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Podolec, Roman; Ulm, Roman

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Photoreceptor-mediated regulation of the COP1/SPA E3 ubiquitin ligase

Roman Podolec[1,2] and Roman Ulm[1,2]

Plants have evolved specific photoreceptors that capture informational cues from sunlight. The phytochrome, cryptochrome, and UVR8 photoreceptors perceive red/far-red, blue/UV-A, and UV-B light, respectively, and control overlapping photomorphogenic responses important for plant growth and development. A major repressor of such photomorphogenic responses is the E3 ubiquitin ligase formed by CONSTITUTIVELY PHOTOMORPHOGENIC 1 (COP1) and SUPPRESSOR OF PHYA-105 (SPA) proteins, which acts by regulating the stability of photomorphogenesis-promoting transcription factors. The direct interaction of light-activated photoreceptors with the COP1/SPA complex represses its activity via nuclear exclusion of COP1, disruption of the COP1-SPA interaction, and/or SPA protein degradation. This process enables plants to integrate different light signals at the level of the COP1/SPA complex to enact appropriate photomorphogenic responses according to the light environment.

Addresses
[1] Department of Botany and Plant Biology, Section of Biology, Faculty of Sciences, University of Geneva, CH-1211 Geneva 4, Switzerland
[2] Institute of Genetics and Genomics of Geneva (iGE3), University of Geneva, Geneva, Switzerland

Corresponding author:

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Introduction

As sessile organisms, plants adapt their development to the prevailing growth conditions. Sunlight is not only crucial as the ultimate source of energy fueling photosynthesis but it also provides important information about the environment, influencing plant growth and development throughout the life cycle [1]. For example, during deetiolation, plants switch from skotomorphogenesis (growth in darkness) to photomorphogenesis (growth in light). This transition is independent of the process of photosynthesis. Photomorphogenesis at the seedling stage is characterized by both changes in seedling morphology (incl. a short hypocotyl and open green cotyledons) and a vast reprogramming of gene expression that allow the plant to accommodate to a photosynthetic lifestyle. Other photomorphogenic responses include germination, phototropism, shade avoidance, leaf and rosette morphogenesis, chloroplast movement, and flowering transition [1].

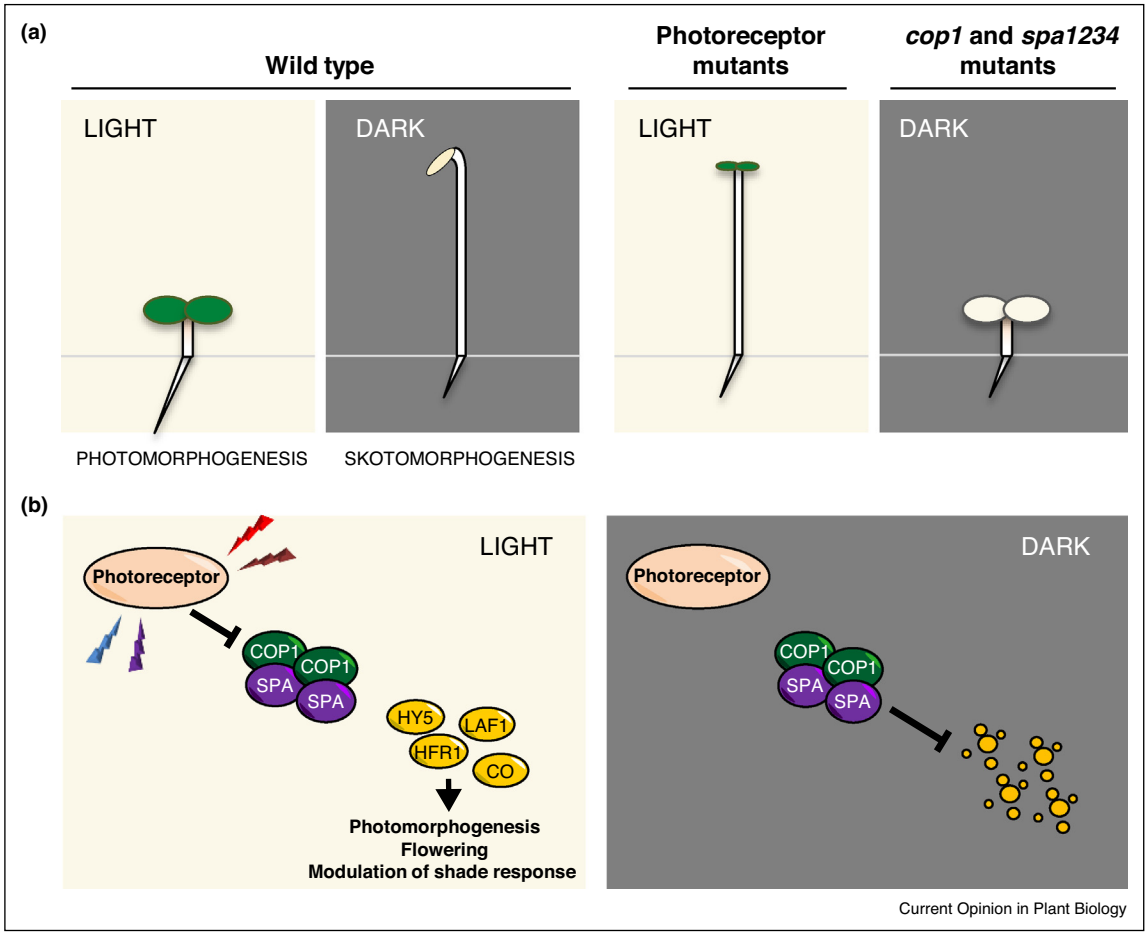
Photomorphogenic responses are initiated by several classes of photoreceptors, namely phytochromes (absorbing red/far-red; phyA to phyE in Arabidopsis), cryptochromes (blue/UV-A; cry1 and cry2), phototropins (blue/UV-A; phot1 and phot2), Zeitlupe family members (blue/UV-A; ztl, fkf1, and lkp2), and the UV-B photoreceptor UV RESISTANCE LOCUS 8 (UVR8) [2]. Several photoreceptor mechanisms of action have been described [3–7]. For phototropins and Zeitlupe family members, light perception by the photoreceptor chromophore leads to a change in intrinsic serine/threonine kinase and E3 ubiquitin ligase activity, respectively [5,6]. However, for phytochromes, cryptochromes, and UVR8, light perception primarily results in protein-protein interactions with key targets [3,4,7]. These key interaction partners include a number of transcription factors [8–12] as well as the COP1/SPA E3 ubiquitin ligase [13–18]. In this review, we will describe the COP1/SPA complex and its activity in darkness, then present the latest findings on how the phytochrome, cryptochrome, and UVR8 photoreceptors interact with and regulate the COP1/SPA complex.

The COP1/SPA E3 ubiquitin ligase is a key repressor of light responses

The COP1/SPA E3 ubiquitin ligase is a crucial repressor of photomorphogenesis [19,20] (Figure 1). In Arabidopsis, *COP1* and *SPA1–SPA4* encode WD40 repeat-containing proteins [21]. COP1 consists of an N-terminal Really Interesting New Gene (RING) domain, a central coiled-coil (CC) domain, and a C-terminal WD40 repeat domain, whereas SPA family proteins are composed of a kinase-like domain, a CC domain, and a WD40 repeat domain [22,23]. Although COP1 shows E3 ubiquitin ligase activity *in vitro* [24,25], its *in vivo* activity depends on SPA accessory proteins [26,27].

cop1 null mutants are seedling lethal, but weak *cop1* alleles exist that are associated with strong photomorphogenesis even in complete darkness [28]. The four SPA proteins show some functional redundancy, thus a constitutive photomorphogenic phenotype is particularly evident in higher order mutants, such as the *spa1234*

Figure 1



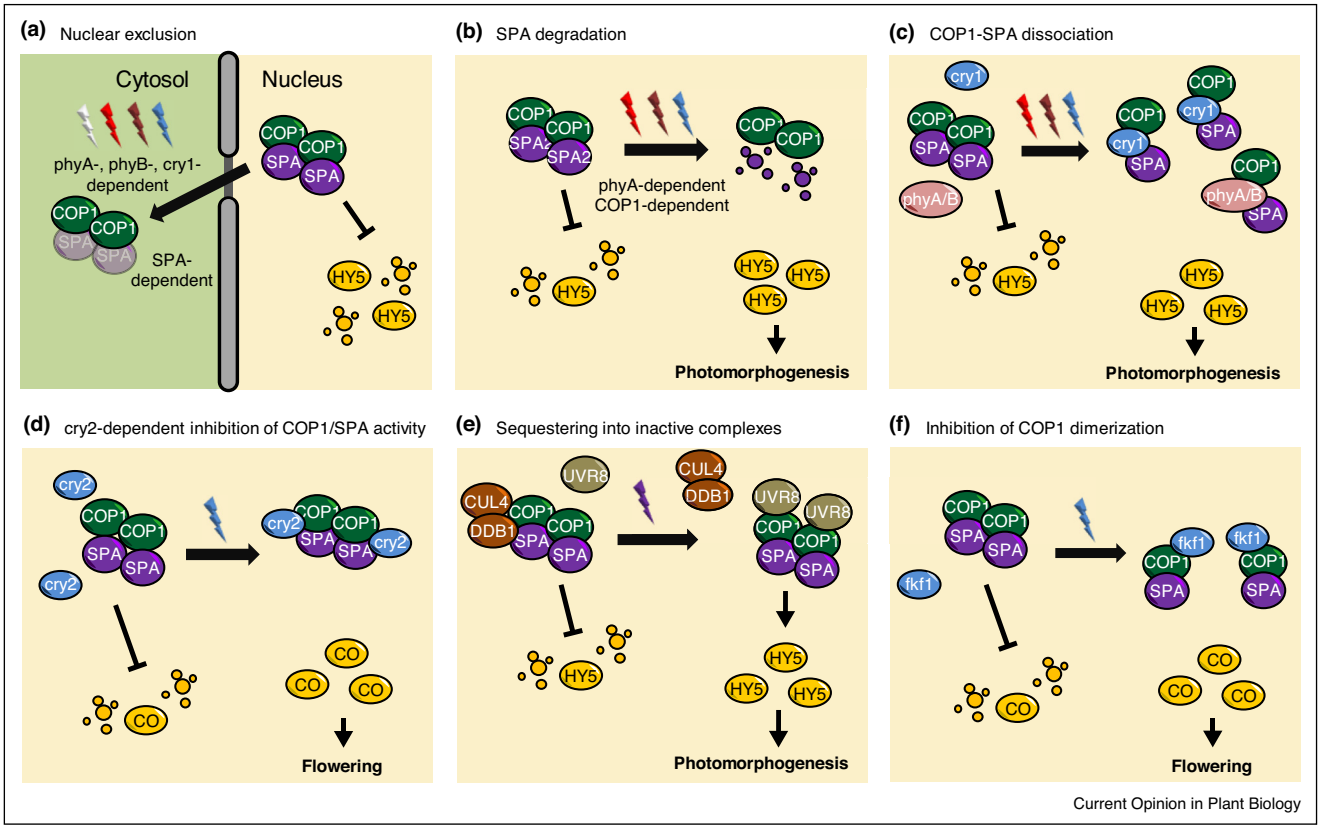
Regulation of photomorphogenesis by photoreceptors and the COP1/SPA complex. **(a)** Light-grown wild-type seedlings undergo photomorphogenesis (open green cotyledons, short hypocotyl) as opposed to dark-grown seedlings that undergo skotomorphogenesis (closed cotyledons, apical hook, elongated hypocotyl). Photoreceptor mutants grown in light resemble dark-grown wild-type seedlings, whereas dark-grown *cop1* and *spa1234* mutants exhibit constitutive photomorphogenesis. **(b)** General model: Light-activated photoreceptors inactivate the COP1/SPA complex through various mechanisms, leading to repression of its E3 ubiquitin ligase activity and stabilization of photomorphogenesis-promoting factors. In darkness, photoreceptors are inactive and photomorphogenesis-promoting factors are ubiquitinated by the COP1/SPA complex and degraded by the 26S proteasome.

quadruple mutant [26] (Figure 1a). However, in contrast to *cop1* null mutants, the *spa1234* null mutant is viable, although with an extreme dwarf phenotype [27].

COP1 and SPA proteins directly interact and form tetrameric complexes composed of two COP1 and two SPA proteins, with the potential of all combinations of the four SPA proteins [29–31]. The COP1/SPA complex is thought to act as a substrate adaptor for CULLIN4-DAMAGED DNA BINDING PROTEIN 1 (CUL4-DDB1)-based E3 ubiquitin ligase complexes [32]. Indeed, both COP1 and SPA proteins contain a WDxR motif associated with DDB1 binding in their WD40 repeats [32]. COP1 homodimerization and COP1 interaction with SPA proteins are required for nuclear E3 ubiquitin ligase activity *in vivo* [26,31,33••]. Although it is clear that the SPA proteins are required for COP1 activity *in vivo*, the function of SPA proteins in the COP1/SPA complex in darkness remains unknown [19]. Notwithstanding this, the COP1/SPA complex targets a broad range of photomorphogenesis-promoting transcription factors for ubiquitination and degradation through the 26S proteasome pathway [34–43] (Figure 1b). Interestingly, several targets contain a conserved valine-proline (VP) containing domain that mediates direct binding with the COP1 WD40 domain [34,35,44,45,46••]. By targeting a wide range of photomorphogenesis-promoting transcription factors, the COP1/SPA complex broadly regulates light-dependent developmental responses, including de-etiolation and photoperiodic flowering [19,20,47].

It is of interest to note that COP1 is conserved between plants and animals, whereas SPA proteins are specific to the

Figure 2



Mechanisms of photoreceptor control over COP1/SPA E3 ligase activity. **(a)** Phytochromes and cryptochromes promote relocation of COP1 to the cytosol, separating it from its nuclear substrates. Whether SPA proteins are also relocated to the cytosol in response to light remains unknown. **(b)** Light induces the phyA-dependent and COP1-dependent degradation of SPA2, leading to a decrease in COP1 E3 ligase activity. **(c)** cry1 and phyA/B interact light-specifically with SPA proteins. This interaction leads to physical separation of COP1 and SPA proteins, leading to a decrease in COP1/SPA E3 ligase activity. Cryptochromes and phytochromes also directly interact with COP1. Note that it is not known whether the COP1-SPA dissociation also disrupts the COP1-COP1 and SPA-SPA interactions. **(d)** cry2 interacts blue light-dependently with COP1 and SPA proteins, leading to an increase in COP1-SPA affinity but a decrease in E3 ligase activity, promoting flowering under long days. **(e)** UV-B-dependent interaction of UVR8 with COP1 induces a change in complex organization from a CUL4-DDB1-COP1/SPA complex that ubiquinates target substrates to a substrate-stabilizing UVR8-COP1/SPA complex. **(f)** fkf1 interacts with COP1 under blue light and inhibits COP1 homodimerization, whereas COP1-SPA heterodimerization is unaffected. This inactivates the COP1/SPA complex and promotes flowering. (a)–(f) HY5 and CO exemplify COP1/SPA substrates promoting seedling photomorphogenesis and flowering, respectively.

green lineage [48]. As the non-plant COP1 orthologs are not regulated by light [49], it has been hypothesized that the evolution of SPA proteins was crucial for photoreceptor-mediated light control of COP1/SPA complex activity (see below) [48,50••]. However, it remains unknown how the *in vivo* E3 ligase activity of plant COP1 evolved to require the presence of SPA proteins. For a more comprehensive description of the various roles of the COP1/SPA complex and its regulation in darkness, we refer the reader to excellent recent reviews [19,20,47,51].

Several photoreceptors regulate activity of the COP1/SPA complex via different mechanisms

Activity of the COP1/SPA complex is required for seedling etiolation in darkness, which is subsequently inhibited by action of the phytochrome, cryptochrome, and UVR8 photoreceptors in light [4,19] (Figure 1b). This inhibition leads to a release of the COP1/SPA complex repressive activity and thus activates photomorphogenic responses. Although the different photoreceptors similarly regulate activity of the COP1/SPA complex, there are clear distinct mechanisms. These regulatory mechanisms include nucleo-cytosolic partitioning, degradation of the accessory SPA proteins, and physical separation of COP1 from SPA proteins or of the COP1/SPA complex from CUL4-DDB1 (Figure 2).

Light-regulated nuclear exclusion of COP1

The regulation of COP1 sub-cellular localization was the first proposed mechanism of light-dependent control of COP1 activity [52] (Figure 2a). In the dark, COP1 is predominantly present in the nucleus, where nuclear

transcription factors are targeted for ubiquitination. Light induces COP1 relocation to the cytosol, separating it from its nuclear substrates [20,52]. It was proposed that COP1 relocation was relatively slow (12–24 h) based on studies with GUS-COP1 fusions [52]. However, this view was recently challenged by the observation that a YFP-COP1 fusion was able to relocate much faster (2.5 h half-life), suggesting this mechanism could possibly contribute to the rather rapid stabilization of COP1 targets under light [53,54]. Conversely, shade promotes the re-accumulation of COP1 in the nucleus to exert its photomorphogenesis-repressing activity [55].

COP1 nuclear localization is dependent on a bipartite nuclear localization signal in the region between the CC and WD40 domains [56,57], and SPA proteins are not required for nuclear localization of COP1 in darkness [50••]. Cytosolic localization of COP1 in response to light involves a cytosolic localization signal in the CC domain [56,57]. Phytochrome and cryptochrome photoreceptors mediate COP1 nuclear exclusion [58,59]; however, how exactly photoreceptor signaling regulates COP1 sub-cellular localization remains unknown. Interestingly, the interplay between different photoreceptors is complex, as is evident when COP1 nuclear exclusion is analyzed under monochromatic conditions. For example, whereas phyA-mediated nuclear exclusion of COP1 under far-red light is dependent on SPA proteins, this response is SPA independent under blue light downstream of cry1 [50••]. Moreover, phyB and red light were found to be less potent in inducing COP1 nuclear exclusion [50••]. Notwithstanding the exact contribution of individual photoreceptors, SPA proteins are necessary for COP1 nucleo-cytosolic partitioning in response to white light [50••]. However, it is clear that nuclear COP1 is inactive in the absence of SPA proteins, both in light as well as in darkness [26,27]. Thus, SPA proteins play a dual role in that they are required for COP1 function and also enable COP1 light-responsiveness. However, it is presently not known whether SPA proteins show light-dependent nucleo-cytosolic partitioning themselves, or whether only COP1 is affected.

Interestingly, supplemental UV-B counteracts the nuclear exclusion of COP1 in white light and causes nuclear COP1 accumulation [60], although it is not known whether UV-B affects COP1 nuclear-cytosolic shuttling per se. The finding that nuclear COP1 accumulation under UV-B is associated with elevated COP1 levels [60,61] suggests that UVR8 may not affect COP1 sub-cellular localization but may cause inhibition of COP1 autoubiquitination and thus affect nuclear accumulation indirectly.

Photoreceptor-mediated regulation of COP1 and SPA protein levels

Given that SPA proteins are required for COP1/SPA complex activity, targeted destabilization of SPA proteins is also a mechanism to control activity of the complex. Indeed, SPA2, and to a lesser extent SPA1, show light-induced, phyA-dependent, and proteasome-mediated degradation [62,63] (Figure 2b). The N-terminal kinase-like domain of SPA2 confers instability to the protein under light [64•]. Interestingly, the photoreceptor-induced degradation of SPA2 seems dependent on COP1 activity, suggesting cross-regulation of stability among COP1/SPA complex components [29]. In contrast, the COP1 protein is stabilized and accumulates in the nucleus after UV-B exposure in a UVR8-dependent manner, and this is accompanied by increased transcription of *COP1* under UV-B [60,61,65]. However, increased nuclear accumulation of COP1 under UV-B is accompanied by increased rather than decreased ELONGATED HYPOCOTYL 5 (HY5) stability, emphasizing that the COP1/SPA complex is efficiently inactivated by UV-B-activated UVR8 [13,60].

Photoreceptor-mediated regulation of the COP1-SPA interaction

Alongside the physical separation of COP1 from substrates, photoreceptor-mediated disruption of the crucial COP1-SPA interaction inactivates COP1/SPA ubiquitin ligase activity and results in stabilization of photomorphogenesis-promoting transcription factors (Figure 2c). This mechanism contributes to both cryptochrome and phytochrome signaling.

Indeed, blue light-dependent interaction of cry1 and cry2 with SPA proteins regulates the activity of the COP1/SPA complex [16–18,66]. The cry1 C-terminal CCT domain interacts with the SPA1 C-terminal region specifically under blue light [16,17]. Mechanistically, the blue light-dependent cry1-SPA1 interaction leads to a reduced SPA1 binding to COP1, thereby inactivating the COP1/SPA ubiquitin ligase and stabilizing, for example, the HY5 transcription factor to promote photomorphogenesis [16,17]. For the blue light-dependent interaction between cry2 and SPA1, it is the N-terminal PHR domain of cry2 that interacts with the N-terminal domain of SPA1 [18,67], which conversely causes the COP1-SPA1 interaction to be strengthened rather than dissociated. Nevertheless, cry2 interaction with the COP1/SPA complex increases the stability of the COP1/SPA complex target CONSTANS (CO) that is involved in the regulation of photoperiodic flowering under long days [18] (Figure 2d). Next to the effect of light-dependent interactions with SPA proteins, cry1 and cry2 C-terminal domains also interact directly with COP1 [68,69]. Whereas the cry1–COP1 interaction is dependent on SPA proteins, the cry2-COP1 interaction is not, and both appear to be blue-light dependent [70••]. The direct interaction of the cryptochromes with COP1 may indeed further contribute to the light-mediated effect on the COP1–SPA interaction and thereby COP1/SPA complex activity.

Similar to cryptochromes, the light-activated phytochromes phyA and phyB interact with SPA proteins

[14,15]. The phytochromes inhibit COP1/SPA complex activity by disrupting the interaction between COP1 and SPA proteins, thereby reorganizing the COP1/SPA complex [14,15], analogous to the cry1 mechanism of action [16,17,66]. Moreover, direct interaction of the phytochromes with COP1 may contribute to the regulation of COP1/SPA complex activity [15,71,72].

UVR8-mediated inhibition of COP1, independent of SPA proteins

The UVR8 photoreceptor was shown to directly interact with the WD40 repeat domain of COP1 in a UV-B-dependent manner [13,65,73–75,76•]. In contrast to phytochromes and cryptochromes, UVR8 does not interact with SPA proteins and UVR8 early signaling is not impaired in *spa1234* quadruple mutants [60,65]. Indeed, although UV-B-activated UVR8 interacts directly with COP1, it is only associated with SPA1 indirectly through COP1 [65]. Moreover, the COP1–SPA interaction remains intact upon interaction with UVR8 [65,73].

Two separate domains of UVR8 are involved in the interaction with COP1, namely a domain of maximum 27 amino acids (C27) in the UVR8 C-terminus and the UVR8 β-propeller core [77,78]. The two COP1 interaction surfaces are not accessible in the inactive UVR8 homodimer but are exposed in monomeric, active UVR8 that forms upon UV-B perception [75,77]. Interaction of COP1 with the β-propeller domain of UVR8 allows UV-B-dependent UVR8-COP1 interaction, whereas the C-terminal UVR8 domain is thought to affect COP1 activity [77]. Interestingly, the C27 domain of UVR8 comprises a functional and conserved VP-containing motif [77] that mimics the COP1-interaction domains of several COP1 substrate proteins [34,35,44,45,46••]. Thus, competition between the UVR8 VP interaction motif and that of COP1 targets may prevent ubiquitination and degradation of the latter through the 26S proteasome pathway and underlie how UVR8 inactivates the COP1/SPA complex [4,13,77]. It is of note that UVR8 stability is not affected by its interaction with COP1 [13,79]. UVR8 binding to COP1 also induces physical and functional dissociation of the COP1/SPA complex core from the HY5-degrading CUL4-DDB1-COP1/SPA E3 ligase complex, thus inactivating the COP1/SPA E3 ligase and creating a UVR8-COP1/SPA complex which may actively promote HY5 stabilization through an unknown mechanism [51,73] (Figure 2e).

Other light-mediated changes in COP1/SPA complex activity

Recently, several post-translational mechanisms have been reported that regulate activity of the COP1/SPA complex. COP1/SPA complex activity is enhanced by COP1 sumoylation in darkness. Light is proposed to negatively regulate COP1 sumoylation; however, this response is yet to be linked to a specific photoreceptor [80•]. Moreover, COP1 is regulated via phosphorylation by the PINOID kinase; however, the mechanistic link between photoreceptor signaling and COP1 phosphorylation remains to be identified [81•]. Alongside post-translational modifications, COP1 activity is also regulated by interaction with PHYTOCHROME INTERACTING FACTOR 1 (PIF1), which enhances activity of the COP1/SPA complex in darkness [82]. PIF1 is destabilized in light in a phytochrome-dependent process and COP1/SPA complex-dependent process, which potentially contributes to inactivation of the COP1/SPA complex in light [83]. Degradation of the PIF1 co-factor is reminiscent of the previously discussed COP1-dependent degradation of SPA2.

A very recent study has implied that fkf1 photoreceptor-dependent control of flowering time involves inactivation of the COP1/SPA complex [33••]. fkf1 interacts with the RING domain of COP1, and this interaction inhibits COP1 dimerization, whereas COP1-SPA1 heterodimerization remains unaffected [33••] (Figure 2f). Whether this inhibition of COP1 dimerization following fkf1 interaction is unique or represents a more general mechanism of COP1 regulation remains to be determined.

Feedback regulation of photoreceptors by the COP1/SPA complex

The COP1/SPA complex may also provide feedback regulation of photoreceptor activities, and indeed has been implicated in the regulation of cryptochrome and phytochrome levels [71,84,85]. On the other hand, UVR8 directly interacts with COP1 but there is no indication that this interaction leads to UVR8 destabilization [13]. Interestingly, however, COP1 is required for the UV-B-induced nuclear accumulation of UVR8, providing an additional mechanism for COP1 photoreceptor signaling feedback regulation [86,87].

Conclusions and future directions

Several mechanisms have been proposed to collectively explain the light-dependent, photoreceptor-mediated regulation of COP1/SPA E3 ligase activity. Firstly, nuclear exclusion of COP1 under light was identified. However, it remains unclear how the different photoreceptors are mechanistically involved, and whether this process is fast enough to account for the light-induced stabilization of COP1 substrates resulting in early gene expression changes. Secondly, light-induced separation of COP1 from its crucial accessory SPA proteins seems to be a common mechanism for phytochrome and cryptochrome signaling [14,15,66]. However, the role that SPA proteins play and how photoreceptor-mediated separation impairs the overall COP1/SPA complex remains unclear. Thirdly, as for UVR8, it has been suggested that dissociation of the CUL4-DDB1 scaffold from the COP1/SPA complex prevents ubiquitination of and therefore stabilizes HY5 [13,65,73]. How the UVR8-COP1/SPA

interaction results in the proposed functional switch of COP1 from repressor to promoter of HY5 stability remains to be investigated. SPA proteins do not seem to play a decisive role in this process [65,73]. Lastly, light-induced destabilization of accessory proteins, such as SPA2 or PIF1, can account for a decrease in COP1/SPA complex activity [62,63,82]. It is presently unknown if and how the mechanisms of COP1/SPA regulation through photoreceptors interact, and what the relative contributions of these mechanisms are in the stabilization of different COP1/SPA substrates.

The COP1/SPA complex has likely arisen early in the evolution of the green lineage as a point of convergence through which photoreceptors can control photomorphogenesis in line with the surrounding light environment. Future research should focus on understanding the precise composition, localization, stability, and E3 ligase activity of the COP1/SPA complex in the presence of different photoreceptors and different light qualities. This should further reveal the common and specific mechanisms through which photoreceptors control COP1/SPA complex activity and thereby photomorphogenic development.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Kami C, Lorrain S, Hornitschek P, Fankhauser C: **Light-regulated plant growth and development**. *Curr Top Dev Biol* 2010, **91**:29-66.
2. Galvao VC, Fankhauser C: **Sensing the light environment in plants: photoreceptors and early signaling steps**. *Curr Opin Neurobiol* 2015, **34**:46-53.
3. Liu H, Liu B, Zhao C, Pepper M, Lin C: **The action mechanisms of plant cryptochromes**. *Trends Plant Sci* 2011, **16**:684-691.
4. Yin R, Ulm R: **How plants cope with UV-B: from perception to response**. *Curr Opin Plant Biol* 2017, **37**:42-48.
5. Fankhauser C, Christie JM: **Plant phototropic growth**. *Curr Biol* 2015, **25**:R384-R389.
6. Ito S, Song YH, Imaizumi T: **LOV domain-containing F-box proteins: light-dependent protein degradation modules in Arabidopsis**. *Mol Plant* 2012, **5**:573-582.
7. Pham VN, Kathare PK, Huq E: **Phytochromes and phytochrome interacting factors**. *Plant Physiol* 2018, **176**:1025-1038.
8. Liu H, Yu X, Li K, Klejnot J, Yang H, Lisiero D, Lin C: **Photoexcited CRY2 interacts with CIB1 to regulate transcription and floral initiation in Arabidopsis**. *Science* 2008, **322**:1535-1539.
9. Pedmale Ullas V, Huang S-shan C, Zander M, Cole Benjamin J, Hetzel J, Ljung K, Reis Pedro AB, Sridevi P, Nito K, Nery Joseph R *et al.*: **Cryptochromes interact directly with PIFs to control plant growth in limiting blue light**. *Cell* 2016, **164**:233-245.
10. Yang Y, Liang T, Zhang L, Shao K, Gu X, Shang R, Shi N, Li X, Zhang P, Liu H: **UVR8 interacts with WRKY36 to regulate *HY5* transcription and hypocotyl elongation in Arabidopsis**. *Nat Plants* 2018, **4**:98-107.
11. Ma D, Li X, Guo Y, Chu J, Fang S, Yan C, Noel JP, Liu H: **Cryptochrome 1 interacts with PIF4 to regulate high temperature-mediated hypocotyl elongation in response to blue light**. *Proc Natl Acad Sci U S A* 2016, **113**:224-229.
12. Liang T, Mei S, Shi C, Yang Y, Peng Y, Ma L, Wang F, Li X, Huang X, Yin Y *et al.*: **UVR8 interacts with BES1 and BIM1 to regulate transcription and photomorphogenesis in Arabidopsis**. *Dev Cell* 2018, **44**:512-523.
13. Favory JJ, Stec A, Gruber H, Rizzini L, Oravecz A, Funk M, Albert A, Cloix C, Jenkins GI, Oakeley EJ *et al.*: **Interaction of COP1 and UVR8 regulates UV-B-induced photomorphogenesis and stress acclimation in Arabidopsis**. *EMBO J* 2009, **28**:591-601.
14. Lu XD, Zhou CM, Xu PB, Luo Q, Lian HL, Yang HQ: **Red-light-dependent interaction of phyB with SPA1 promotes COP1-SPA1 dissociation and photomorphogenic development in Arabidopsis**. *Mol Plant* 2015, **8**:467-478.
15. Sheerin DJ, Menon C, zur Oven-Krockhaus S, Enderle B, Zhu L, Johnen P, Schleifenbaum F, Stierhof YD, Huq E, Hiltbrunner A: **Light-activated phytochrome A and B interact with members of the SPA family to promote photomorphogenesis in Arabidopsis by reorganizing the COP1/SPA complex**. *Plant Cell* 2015, **27**:189-201.
16. Liu B, Zuo Z, Liu H, Liu X, Lin C: **Arabidopsis cryptochrome 1 interacts with SPA1 to suppress COP1 activity in response to blue light**. *Genes Dev* 2011, **25**:1029-1034.
17. Lian HL, He SB, Zhang YC, Zhu DM, Zhang JY, Jia KP, Sun SX, Li L, Yang HQ: **Blue-light-dependent interaction of cryptochrome 1 with SPA1 defines a dynamic signaling mechanism**. *Genes Dev* 2011, **25**:1023-1028.
18. Zuo Z, Liu H, Liu B, Liu X, Lin C: **Blue light-dependent interaction of CRY2 with SPA1 regulates COP1 activity and floral initiation in Arabidopsis**. *Curr Biol* 2011, **21**:841-847.
19. Hoecker U: **The activities of the E3 ubiquitin ligase COP1/SPA, a key repressor in light signaling**. *Curr Opin Plant Biol* 2017, **37**:63-69.
20. Lau OS, Deng XW: **The photomorphogenic repressors COP1 and DET1: 20 years later**. *Trends Plant Sci* 2012, **17**:584-593.
21. Lee JH, Terzaghi W, Gusmaroli G, Charron JB, Yoon HJ, Chen H, He YJ, Xiong Y, Deng XW: **Characterization of Arabidopsis and rice DWD proteins and their roles as substrate receptors for CUL4-RING E3 ubiquitin ligases**. *Plant Cell* 2008, **20**:152-167.
22. Hoecker U, Tepperman JM, Quail PH: **SPA1, a WD-repeat protein specific to phytochrome A signal transduction**. *Science* 1999, **284**:496-499.
23. Deng XW, Matsui M, Wei N, Wagner D, Chu AM, Feldmann KA, Quail PH: **COP1, an Arabidopsis regulatory gene, encodes a protein with both a zinc-binding motif and a G beta homologous domain**. *Cell* 1992, **71**:791-801.
24. Saijo Y, Sullivan JA, Wang H, Yang J, Shen Y, Rubio V, Ma L, Hoecker U, Deng XW: **The COP1–SPA1 interaction defines a critical step in phytochrome A-mediated regulation of HY5 activity**. *Genes Dev* 2003, **17**:2642-2647.
25. Seo HS, Yang JY, Ishikawa M, Bolle C, Ballesteros ML, Chua NH: **LAF1 ubiquitination by COP1 controls photomorphogenesis and is stimulated by SPA1**. *Nature* 2003, **423**:995-999.
26. Laubinger S, Fittinghoff K, Hoecker U: **The SPA quartet: a family of WD-repeat proteins with a central role in suppression of photomorphogenesis in Arabidopsis**. *Plant Cell* 2004, **16**:2293-2306.
27. Ordonez-Herrera N, Fackendahl P, Yu X, Schaefer S, Koncz C, Hoecker U: **A *cop1 spa* mutant deficient in COP1 and SPA proteins reveals partial co-action of COP1 and SPA during**

Arabidopsis post-embryonic development and photomorphogenesis. *Mol Plant* 2015, **8**:479-481.

28. McNellis TW, von Arnim AG, Araki T, Komeda Y, Misera S, Deng XW: **Genetic and molecular analysis of an allelic series of cop1 mutants suggests functional roles for the multiple protein domains**. *Plant Cell* 1994, **6**:487-500.

29. Zhu D, Maier A, Lee JH, Laubinger S, Saijo Y, Wang H, Qu LJ, Hoecker U, Deng XW: **Biochemical characterization of Arabidopsis complexes containing CONSTITUTIVELY PHOTOMORPHOGENIC1 and SUPPRESSOR OF PHYA proteins in light control of plant development**. *Plant Cell* 2008, **20**:2307-2323.

30. Hoecker U, Quail PH: **The phytochrome A-specific signaling intermediate SPA1 interacts directly with COP1, a constitutive repressor of light signaling in Arabidopsis**. *J Biol Chem* 2001, **276**:38173-38178.

31. Torii KU, McNellis TW, Deng XW: **Functional dissection of Arabidopsis COP1 reveals specific roles of its three structural modules in light control of seedling development**. *EMBO J* 1998, **17**:5577-5587.

32. Chen H, Huang X, Gusmaroli G, Terzaghi W, Lau OS, Yanagawa Y, Zhang Y, Li J, Lee JH, Zhu D *et al.*: **Arabidopsis CULLIN4-damaged DNA binding protein 1 interacts with CONSTITUTIVELY PHOTOMORPHOGENIC1-SUPPRESSOR OF PHYA complexes to regulate photomorphogenesis and flowering time**. *Plant Cell* 2010, **22**:108-123.

33. •• Lee BD, Kim MR, Kang MY, Cha JY, Han SH, Nawkar GM, Sakuraba Y, Lee SY, Imaizumi T, McClung CR *et al.*: **The F-box protein FKF1 inhibits dimerization of COP1 in the control of photoperiodic flowering**. *Nat Commun* 2017, **8**:2259.
This work describes the inhibition of COP1 dimerization by the FKF1 photoreceptor as a novel mechanism of COP1 regulation, contributing to the regulation of photoperiodic flowering. The COP1-SPA interaction remains unaffected by the interaction with FKF1.

34. Holm M, Ma LG, Qu LJ, Deng XW: **Two interacting bZIP proteins are direct targets of COP1-mediated control of light-dependent gene expression in Arabidopsis**. *Genes Dev* 2002, **16**:1247-1259.

35. Jang IC, Yang JY, Seo HS, Chua NH: **HFR1 is targeted by COP1 E3 ligase for post-translational proteolysis during phytochrome A signaling**. *Genes Dev* 2005, **19**:593-602.

36. Osterlund MT, Hardtke CS, Wei N, Deng XW: **Targeted destabilization of HY5 during light-regulated development of Arabidopsis**. *Nature* 2000, **405**:462-466.

37. Xu D, Jiang Y, Li J, Lin F, Holm M, Deng XW: **BBX21, an Arabidopsis B-box protein, directly activates HY5 and is targeted by COP1 for 26S proteasome-mediated degradation**. *Proc Natl Acad Sci U S A* 2016, **113**:7655-7660.

38. Yang J, Lin R, Hoecker U, Liu B, Xu L, Wang H: **Repression of light signaling by Arabidopsis SPA1 involves post-translational regulation of HFR1 protein accumulation**. *Plant J* 2005, **43**:131-141.

39. Jang S, Marchal V, Panigrahi KC, Wenkel S, Soppe W, Deng XW, Valverde F, Coupland G: **Arabidopsis COP1 shapes the temporal pattern of CO accumulation conferring a photoperiodic flowering response**. *EMBO J* 2008, **27**:1277-1288.

40. Liu LJ, Zhang YC, Li QH, Sang Y, Mao J, Lian HL, Wang L, Yang HQ: **COP1-mediated ubiquitination of CONSTANS is implicated in cryptochrome regulation of flowering in Arabidopsis**. *Plant Cell* 2008, **20**:292-306.

41. Laubinger S, Marchal V, Le Gourrierec J, Wenkel S, Adrian J, Jang S, Kulajta C, Braun H, Coupland G, Hoecker U: **Arabidopsis SPA proteins regulate photoperiodic flowering and interact with the floral inducer CONSTANS to regulate its stability**. *Development* 2006, **133**:3213-3222.

42. Ordonez-Herrera N, Trimborn L, Menje M, Henschel M, Robers L, Kaufholdt D, Hansch R, Adrian J, Ponnu J, Hoecker U: **The transcription factor COL12 is a substrate of the COP1/SPA E3 ligase and regulates flowering time and plant architecture**. *Plant Physiol* 2018, **176**:1327-1340.

43. Yu JW, Rubio V, Lee NY, Bai S, Lee SY, Kim SS, Liu L, Zhang Y, Irigoyen ML, Sullivan JA *et al.*: **COP1 and ELF3 control circadian function and photoperiodic flowering by regulating GI stability**. *Mol Cell* 2008, **32**:617-630.

44. Datta S, Hettiarachchi GH, Deng XW, Holm M: **Arabidopsis CONSTANS-LIKE3 is a positive regulator of red light signaling and root growth**. *Plant Cell* 2006, **18**:70-84.

45. Holm M, Hardtke CS, Gaudet R, Deng XW: **Identification of a structural motif that confers specific interaction with the WD40 repeat domain of Arabidopsis COP1**. *EMBO J* 2001, **20**:118-127.

46. •• Uljon S, Xu X, Durzynska I, Stein S, Adelmant G, Marto JA, Pear WS, Blacklow SC: **Structural basis for substrate selectivity of the E3 ligase COP1**. *Structure* 2016, **24**:687-696.
This work describes the crystal structure of the WD40 repeat domain of human and Arabidopsis COP1 in complex with a VP-containing peptide based on the COP1-interacting motif of the human TRIB1 protein, suggesting a conserved mechanism for substrate binding to COP1.

47. Menon C, Sheerin DJ, Hiltbrunner A: **SPA proteins: SPAnning the gap between visible light and gene expression**. *Planta* 2016, **244**:297-312.

48. Ranjan A, Dickopf S, Ullrich KK, Rensing SA, Hoecker U: **Functional analysis of COP1 and SPA orthologs from *Physcomitrella* and rice during photomorphogenesis of transgenic Arabidopsis reveals distinct evolutionary conservation**. *BMC Plant Biol* 2014, **14**:178.

49. Marine JC: **Spotlight on the role of COP1 in tumorigenesis**. *Nat Rev Cancer* 2012, **12**:455-464.

50. •• Balcerowicz M, Kerner K, Schenkel C, Hoecker U: **SPA proteins affect the subcellular localization of COP1 in the COP1/SPA ubiquitin ligase complex during photomorphogenesis**. *Plant Physiol* 2017, **174**:1314-1321.
This study shows that the light-dependent relocation of COP1 from the nucleus to the cytosol requires the presence of SPA proteins, whereas the nuclear localization of COP1 in darkness does not.

51. Huang X, Ouyang X, Deng XW: **Beyond repression of photomorphogenesis: role switching of COP/DET/FUS in light signaling**. *Curr Opin Plant Biol* 2014, **21**:96-103.

52. von Arnim AG, Deng XW: **Light inactivation of Arabidopsis photomorphogenic repressor COP1 involves a cell-specific regulation of its nucleocytoplasmic partitioning**. *Cell* 1994, **79**:1035-1045.

53. Pacin M, Legris M, Casal JJ: **Rapid decline in nuclear CONSTITUTIVE PHOTOMORPHOGENESIS1 abundance anticipates the stabilization of its target ELONGATED HYPOCOTYL5 in the light**. *Plant Physiol* 2014, **164**:1134-1138.

54. Moriconi V, Binkert M, Costigliolo Rojas MC, Sellaro R, Ulm R, Casal JJ: **Perception of sunflecks by the UV-B photoreceptor UV RESISTANCE LOCUS 8**. *Plant Physiol* 2018, **177**:75-81.

55. Pacin M, Legris M, Casal JJ: **COP1 re-accumulates in the nucleus under shade**. *Plant J* 2013, **75**:631-641.

56. Stacey MG, Hicks SN, von Arnim AG: **Discrete domains mediate the light-responsive nuclear and cytoplasmic localization of Arabidopsis COP1**. *Plant Cell* 1999, **11**:349-364.

57. Subramanian C, Kim BH, Lyssenko NN, Xu X, Johnson CH, von Arnim AG: **The Arabidopsis repressor of light signaling, COP1, is regulated by nuclear exclusion: mutational analysis by bioluminescence resonance energy transfer**. *Proc Natl Acad Sci U S A* 2004, **101**:6798-6802.

58. Gu NN, Zhang YC, Yang HQ: **Substitution of a conserved glycine in the PHR domain of Arabidopsis cryptochrome 1 confers a constitutive light response**. *Mol Plant* 2012, **5**:85-97.

59. Osterlund MT, Deng XW: **Multiple photoreceptors mediate the light-induced reduction of GUS-COP1 from Arabidopsis hypocotyl nuclei**. *Plant J* 1998, **16**:201-208.

60. Oravecz A, Baumann A, Mate Z, Brzezinska A, Molinier J, Oakeley EJ, Adam E, Schafer E, Nagy F, Ulm R: **CONSTITUTIVELY PHOTOMORPHOGENIC1 is required for the UV-B response in Arabidopsis**. *Plant Cell* 2006, **18**:1975-1990.

61. Huang X, Ouyang X, Yang P, Lau OS, Li G, Li J, Chen H, Deng XW: **Arabidopsis FHY3 and HY5 positively mediate induction of COP1 transcription in response to photomorphogenic UV-B light**. *Plant Cell* 2012, **24**:4590-4606.

62. Balcerowicz M, Fittinghoff K, Wirthmueller L, Maier A, Fackendahl P, Fiene G, Koncz C, Hoecker U: **Light exposure of Arabidopsis seedlings causes rapid de-stabilization as well as selective post-translational inactivation of the repressor of photomorphogenesis SPA2**. *Plant J* 2011, **65**:712-723.

63. Chen S, Lory N, Stauber J, Hoecker U: **Photoreceptor specificity in the light-induced and COP1-mediated rapid degradation of the repressor of photomorphogenesis SPA2 in Arabidopsis**. *PLoS Genet* 2015, **11**:e1005516.

64. • Chen S, Wirthmueller L, Stauber J, Lory N, Holtkotte X, Leson L, Schenkel C, Ahmad M, Hoecker U: **The functional divergence between SPA1 and SPA2 in Arabidopsis photomorphogenesis maps primarily to the respective N-terminal kinase-like domain**. *BMC Plant Biol* 2016, **16**:165.
This work shows that the N-terminal kinase-like domain of SPA1 and SPA2 largely defines their divergent activities, including affinity to cry2 and light-induced instability.

65. Heijde M, Binkert M, Yin R, Ares-Orpel F, Rizzini L, Van De Slijke E, Persiau G, Nolf J, Gevaert K, De Jaeger G *et al.*: **Constitutively active UVR8 photoreceptor variant in Arabidopsis**. *Proc Natl Acad Sci U S A* 2013, **110**:20326-20331.

66. Fankhauser C, Ulm R: **Light-regulated interactions with SPA proteins underlie cryptochrome-mediated gene expression**. *Genes Dev* 2011, **25**:1004-1009.

67. Holtkotte X, Dieterle S, Kokkelink L, Artz O, Leson L, Fittinghoff K, Hayama R, Ahmad M, Hoecker U: **Mutations in the N-terminal kinase-like domain of the repressor of photomorphogenesis SPA1 severely impair SPA1 function but not light responsiveness in Arabidopsis**. *Plant J* 2016, **88**:205-218.

68. Wang H, Ma LG, Li JM, Zhao HY, Deng XW: **Direct interaction of Arabidopsis cryptochromes with COP1 in light control development**. *Science* 2001, **294**:154-158.

69. Yang HQ, Tang RH, Cashmore AR: **The signaling mechanism of Arabidopsis CRY1 involves direct interaction with COP1**. *Plant Cell* 2001, **13**:2573-2587.

70. •• Holtkotte X, Ponnu J, Ahmad M, Hoecker U: **The blue light-induced interaction of cryptochrome 1 with COP1 requires SPA proteins during Arabidopsis light signaling**. *PLoS Genet* 2017, **13**:e1007044.
This work shows that cryptochromes interact in a blue light-dependent manner with COP1. Whereas the cry1–COP1 interaction requires SPA proteins, cry2 interacts with COP1-independently of SPAs.

71. Seo HS, Watanabe E, Tokutomi S, Nagatani A, Chua NH: **Photoreceptor ubiquitination by COP1 E3 ligase desensitizes phytochrome A signaling**. *Genes Dev* 2004, **18**:617-622.

72. Viczian A, Adam E, Wolf I, Bindics J, Kircher S, Heijde M, Ulm R, Schafer E, Nagy F: **A short amino-terminal part of Arabidopsis phytochrome A induces constitutive photomorphogenic response**. *Mol Plant* 2012, **5**:629-641.

73. Huang X, Ouyang X, Yang P, Lau OS, Chen L, Wei N, Deng XW: **Conversion from CUL4-based COP1-SPA E3 apparatus to UVR8-COP1-SPA complexes underlies a distinct biochemical function of COP1 under UV-B**. *Proc Natl Acad Sci U S A* 2013, **110**:16669-16674.

74. Heijde M, Ulm R: **UV-B photoreceptor-mediated signalling in plants**. *Trends Plant Sci* 2012, **17**:230-237.

75. Rizzini L, Favory JJ, Cloix C, Faggionato D, O'Hara A, Kaiserli E, Baumeister R, Schafer E, Nagy F, Jenkins GI *et al.*: **Perception of UV-B by the Arabidopsis UVR8 protein**. *Science* 2011, **332**:103-106.

76. • Tilbrook K, Dubois M, Crocco CD, Yin R, Chappuis R, Allorent G, Schmid-Siegert E, Goldschmidt-Clermont M, Ulm R: **UV-B perception and acclimation in *Chlamydomonas reinhardtii***. *Plant Cell* 2016, **28**:966-983.
This work describes functional conservation of the UVR8-COP1 UV-B signaling module in green algae, suggesting early evolution of light control of COP1 activity by photoreceptors.

77. Yin R, Arongaus AB, Binkert M, Ulm R: **Two distinct domains of the UVR8 photoreceptor interact with COP1 to initiate UV-B signaling in Arabidopsis**. *Plant Cell* 2015, **27**:202-213.

78. Cloix C, Kaiserli E, Heilmann M, Baxter KJ, Brown BA, O'Hara A, Smith BO, Christie JM, Jenkins GI: **C-terminal region of the UV-B photoreceptor UVR8 initiates signaling through interaction with the COP1 protein**. *Proc Natl Acad Sci U S A* 2012, **109**:16366-16370.

79. Kaiserli E, Jenkins GI: **UV-B promotes rapid nuclear translocation of the Arabidopsis UV-B specific signaling component UVR8 and activates its function in the nucleus**. *Plant Cell* 2007, **19**:2662-2673.

80. • Lin X-L, Niu D, Hu Z-L, Kim DH, Jin YH, Cai B, Liu P, Miura K, Yun D-J, Kim W-Y *et al.*: **An Arabidopsis SUMO E3 ligase, SIZ1, negatively regulates photomorphogenesis by promoting COP1 activity**. *PLOS Genet* 2016, **12**:e1006016.
This work shows that COP1 sumoylation by the SUMO E3 ligase SIZ1 enhances COP1 activity and suggests a light-regulated mechanism that favors COP1 sumoylation in darkness as opposed to light conditions.

81. • Lin F, Xu D, Jiang Y, Chen H, Fan L, Holm M, Deng XW: **Phosphorylation and negative regulation of CONSTITUTIVELY PHOTOMORPHOGENIC 1 by PINOID in Arabidopsis**. *Proc Natl Acad Sci U S A* 2017, **114**:6617-6622.
This work describes PINOID kinase-dependent phosphorylation as a novel post-translational mechanism of COP1 regulation.

82. Xu X, Paik I, Zhu L, Bu Q, Huang X, Deng XW, Huq E: **PHYTOCHROME INTERACTING FACTOR1 enhances the E3 ligase activity of CONSTITUTIVE PHOTOMORPHOGENIC1 to synergistically repress photomorphogenesis in Arabidopsis**. *Plant Cell* 2014, **26**:1992-2006.

83. Zhu L, Bu Q, Xu X, Paik I, Huang X, Hoecker U, Deng XW, Huq E: **CUL4 forms an E3 ligase with COP1 and SPA to promote light-induced degradation of PIF1**. *Nat Commun* 2015, **6**:7245.

84. Debrieux D, Trevisan M, Fankhauser C: **Conditional involvement of CONSTITUTIVE PHOTOMORPHOGENIC1 in the degradation of phytochrome A**. *Plant Physiol* 2013, **161**:2136-2145.

85. Weidler G, Zur Oven-Krockhaus S, Heunemann M, Orth C, Schleifenbaum F, Harter K, Hoecker U, Batschauer A: **Degradation of Arabidopsis CRY2 is regulated by SPA proteins and phytochrome A**. *Plant Cell* 2012, **24**:2610-2623.

86. Qian C, Mao W, Liu Y, Ren H, Lau OS, Ouyang X, Huang X: **Dual-source nuclear monomers of UV-B light receptor direct photomorphogenesis in Arabidopsis**. *Mol Plant* 2016, **9**:1671-1674.

87. Yin R, Skvortsova MY, Loubery S, Ulm R: **COP1 is required for UV-B-induced nuclear accumulation of the UVR8 photoreceptor**. *Proc Natl Acad Sci U S A* 2016, **113**:E4415-E4422.