005; Lau and Deng, 2012). Loss-of-function mutations of COP1 result in photomorphogenic phenotypes in darkness, and null *cop1* alleles also cause lethality after the seedling phase (McNellis et al., 1994; Stoop-Myer et al., 1999).

Accumulated evidence has indicated that COP1 functions at the heart of light-signaling networks; it is capable of integrating signals from various photoreceptors and regulating a batch of downstream factors to mediate light responses (Lau and Deng, 2012; Podolec and Ulm, 2018). COP1 is regarded as a central switch of global light-responsive gene expression in *Arabidopsis* (Ma et al., 2002), exerting its effect through destabilizing HY5 (ELONGATED HYCOTYL 5) and other transcriptional regulators critical for photomorphogenesis in darkness (Osterlund et al., 2000a; Wang et al., 2016).

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**Figure 1. The Protein Domains and Phylogenetic Analyses of COP1 and SPAs.**

**(A)** Schematic diagrams showing functional domains of *Arabidopsis* SPA1 and COP1. Conserved domains are shown in the same shapes and colors. Numbers indicate the positions of amino acids.

**(B)** The phylogenetic relationships of COP1 orthologs. Using AtCOP1 as query, all significantly similar proteins in HMMER reference proteomes containing the COP1 structural domains shown in **(A)** were identified as COP1 orthologs. The maximum-likelihood tree was constructed following our previous study (Han et al., 2019). COP1 exists widely in eukaryotic clades, and only in eukaryotes.

**(C)** The phylogenetic relationships of SPA1 orthologs. Candidate SPA1 orthologs were identified as described above. SPA1 orthologs found in HMMER reference proteomes were combined with those previously identified in representative plant genomes (Han et al., 2019). SPA1 orthologs are only present in green plant lineages.

distinct biological contexts in plants and animals, COP1 is proposed to be functionally conserved according to the energy supply transition hypothesis: COP1 takes part in regulating the dark-to-light transition in plants and the feeding-to-fasting transition in mammals (Sanchez-Barcelo et al., 2016). The functional conservation and divergence implies an intriguing evolutionary history of COP1 in plants and animals.

In this review, we summarize the studies on COP1 during the past 30 years and highlight the latest discoveries. Accumulating evidence from parallel comparison of COP1 roles in *Arabidopsis*, early-originating plants, and mammals, will help extend our understanding of the evolutionary conser-

vation and functional diversification of the COP1-containing regulatory apparatus.

## COP1 IS A CONSERVED E3 UBIQUITIN LIGASE IN EUKARYOTES

E3 ubiquitin ligases containing the RING domain represent the largest E3 family and interact with both protein substrates and E2 ubiquitin-conjugating enzymes (Zheng et al., 2000). COP1 protein contains three functional domains required for its activity: an N-terminal RING-finger domain, a middle coiled-coil domain, and a C-terminal WD40 domain (Figure 1A; Deng and Quail, 1992; Deng et al., 1992; Stoop-Myer et al., 1999; Holm et al., 2001). COP1 was first identified as an E3 ligase of the downstream photomorphogenesis-promoting transcription factor HY5; COP1 was found to directly interact with HY5 via its WD40 domain and degrade HY5 in darkness through the ubiquitin-proteasome

COP1 is well conserved in plants and animals, and its orthologs share high similarities in their cellular properties, biochemical activities, and predicted molecular structures (Deng et al., 1992; Chamovitz and Deng, 1995; Osterlund et al., 2000a; Yi et al., 2002; Marine, 2012; Sanchez-Barcelo et al., 2016). Besides the studies on *Arabidopsis* photomorphogenesis, recent reports have revealed the crucial roles of COP1 in different plant systems and developmental processes, such as photoprotection in algae (Schierenbeck et al., 2015; Tilbrook et al., 2016; Gabilly et al., 2019; Tokutsu et al., 2019), and gravitropism in mosses (Artz et al., 2019). In addition to plant development, COP1 also plays a role in mammalian metabolism (Sanchez-Barcelo et al., 2016; Ren et al., 2019a), tumorigenesis (Dornan et al., 2004; Wertz et al., 2004; Yi and Deng, 2005; Marine, 2012; Choi and Lee, 2015), and neuron development (Newton et al., 2018). Although it functions in

system (Ang and Deng, 1994; Ang et al., 1998; Osterlund et al., 2000a, 2000b). Later a batch of light-signaling factors were identified as COP1's targets, including HYH (HY5-HOMOLOG) (Holm et al., 2002), LAF1 (LONG AFTER FAR-RED LIGHT 1) (Seo et al., 2003), HFR1 (LONG HYPOCOTYL IN FAR-RED 1) (Kim et al., 2002; Jang et al., 2005; Yang et al., 2005), PHYA (PHYTOCHROME A) (Seo et al., 2004), PHYB (PHYTOCHROME B) (Jang et al., 2010), and a series of BBX (B-BOX) proteins (Xu et al., 2016; Lin et al., 2018). The ubiquitination activity of COP1 can be detected toward both its target proteins and itself *in vitro* (Saijo et al., 2003; Seo et al., 2003). Light conditions and COP1-interacting proteins affect its E3 ligase activity *in vivo* (Saijo et al., 2003; Yi and Deng, 2005; Lau and Deng, 2012). Notably, the activity of COP1 was reported to be regulated by several post-translational mechanisms. In darkness, SUMO (small ubiquitin-like modifier) modification of COP1 enhances its *trans*-ubiquitination activity, which causes increased degradation of COP1 targets (Lin et al., 2016). In addition, a Ser/Thr kinase, PID (PINOID), directly interacts with COP1 and phosphorylates it to repress its activity in *Arabidopsis* (Lin et al., 2017).

*Arabidopsis* seedlings carrying *cop1*-weak alleles exhibit strong photomorphogenic developmental patterns even in complete darkness, with typical short hypocotyls as well as open and expanded cotyledons (Deng and Quail, 1992; McNellis et al., 1994). The nuclear accumulation of COP1 can be drastically reduced by extended light exposure (von Arnim and Deng, 1994), but restored under shade (Pacin et al., 2013). Photoactivated photoreceptors interact with the WD40 domain of COP1 via their VP domains, sequestering COP1 from its interacting substrate proteins, so as to repress COP1 E3 activity and direct photomorphogenic development (Osterlund et al., 2000a, 2000b; Lau and Deng, 2012; Lau et al., 2019; Ponnu et al., 2019).

COP1 is also a hotspot of investigation in mammals because of its multi-faceted roles in mammalian development, metabolism, and tumorigenesis (Liu et al., 2008; Marine, 2012; Sanchez-Barcelo et al., 2016). It has E3 ligase activity toward various substrate proteins, including the oncoprotein c-Jun (Bianchi et al., 2003; Yi et al., 2005) and tumor suppressor p53 (Dornan et al., 2004; Koeppen and Dixit, 2004). Although it is ubiquitously expressed and harbors three conserved domains like *Arabidopsis* COP1, mammalian COP1 failed to rescue the defects of *Arabidopsis cop1* mutants (Bianchi et al., 2003; Marine, 2012). However, similarly with *Arabidopsis* COP1, the localization of mammalian COP1 could be regulated by light when expressed in plant cells (Wang et al., 1999). In addition, human COP1 possesses intrinsic E3 ligase activity in its RING domain together with the coiled-coil domain *in vitro* (Dornan et al., 2004), and targets tumorigenic factors for degradation *in vivo* (Bianchi et al., 2003; Migliorini et al., 2011; Vitari et al., 2011). Human COP1 basically localizes in the nuclear envelope, and extracellular cues rapidly induce its nucleoplasm localization (Ouyang et al., 2020). Human COP1 also undergoes nuclear export. This process, correlated with its stability, is controlled by a DNA-damage stimulus and a regulatory chaperone, 14-3-3 $\sigma$  (Dornan et al., 2006; Su et al., 2010).

COP1 orthologs exist extensively in eukaryotes in addition to those studied previously, (Figure 1B). Although fungal COP1

orthologs have not been reported to function in physiological and developmental regulation, they may potentially play key roles relying on the three conserved functional domains. No candidate COP1 ortholog was found in the HMMER reference proteomes of eubacteria, archaea, or viruses. Therefore, COP1 likely originated in the common ancestor of all eukaryotic organisms.

## COP1 IS A CORE SUBUNIT OF SEVERAL PROTEIN COMPLEXES

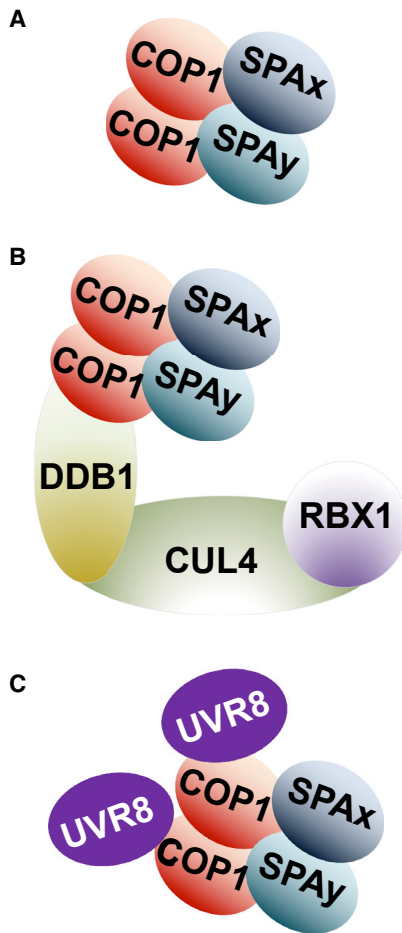
### COP1/SPA Complexes

Size-fractionation analyses in higher plants have indicated that COP1 is a part of a ~700-kDa multimeric protein complex in dark-grown *Arabidopsis* seedlings (Saijo et al., 2003). SPA1 (SUPPRESSOR OF PHYA-105 1) was the first biochemically identified new component of the COP1 complex (Saijo et al., 2003, 2008; Zhu et al., 2008), and contains an N-terminal kinase-like domain, a middle coiled-coil domain, and C-terminal WD40 repeats (Figure 1A), with the latter two domains being highly similar to those of COP1 (Hoecker et al., 1999; Laubinger et al., 2004). SPA1 is a nucleus-localized repressor of phyA signaling (Hoecker et al., 1999) and physically interacts with COP1 and HY5 to mediate HY5 degradation (Saijo et al., 2003). SPA1 belongs to an *Arabidopsis* gene family of consisting of four members that function redundantly in photomorphogenesis (Laubinger et al., 2004; Fittinghoff et al., 2006). These members associate tightly with COP1 to form hetero-tetrameric complexes (Figure 2A) (Saijo et al., 2008; Zhu et al., 2008), and probably act as regulatory subunits of large COP1/SPA complexes in multiple light-signaling events (Lau and Deng, 2012; Hoecker, 2017; Podolec and Ulm, 2018). Besides the dark-induced degradation of HY5, SPAs are also necessary for the light-induced phosphorylation, ubiquitination, and degradation of PIF1 (Saijo et al., 2003; Zhu et al., 2008, 2015; Paik et al., 2019). To modulate the E3 ligase activity of COP1, SPAs not only interact with COP1-interacting photoreceptors (Lian et al., 2011; Liu et al., 2011; Zuo et al., 2011; Lu et al., 2015; Sheerin et al., 2015) but also regulate the subcellular localization of COP1 (Balcerowicz et al., 2017). The stability of SPA2 itself is rapidly downregulated by light exposure in a phytochrome-dependent fashion (Balcerowicz et al., 2011; Chen et al., 2015).

Unlike COP/DET/FUS proteins, SPA proteins are only found in green algae and land plants (Han et al., 2019, Figure 1C). Therefore, COP1/SPA protein complexes are specific to the green plant lineage. As mammalian COP1 also exists in a large protein complex of ~700 kDa (Yi et al., 2002), the molecular mechanism for multimerization is possibly conserved and dependent on COP1-interacting, SPA-like, but mammalian-lineage-specific proteins. Since COP1 and the SPAs have conserved coiled-coil and WD40 domains (Figure 1A), formation of a core COP1 tetramer in mammals is also a possibility.

### CUL4-Based COP1 Complexes

CUL4 (CULLIN4) is a well-conserved scaffold protein in multimeric CULLIN-based E3 ligases (Jackson and Xiong, 2009). Through an adaptor protein, DDB1 (DNA DAMAGE BINDING PROTEIN 1), CUL4 recruits DWD (DDB1 BINDING WD40)



**Figure 2. Three COP1/SPA-Containing Complexes Are Involved in Light Regulation of Plant Development.**

- (A) COP1/SPA core tetramer complex.  
 (B) CUL4-DDB1-COP1/SPA ubiquitin ligase complex.  
 (C) UVR8-COP1/SPA complex.

proteins, which serve as substrate receptors, to form multimeric E3 ligases regulating diverse biological processes in plants and animals (Lee and Zhou, 2007). In *Arabidopsis*, CUL4 negatively regulates photomorphogenesis and flowering by biochemically linking three COP/DET/FUS complexes: COP1/SPA complexes, CSN (COP9 signalosome), and the CDD (COP10, DDB1, and DET1) complex (Yanagawa et al., 2004; Chen et al., 2006, 2010; Zhu et al., 2008). Distinct from human COP1, which associates with CUL4-DDB1 by interacting with DET1 (Wertz et al., 2004), *Arabidopsis* COP1 and SPA proteins are all DWD proteins that directly associate with CUL4-DDB1 independently of DET1 (Figure 2B; Chen et al., 2010). Consequently, CUL4-DDB1-COP1/SPA works in concert with CUL4-CDD to destabilize HY5 and repress photomorphogenesis in darkness (Figure 2B; Yanagawa et al., 2004; Chen et al., 2006, 2010; Huang et al., 2014). One way to attenuate CUL4-DDB1-COP1/SPA E3 ligase activity is to degrade its cofactor PIF1 in response to light (Zhu et al., 2015).

### UVR8-COP1/SPA Complexes

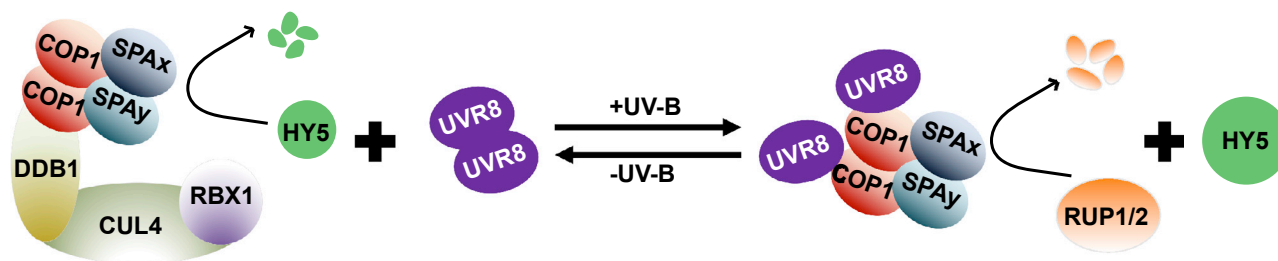
Unlike its repressive role under visible light, COP1 positively regulates UV-B light signaling that is initiated by the UV-B photore-

ceptor UVR8 (UV RESISTANCE LOCUS 8) (Figure 3). In a rapid response to UV-B light, UVR8 is photoactivated and monomerized, allowing COP1 to recruit it into COP1/SPA complexes via direct interaction Wu et al., 2012 (Favory et al., 2009; Heijde and Ulm, 2013; Huang et al., 2013). It is worth noting that the interaction between COP1 and UVR8 relies on the flexible C-terminal WD40 domain of COP1 and the VP motif of UVR8 (Figure 2C; Rizzini et al., 2011; Cloix et al., 2012; Yin et al., 2015; Lau et al., 2019). Such an interaction mode is generally employed by COP1-targeted photoreceptors and transcription factors in order to compete for the binding domain and modulate the E3 ligase activity of COP1 (Lau et al., 2019; Ponnu et al., 2019). In addition, the assembly of the UV-B-specific UVR8-COP1/SPA complexes leads to a reduced amount of CUL4-DDB1-COP1/SPA complexes *in vivo* (Huang et al., 2013) and a switch of the substrate receptor for HY5 degradation from COP1/SPA to RUP1/2 (REPRESSOR OF UV-B PHOTOMORPHOGENESIS 1/2), which is the substrate-recognizing module in another CUL4-DDB1 E3 ligase (Ren et al., 2019b). Furthermore, the positive role of COP1 in UVR8 signaling is closely tied to its role in the polyubiquitination and degradation of RUP1/2 (Ren et al., 2019b). Therefore, the disruption of these two E3 ligases (CUL4-DDB1-COP1/SPA and CUL4-DDB1-RUP1/2) that target HY5 protects HY5 from degradation and allows it to accumulate and mediate downstream UV-B-responsive gene expression (Ren et al., 2019b; Jin and Zhu, 2019). Besides RUP1/2, UVR8 and COP1 also destabilize PIF4/5, which leads to UV-B-induced inhibition of hypocotyl elongation (Sharma et al., 2019).

## COP1 PLAYS EVOLUTIONARILY CONSERVED AND DIVERGENT ROLES IN PLANTS

### COP1: A Central Repressor of Photomorphogenesis in *Arabidopsis*

In the past 30 years, tremendous progress has been achieved in the characterization of hierarchical regulatory networks in *Arabidopsis* photomorphogenesis (Figure 4). Readers are encouraged to consult these specific reviews for detailed information (Yi and Deng, 2005; Jiao et al., 2007; Lau and Deng, 2012; Huang et al., 2014; Pan and Shi, 2017). Photoreceptors responsible for light perception are categorized into three groups according to the light wavelengths they detect. Far-red and red light is perceived by phytochromes (PHYs) (Bae and Choi, 2008). Blue and UV-A light is perceived by cryptochromes (CRYs), phototropins (PHOTs), and Zeitlupes (ZTLs) (Lin and Shalitin, 2003; Christie, 2007; Suetsugu and Wada, 2013). UV-B light is perceived by UVR8 (Rizzini et al., 2011). Light modulates the protein conformation, subcellular localization, and molecular activity of photoreceptors. Downstream of activated photoreceptors a series of regulatory factors, which usually function in the form of multimeric protein complexes, mediate light signal transduction (Chen et al., 2010; Huang et al., 2013; Paik et al., 2019; Ren et al., 2019b). COP/DET/FUS proteins have been widely recognized as the central repressors of photomorphogenesis networks, functioning in the form of E3 ligase complexes, such as COP1/SPA complexes and their regulators (Lau and Deng, 2012). The key transcription factors that are targeted by central repressor complexes directly control the transcription of light-responsive genes.



**Figure 3. A Model Depicting the Conversion between Two Distinct COP1/SPA-Containing Complexes in the Presence or Absence of UV-B Light.**

Without UV-B irradiation, the CUL4–DDB1–COP1/SPA complex is the primary functional COP1/SPA core tetramer, and targets HY5 and other promoters of light signaling for degradation to repress photomorphogenic or photoprotective gene expression. RUP1 and RUP2 function redundantly to mediate UVR8 redimerization and halt UVR8 signaling (Heijde and Ulm, 2013). Upon UV-B irradiation, UVR8 monomerizes and associates with the COP1/SPA core tetramer complex to form a new complex. The E3 ligase responsible for HY5 degradation switches from CUL4–DDB1–COP1/SPA to CUL4–DDB1–RUP1/2. COP1, possibly in the UVR8–COP1/SPA complex, targets RUP1/2 for proteolysis and thus stabilizes HY5.

In darkness, photoreceptors are inactive (Heijde and Ulm, 2012; Ahmad, 2016; Pham et al., 2018a), and COP1 is largely present in the nucleus as part of COP1/SPA E3 ligase complexes (von Arnim and Deng, 1994; Zhu et al., 2008). COP1/SPA complexes are most likely to form larger E3 complexes with the CUL4 scaffold via the DDB1 adaptor (Chen et al., 2010). These COP1-containing complexes, in concert with other E3 complexes (Saijo et al., 2008; Zhu et al., 2008; Chen et al., 2010), target photomorphogenesis-promoting transcription factors such as HY5/HYH (Holm et al., 2002; Saijo et al., 2003) and LAF1 (Seo et al., 2003) for ubiquitination and degradation through the 26S-proteasome pathway (Lau and Deng, 2012). On the other hand, COP1 positively regulates photomorphogenesis-repressing transcription factors, PIFs (PHYTOCHROME-INTERACTING FACTORS) (Bauer et al., 2004; Ling et al., 2017; Pham et al., 2018b), and EIN3/EIL (ETHYLENE-INSENSITIVE3/EIN3-LIKE 1) (Shi et al., 2016) to maintain skotomorphogenesis (Pan and Shi, 2017). COP1 stabilizes PIFs and EIN3/EIL by targeting CUL1–EBF1/2, the E3 ligases for PIFs and EIN3/EIL, for ubiquitination and degradation (Shi et al., 2016; Dong et al., 2017). PHYs and CRYs are the primary receptors sensing visible light. Photoactivation of these photoreceptors impairs the assembly and activity of CUL4–COP1/SPA complexes (Hoecker, 2017; Podolec and Ulm, 2018). Release of its substrates from COP1 alters the expression levels of light-responsive genes (Lee et al., 2007; Paik et al., 2019). In negative feedback regulation, CUL4–DDB1–COP1/SPA complexes target photoreceptors including PHYs and CRYs for 26S-proteasome-mediated degradation (Seo et al., 2004; Weidler et al., 2012; Debrieux et al., 2013). Therefore, COP/DET/FUS proteins, which act like a brake, antagonize the photoreceptors in the photomorphogenesis regulatory network, which act like the gas pedal (accelerator). The COP/DET/FUS proteins and photoreceptors thus coordinate to precisely control downstream signaling regulators and events (Figure 4).

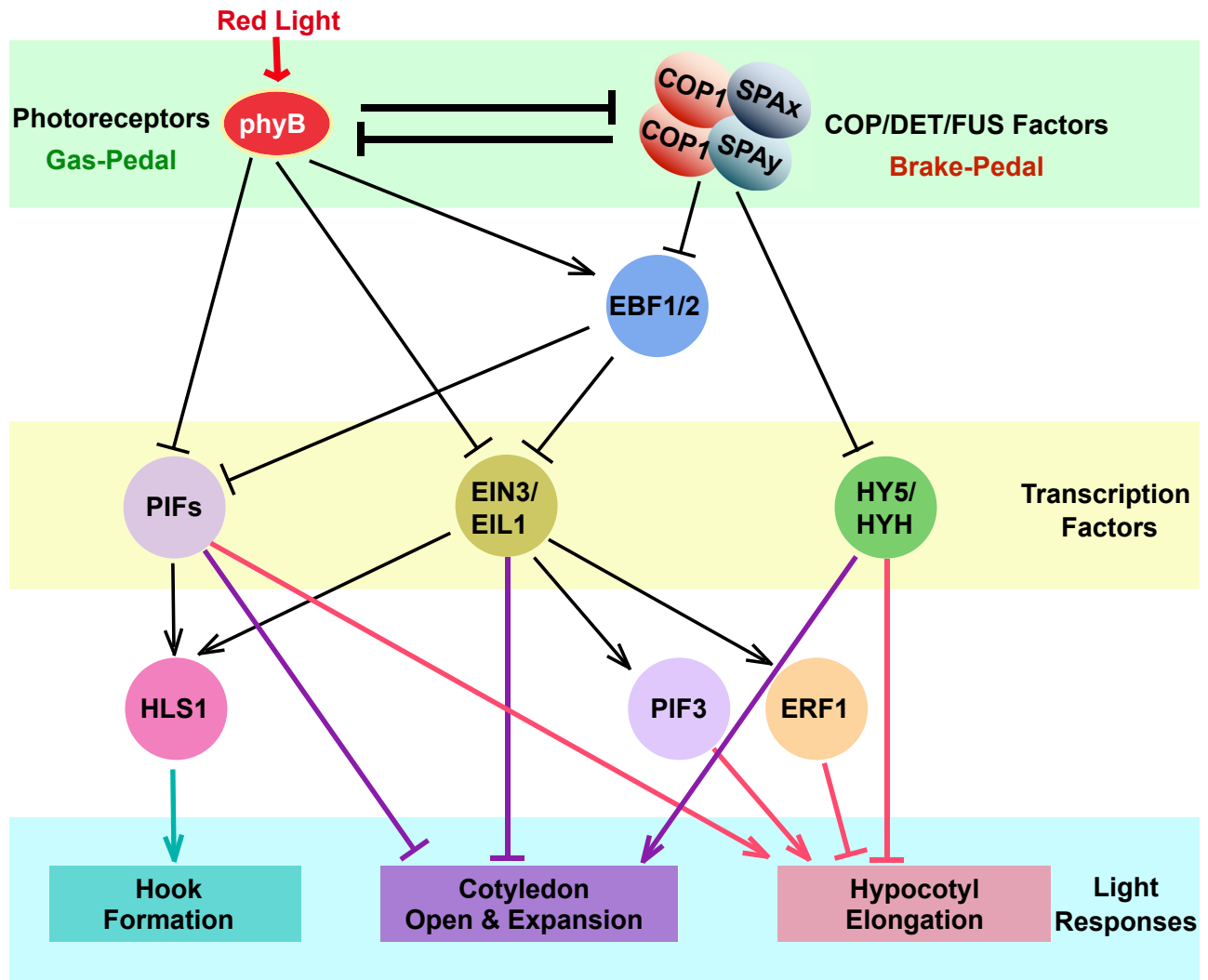
Notably, although initiated by specific photoreceptors, multiple light-signaling pathways converge at COP1 and directly modulate COP1 activity on specific targets (Lau and Deng, 2012; Podolec and Ulm, 2018). COP1 interacts with both photoreceptors and its target transcription factors via its WD40 repeats. The components of such photoreceptor–COP1–target modules seem to have co-evolved to preserve their tripartite interaction pattern during plant terrestrialization (Lau et al., 2019; Wang and Lin, 2019).

### Role of COP1 in Seedling Emergence from Soil in *Arabidopsis*

A COP1-containing apparatus is employed in *Arabidopsis* while seedlings effectively penetrate upward through soil. In nature, a germinating seed buried under the soil has to deal with two issues before it reaches the light: the distance from the soil surface and mechanical pressure by the covering soil. The mechanical pressure leads to the production of ethylene while the reduction of distance to soil surface is measured by a slight increase of dim light, which downregulates COP1 activity (Figure 5). Recent studies have revealed that COP1 directly targets EBF1/2 (EIN3-BINDING F-BOX protein 1/2) for ubiquitination and degradation through its E3 activity, while EBF1/2 degrades the central transcription factors EIN3/EIL1 (EIN3-LIKE 1) and PIFs in darkness (Shi et al., 2016; Dong et al., 2017). It is therefore thought that the light-signaling repressor COP1 is also involved in measuring the distance from a germinating seedling to soil surface and coordinates with the mechanical pressure-triggered ethylene signaling cascade to optimally allow seedlings to emerge from soil (Figure 5). So far, three families of transcription factors, HY5, EIN3/EIL, and PIFs, have been reported to play key roles in seedling emergence, all of which are regulated by COP1 (Shi et al., 2018). Upon seed germination in soil (Figure 5A), under mechanical pressure, which triggers an ethylene response, and darkness, HY5 is degraded by the nuclear COP1 apparatus, whereas PIFs and EIN3/EIL1, the negative regulators of photomorphogenesis, are relatively stable and promote skotomorphogenesis. During the course of hypocotyl elongation, the increasing amount of dim light that penetrates through soil pores negatively modulates COP1 activity and indirectly modulates EIN3/EIL activities (Figure 5B). When seedlings finally break out of the soil, COP1 is inactivated by light, and EIN3/EIL and PIFs are targeted by accumulated EBF1/2 for degradation, which switches the developmental pattern from skotomorphogenesis to photomorphogenesis (Figure 5C).

### COP1 Regulates Gravitropism in *Physcomitrella*

Nine COP1 orthologs and two SPA orthologs have been found in the moss *Physcomitrella patens*. *PpCOP1* partially rescued the defects of the *Arabidopsis cop1* null mutant, indicating a conserved function of COP1 in land plants (Ranjan et al., 2014). However, *PpSPAb* failed to rescue the *Arabidopsis spa* triple



**Figure 4. A Simplified Network Antagonistically Regulated by phyB and the COP1/SPA Complex during Photomorphogenesis in Arabidopsis.**

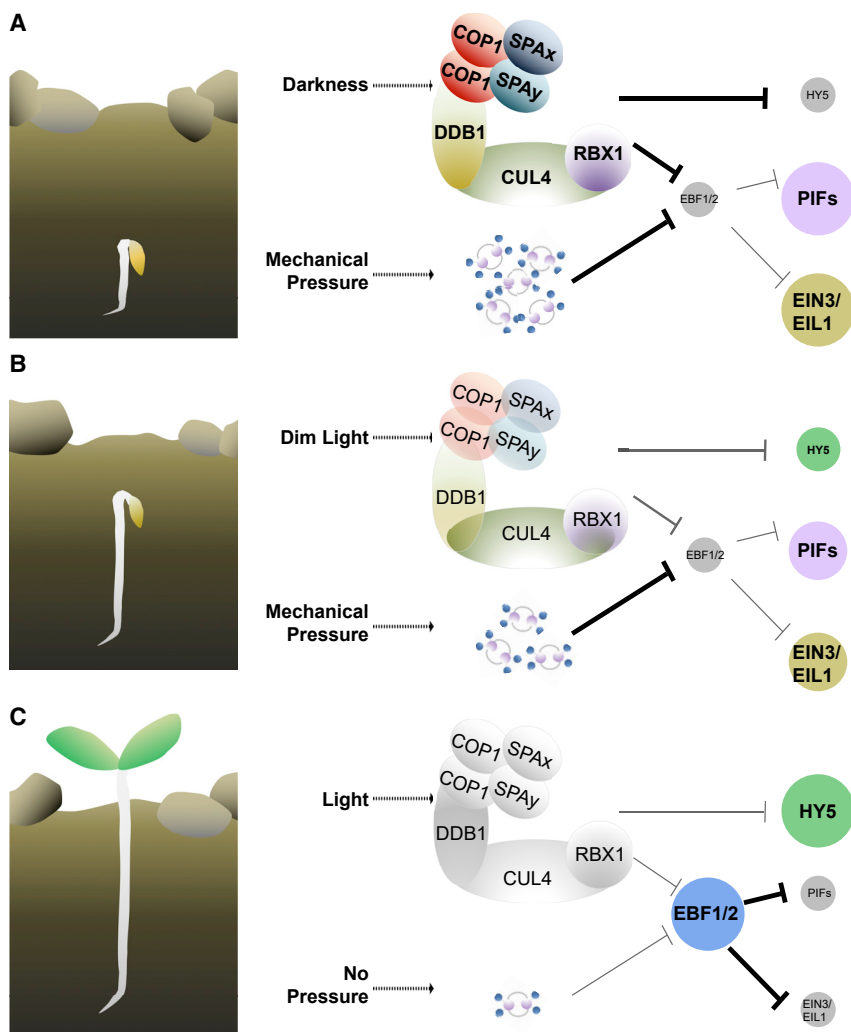
Photoreceptors perceive environmental light signals to promote light responses, while COP/DET/FUS proteins function as central repressors to inhibit light responses. Under red light conditions, activated phyB inhibits the activity of the photomorphogenesis-repressing transcription factors PIFs (1–3), and EIN3/EIL (Shi et al., 2016). On the contrary, the COP1/SPA complex stabilizes these transcription factors by targeting their E3 ligase EBF1/2 for degradation (1,2), and meanwhile destabilizes photomorphogenesis-promoting transcription factor HY5/HYH (1–5) to maintain skotomorphogenesis in darkness. PIFs and EIN3/EIL1 act in parallel to activate *HLS1* expression to promote the formation of the apical hook (1,2). These two groups of transcription factors cooperatively repress cotyledon development but promote hypocotyl elongation (1–3). In contrast, HY5/HYH promote cotyledon expansion but inhibit hypocotyl elongation by regulating the expression of light-responsive genes.

mutant, implying the functional divergence of SPA genes during the evolution of land plants (Ranjan et al., 2014). Dark-cultivated moss grows in an opposite direction to gravity, presumably to break through the soil and get back under light as soon as possible (Sack et al., 2001). This reversed gravitropic response in moss is regarded as a physiological response comparable with skotomorphogenesis in *Arabidopsis*. PpCOP1 is required for this process and physically interacts with PpHY5 and PpSPA (Yamawaki et al., 2011; Artz et al., 2019; Kreiss et al., 2019). *PpspaAB* double mutants exhibited reduced gametophore gravitropism but normal etiolation in darkness (Ranjan et al., 2014; Artz et al., 2019). Light-responsive gene expression in these mutants is mostly not constitutive, further supporting functional divergence of moss

and *Arabidopsis* SPA genes (Artz et al., 2019). Therefore, it is reasonable to speculate that COP1 was more functionally conserved than SPA during the evolution of plants.

**COP1 Is Involved in Photoprotective Responses in *Chlamydomonas***

To minimize the damage from high light irradiation, photosynthetic organisms have evolved a protection mechanism termed non-photochemical quenching (Niyogi and Truong, 2013). In the green alga *Chlamydomonas reinhardtii* grown under high light conditions, *LHCSR* (*LIGHT-HARVESTING COMPLEX STRESS RELATED PROTEIN*) genes are activated to mediate energy-dependent quenching (Peers et al., 2009). The newly evolved



**Figure 5. The Seedling Emergence Signaling Networks Regulated by Light and Mechanical Pressure.**

(A) Upon germination deep in the soil, the seedlings covered by soil face two stress stimuli: darkness and mechanical pressure. The active COP1/SPA complexes promote skotomorphogenesis by regulating three transcription factors (HY5, PIFs, and EIN3). In addition, mechanical impedance boosts endogenous ethylene accumulation, which induces crosstalk between ethylene and light signals.

(B) During the course of hypocotyl elongation under soil, dim light penetrates into soil and reduces the activity of COP1/SPA complexes. However, ethylene responses remain highly variable depending on soil conditions.

(C) After breaking out of the soil, seedlings free from mechanical pressure and under sunlight switch to photomorphogenic development. The activity of COP1/SPA complexes is completely repressed.

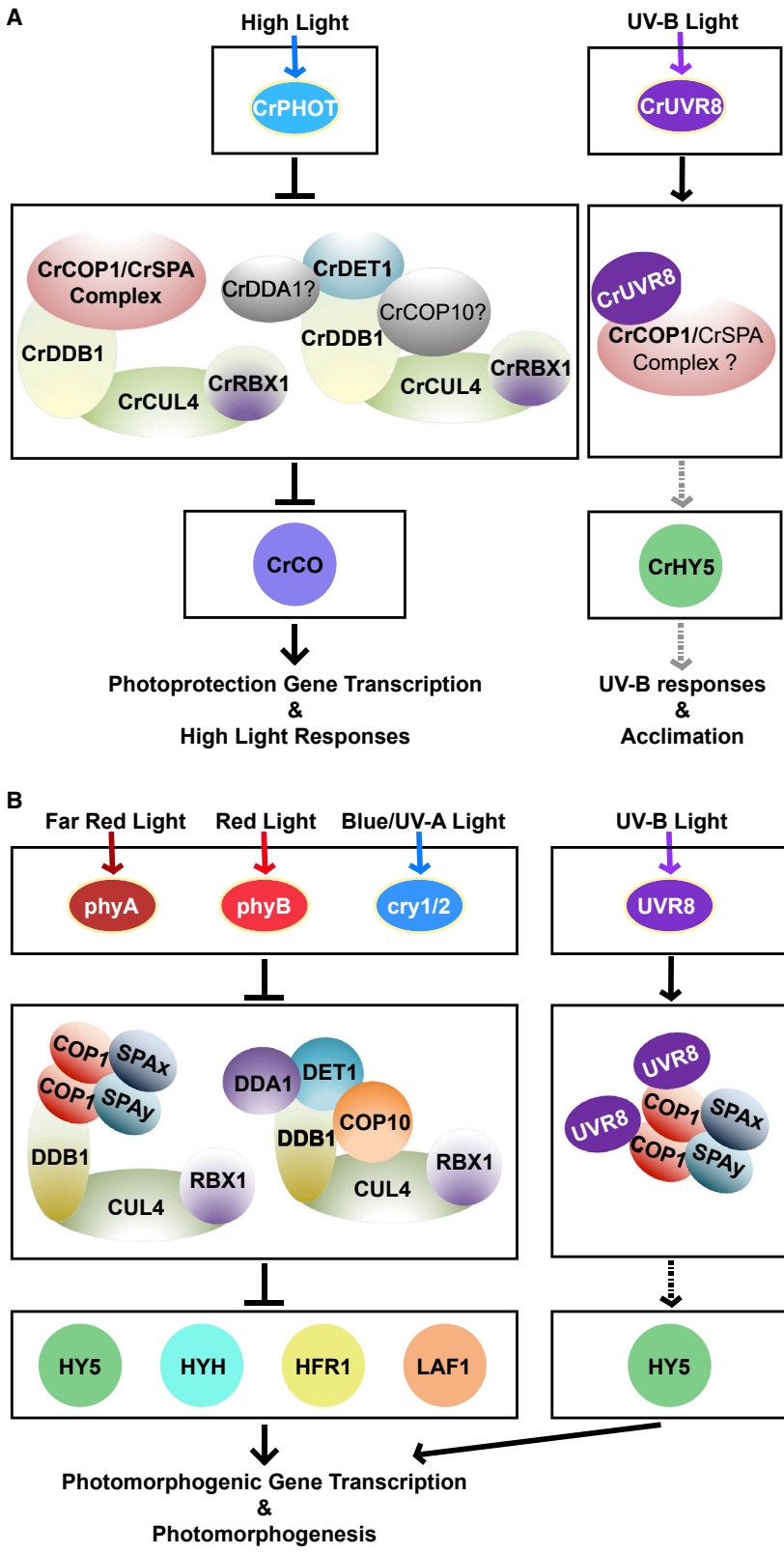
target of the COP1/SPA E3 complex in *Chlamydomonas* under high light conditions (Figure 6A; Gabilly et al., 2019; Tokutsu et al., 2019). While CO controls flowering time in *Arabidopsis*, CrCO is functionally more similar to *Arabidopsis* HY5 in activating high light-responsive gene expression. A regulatory module consisting of COP/DET/FUS E3 ligases and CO seems to have been established in an ancestral green photosynthetic organism when both SPA and PHOT evolutionarily appeared (Han et al., 2019; Tokutsu et al., 2019).

*Chlamydomonas* photoreceptor PHOT is responsible for the initiation of photoprotective signal transduction and light-dependent *LHCSR* expression under high light intensity (Li and Mathews, 2016; Petroutsos et al., 2016).

In 2015, two *Chlamydomonas* mutants showing tolerance to high light were identified to harbor different mutations within the *COP1* locus. This study uncovered a novel role of COP1 in high light adaptation in unicellular green algae (Schierenbeck et al., 2015). A subsequent suppressor screen for *phot* mutants identified *DET1* and *DDB1*, which both encode the components of the CUL4-based E3 ligase (Aihara et al., 2019). Another two genetic screens based on deficient *LHCSR* expression in *Chlamydomonas* also identified a series of core regulators: CO (CONSTANS), CUL4, and SPA (Gabilly et al., 2019; Tokutsu et al., 2019). It has been suggested that CrCOP1 and CrSPA form complexes and that they associate with the CUL4–DDB1 scaffold under high light conditions (Figure 6A; Gabilly et al., 2019). Similarly to their coordinated roles in *Arabidopsis* photomorphogenesis, both CUL4–DDB1–COP1/SPA and CUL4–DDB1–DET1 function as putative E3 ligases in the photoprotective response to high light in *Chlamydomonas* (Figure 6A; Aihara et al., 2019; Gabilly et al., 2019). Remarkably, CrCO is a

In *Chlamydomonas*, the UV-B photoreceptor UVR8 is responsible for UV-B acclimation and responses (Allorent et al., 2016). The *cop1* mutation resulted in the loss of UV-B response and acclimation, suggesting a critical role of COP1 (Tilbrook et al., 2016). Although the UV-B photoreceptor UVR8 only originated in Chlorophytes including *Chlamydomonas*, the CrUVR8–CrCOP1 regulatory module seems to function in the same manner as in *Arabidopsis* (Tilbrook et al., 2016). Additionally, the interaction among CrUVR8, CrCOP1, and CrSPA implies the formation of a UVR8–COP1/SPAs complex under UV-B light (Tilbrook et al., 2016; Tokutsu et al., 2019), in a manner conserved with that in *Arabidopsis* (Figure 6A). Although the transcript level of CrHY5 is upregulated in response to UV-B light in a UVR8-dependent manner (Tilbrook et al., 2016), whether CrHY5 is the core regulator of UV-B photomorphogenesis in green algae is still unresolved.

It is worth noting that PHOT, UVR8, and SPAs are green plant lineage specific, whereas COP1/DET/FUS proteins are ubiquitously present in all eukaryotic organisms. COP1/SPA complexes are involved in both PHOT-mediated high light protection and UVR8-mediated UV-B response in *Chlamydomonas*, although SPA, PHOT, and UVR8 only originated in Chlorophytes. Thus, COP1/SPA complexes in higher



**Figure 6. Conserved COP/DET/FUS Proteins Are Involved in Distinct Light-Regulatory Pathways in *Chlamydomonas* and *Arabidopsis*.**

**(A)** In *Chlamydomonas*, CrPHOT senses high light and induces photoprotection responses. In low light, both the CDD complex and COP1/SPA complex repress high light responses. In high light the activity of these E3 ubiquitin ligases is inhibited, allowing CrCO accumulation and the expression of high light-responsive genes. Under UV-B light, activated CrUVR8 monomers interact with CrCOP1 and induce the accumulation of CrHY5, and thus promote UV-B responses and acclimation.

**(B)** In *Arabidopsis*, light-activated photoreceptors inactivate COP/DET/FUS protein complexes, thus allowing the accumulation of photomorphogenesis-promoting regulators such as HY5 to globally activate light-responsive genes and photomorphogenic development. Similarly to *Chlamydomonas* CrUVR8, *Arabidopsis* UVR8 senses UV-B light and forms a new complex with the COP1/SPA core apparatus, which indirectly promotes the accumulation of HY5 and photomorphogenic development.

the light regulation of plant development differ in specific green plant lineages, from photoprotection, to gravitropism, to photomorphogenesis.

## CONCLUDING REMARKS AND FUTURE PERSPECTIVES

COP1 is a highly conserved E3 ligase that possibly originated in the common ancestor of all eukaryotes. COP1 is involved in diverse biological processes in plants and animals, including development and metabolism, and responses to abiotic and biotic stimuli (Lau and Deng, 2012; Marine, 2012; Artz et al., 2019; Sharma et al., 2019; Tokutsu et al., 2019; Wang and Lin, 2019). The pleiotropic roles of COP1 are at least partly determined by its functional domains, which are responsible for flexible protein-protein interactions (Uljon et al., 2016). COP1 selectively targets interacting proteins to function in specific contexts. From an evolutionary point of view, COP1 and its interacting partners display an intricate co-evolutionary pattern and their regulatory activity has been optimized during plant terrestrialization (Han et al., 2019; Lau et al., 2019). However, it is certainly of great interest to study how exactly COP1 acts at the biochemical and cellular levels in each biological process in future investigations.

There are recent reports that in a number of cases, COP1/SPA-interacting proteins somehow become activated/stabilized rather than degraded, such as PIF3 in darkness (Ling et al., 2017), PIF5 under shady environments (Sharma et al., 2019), and HY5 under UV-B light (Huang et al., 2013). Thus, non-canonical roles,

plants have evolved a role in seedling photomorphogenesis, and have maintained their conserved roles in UV-B response. Taken together, the roles of COP1/SPA complexes in

degraded, such as PIF3 in darkness (Ling et al., 2017), PIF5 under shady environments (Sharma et al., 2019), and HY5 under UV-B light (Huang et al., 2013). Thus, non-canonical roles,



e.g., certain COP1 activities not resulting from its proteolysis mechanism, may be involved. While COP1 directly interacts with BIN2 and modulates its kinase activity (Ling et al., 2017), the initially reported stabilization of HY5 by COP1/SPA under UV-B light is likely due to the UV-B-induced formation of the new UVR8–COP1/SPA complex, which targets RUP1/2 instead of HY5 for degradation (Ren et al., 2019b). It is likely that more possible non-canonical roles of COP1/SPA will be uncovered in future studies.

As tightly related partners of COP1, SPA proteins are absent in all other organisms except green lineage plants. Therefore, COP1 functions without assistance from SPA “stabilizers” in ancient algae systems, such as red alga, or in animals. In the case of algae systems without SPAs, what is the configuration of the core COP1 complex? Does COP1 act via similar mechanisms in early-originating algae and in animal systems? These open questions, together with the exact structural and functional significance of SPAs in COP1 complexes in green plants, await further investigation.

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## AUTHOR CONTRIBUTIONS

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