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# Stem phototropism towards blue and ultraviolet light.

Martina Legris[1*], Alessandra Boccaccini[1]

**Authors Affiliations**

[1] Center for Integrative Genomics, Faculty of Biology and Medicine, University of Lausanne, CH-1015, Lausanne, Switzerland. * martina.legris@unil.ch

**Abstract**

Positive phototropism is the process through which plants orient their organs towards a directional light source. While the blue light receptors phototropins (phot) play a major role in phototropism towards blue (B) and ultraviolet (UV) radiation, recent research showed that the UVB light receptor UVR8 also triggers phototropism towards UVB. In addition, new details of the molecular mechanisms underlying the activity of these receptors and interaction with other environmental signals have emerged in the past years. In this review we summarize the current knowledge about hypocotyledoneous and inflorescence stem growth reorientation towards B and UVB, with focus on the molecular mechanisms.

**Abbreviations**

B, blue light

FR, far-red light

GA, gibberellins

HB, high blue light

LB, low blue light (below 1µmol.$m^{-2}$.$s^{-1}$)

LOV, light oxygen or voltage FMN-binding

R, red light

R:FR, red to far-red ratio

STK, serine-threonine kinase

UV, ultraviolet radiation

## Introduction

Developmental plasticity is a distinctive feature of plants. After germination, the number, shape and functionality of plant organs is regulated to fit the prevailing environmental conditions. In this review we will discuss phototropism, the process through which plants regulate their shape to position their organs towards the most favorable light conditions.

Plants perceive a broad range of the light spectrum, from ultraviolet (UV) to far-red light (FR), using wavelength-specific light receptors. However, only blue light (B, 380-500nm) and ultraviolet radiation (UVA, 315-380nm and UVB, 280-315nm) can trigger phototropism (Liscum et al. 2014, Fankhauser and Christie 2015). These short-wavelength radiations are scattered and absorbed by the plant tissues, so when the light stimulus is directional light gradients are created within the organs which allow plants to determine their relative position to the light source. BL and UV are perceived by phototropins (phot) and the UV-B receptor UV RESISTANCE LOCUS 8 (UVR8), which upon unilateral irradiation are differentially activated in the lit and the shaded side of the stem (Liscum et al. 2014, Vandenbussche et al. 2014, Fankhauser and Christie 2015, Vanhaelewyn et al. 2019). This differential photoreceptor activation leads to the creation of an auxin gradient across the stem, which promotes differential cell expansion between the lit and the shaded side, eventually causing bending.

Here we will discuss the current knowledge about how plants perceive light signals, from the photoreceptor-mediated light perception, the downstream signaling mechanisms and finishing with how these pathways are integrated with other light signals to fine tune stem phototropism. While the physiological response is largely conserved among plants, the molecular mechanisms have mostly been studied in Arabidopsis, so we will focus on this model and point out whenever differences were found in other species. We apologize to colleagues whose work could not be cited due to space constraints. Primary references for earlier work are available in recent reviews (Liscum et al. 2014, Christie et al. 2015, Okajima 2016, Jenkins 2017, Christie et al. 2018, Podolec and Ulm 2018, Liang et al. 2019).

## Photoreceptor activation

phot are the main photoreceptors involved in phototropism towards B, UVA and also UVB in hypocotyls (Liscum et al. 2014, Vandenbussche et al. 2014). Land plants have two phot, phot1 and phot2, which in addition to stem phototropism control other processes that improve photosynthetic efficiency such as stomatal opening, leaf flattening and positioning and chloroplast localization (Christie et al. 2015, Li and Mathews 2016). Although both phot control the same processes, their relative contribution depends on the environmental conditions. In the case of phototropism both receptors promote bending towards B, but phot1 can do it in response to a broad range of B intensities, even below 1$\mu mol.m^{-2}.s^{-1}$ (LB), while phot2 is

specialized in perceiving higher B intensities (HB) (Kagawa et al. 2009, Liscum et al. 2014). This is consistent with the fact that phot1 is light labile and its abundance is down regulated by light, while phot2 levels increase with irradiation (Liscum et al. 2014, Sullivan et al. 2019). Whether phot1 and phot2 have different roles in response to UVB has not been tested, but according to *phot1phot2* mutants phot have a major role driving phototropism of hypocotyls towards low fluencies of monochromatic UVB (0.002 µmol. $m^{-2}$. $s^{-1}$) and a minor role in response to higher UVB fluencies (0.12 µmol. $m^{-2}$. $s^{-1}$) (Vanhaelewyn et al. 2016). It is worth noting that the effect of phot on UVB signaling was evaluated in the absence of B, so the physiological role of phot activation by UVB in natural conditions, where B predominates is still unclear.

phot are light activated serine-threonine kinases with two N-terminal Light Oxygen or Voltage (LOV1 and LOV2) domains that bind flavine mononucleotide (FMN) and a C-terminal serine-threonine kinase domain of the AGC family (STK) (Fig. 1A) (Christie et al. 2015, Okajima 2016). While the LOV domains are structurally similar, they have different functions. LOV1 has been proposed to promote phot dimerization and modulate LOV2 photoreactivity, while LOV2 has a major role controlling the kinase activity of the receptors (Christie et al. 2015, Okajima 2016).

In the dark phot are inactive. LOV2 binds FMN non-covalently, and interacts with the STK inhibiting its kinase activity. Upon absorption of the inductive wavelengths a covalent adduct is formed between the FMN and a conserved cysteine in LOV domains, causing structural changes in LOV2 and in two helical structures flanking it, named A'α and Jα, finally leading to de-repression of the STK (Fig. 1A) (Christie et al. 2015, Okajima 2016). This leads to autophosphorylation of phot as well as phosphorylation of other downstream signaling factors, triggering morphogenic responses to B (Fig. 1A) (Liscum et al. 2014, Suzuki et al. 2019). Interestingly, these conformational changes can be achieved by single aminoacid changes rendering the STK constitutively active (Okajima 2016, Petersen et al. 2017). Consistent with the notion that a gradient of phot activation is required for phototropism, plants expressing a constitutively active kinase variant of phot1 have reduced phototropic responses (Petersen et al. 2017).

phot are phosphorylated in several residues, localized in the N-terminal region upstream LOV1, in the linker region between LOV1 and LOV2, and in the STK (Fig. 1A) (Christie et al. 2015). phot phosphorylation is essential for signaling, and two residues within the kinase activation loop (S849 and S851 in phot1, S761 and S763 in phot2 in Arabidopsis) play a key role (Fig. 1A) (Christie et al. 2015, Okajima 2016). A recent analysis showed that upon B activation phot1 dimerizes in a phosphorylation-independent manner (Xue et al. 2018). This suggests a model in which B triggers phot1 dimerization, and phosphorylation occurs as a second step. In this scenario it will be interesting to test if, alternatively to being autophosphorylated, phot1 monomers in a dimer can phosphorylate each other. In favor of this model, a constitutively active kinase variant of phot1 can trigger phosphorylation of a kinase dead mutant in vitro in the dark (Petersen et al.

2017). However, whether phot1 dimerization precedes or is required for phot1 phosphorylation remains to be established.

Within seconds or minutes, the FMN-cysteinyl adduct reverts to the dark state, and the speed of this reversion affects phot activity. It has been proposed that the longer decay time of phot1 compared to phot2 would explain its role in phototropism towards LB (Okajima 2016). However, etiolated Arabidopsis seedlings expressing slow-photocycling versions of phot1 or phot2, obtained by single aminoacid substitutions within the LOV2 domain, have impaired phototropism instead of increased sensitivity, suggesting that other aspects of the system are regulated to enhance sensitivity to the unidirectional stimulus (Hart et al. 2019). Nevertheless, slow phot photocycling improved other phot-mediated responses, suggesting that changing phot reversion rate using guided mutagenesis could be a useful approach to improve photosynthetic efficiency (Hart et al. 2019). phot inactivation speed not only depends on specific aminoacids within the LOV2 domain, but also can be modulated by LOV1 and it has been recently shown that it is also regulated by temperature (Christie et al. 2015, Okajima 2016, Fujii et al. 2017, Hart et al. 2019). Given its strong impact on photosynthesis-related traits, the study of phot variants with altered photocycle will be an interesting topic for future research. An important tool that remains unexplored to study phot variants is the collection of Arabidopsis accessions. Here may lay useful resources to understand how changes in phot protein sequence affect its activity in vivo.

Despite their hydrophilic nature, both phot1 and phot2 localize to the intracellular part of the plasma membrane (Fig. 2A) (Liscum et al. 2014, Preuten et al. 2015). How phot associate with the membrane is still unknown but certain residues in the C-terminal domain may be involved in their subcellular localization pattern (Christie et al. 2015). In the case of phot1 upon light perception it localizes to membrane microdomains and is internalized to the cytoplasm (Preuten et al. 2015, Xue et al. 2018). Localization to membrane microdomains depends on phot1 phosphorylation and appears to be important for hypocotyl phototropism since treatments with MβCD, a sterol-disrupting agent, inhibits phototropism and can be rescued adding sterols (Xue et al. 2018). On the other hand, phot1 internalization appears to be irrelevant for hypocotyl phototropism, since anchoring phot1 to the membrane through lipid modifications inhibits internalization and doesn´t affect hypocotyl bending (Preuten et al. 2015). In the case of phot2, light triggers its translocation to the Golgi apparatus (Christie et al. 2015). In both cases phot internalization requires a functional STK (Christie et al. 2015).

phot are the most relevant light receptors triggering hypocotyl bending towards B and UV, and inflorescence bending towards B. However, in inflorescence stems the response to UVB depends predominantly on UVR8 (Kagawa et al. 2009, Liscum et al. 2014, Vandenbussche et al. 2014, Fankhauser and Christie 2015, Vanhaelewyn et al. 2019). UVR8 is the only UV-B specific receptor described to date

and has a role in seedling de-etiolation and UVB protection, as well as a small role controlling hypocotyl phototropism towards UVB among other functions (Vandenbussche et al. 2014, Jenkins 2017).

UVR8 is a seven-bladed β-propeller protein. In the absence of UVB it exists as a dimer, and upon UVB perception the dimer dissociates allowing monomeric UVR8 to initiate signaling (Fig. 1B) (Jenkins 2017). UVR8 is different from other plant light receptors since instead of binding a chromophore it uses tryptophan residues in its primary structure for UV-B absorption. Photoperception changes the structure of tryptophans, remarkably W233 and W285 which are present in the dimerization interface, which in turn weaken the interactions between arginines R286 and R338 and specific aspartate and glutamate residues in the complementary monomer, promoting dissociation of the dimer (Fig. 1B) (Jenkins 2017, Liang et al. 2019).

UVR8 monomers localize to the nucleus, where they control transcriptional responses to UVB (Fig. 2B) (Jenkins 2017, Liang et al. 2019). Given that UVR8 doesn't have a nuclear localization signal (NLS) it has been proposed that nuclear translocation involves interaction with an NLS-containing protein. One candidate for this function is CONSTITUTIVELY PHOTOMORPHOGENIC1 (COP1), a protein that interacts with UVR8 and is required for its nuclear localization and signaling (Fig. 2B). Alternatively, other proteins might enable UVR8 nuclear import and COP1 would be required for maintenance of UVR8 in the nucleus (Jenkins 2017, Liang et al. 2019). It will be interesting to know whether in response to unilateral UVB irradiation a gradient of UVR8 nuclear localization is established in the stem. Also, the involvement of COP1 in UVR8 nuclear localization could be more easily studied in inflorescence stems where the *cop1* mutation does not have such a strong developmental effect as in the hypocotyl.

In the absence of UVB, UVR8 returns to the dimeric state in less than an hour (Jenkins 2017). This inactivation is promoted by the REPRESSOR OF UVB PHOTOMORPHOGENESIS (RUP) proteins, RUP1 and RUP2. In addition, RUPs inhibit UVR8 signaling since they bind to the same region as COP1, and inhibit UVR8 nuclear accumulation (Jenkins 2017, Liang et al. 2019). Whether RUPs are important for UVR8-mediated phototropism is still unknown. However, in etiolated hypocotyls enhanced UVR8 signaling in *rup1rup2* interferes with the phototropic response towards low intensity UVB (which, as mentioned before, is driven by phot), pointing at a role of these proteins in the interaction between phot and UVR8 signaling in phototropism towards UVB (Vanhaelewyn et al. 2016).

While phot and UVR8 are expressed in most tissues, the analysis of transgenic lines expressing these photoreceptors under the control of tissue-specific promoters combined with localized light treatments showed that their action is site-specific (Kagawa et al. 2009, Preuten et al. 2013, Liscum et al. 2014, Vanhaelewyn et al. 2019). In Arabidopsis hypocotyls the site of perception and response to B is below the meristem, in the elongation zone (Preuten et al. 2013, Yamamoto et al. 2014, Sullivan et al. 2016b). In

contrast, in grasses the emerging shoot is covered by a protective sheath called coleoptile, and in this case the perception of the light signal occurs in the tip of the organ (Matsuda et al. 2011). In inflorescence stems the phototropic B stimulus can be perceived and trigger bending along the whole organ (Kagawa et al. 2009). So far, the site of perception of UVB triggering phototropism has not been established. phot1 expressed in the hypocotyl epidermis, cortex or endodermis complements the phototropic defects in *phot1phot2* hypocotyls, while UVR8 is mostly active triggering inflorescence stems bending towards UVB when it´s expressed in the cortex and epidermis, and to a smaller extent in the endodermis (Preuten et al. 2013, Vanhaelewyn et al. 2019).

**Early signaling for phototropism**

Upon unilateral irradiation a light gradient is established across the stem which creates a photoreceptor activation gradient between the lit and the shaded side (Fig. 2) (Liscum et al. 2014, Vandenbussche and Van Der Straeten 2014, Suzuki et al. 2019). Although in Arabidopsis this hasn´t been tested directly for phot nor UVR8, in maize and oat differential phot1 phosphorylation occurs between the lit and shaded side of the coleoptile (Suzuki et al. 2019). In Arabidopsis this activation gradient can be inferred visualizing changes in the abundance or localization of downstream targets.

In the case of phot, a fast signaling event following photoreceptor activation is the de-phosphorylation of NON PHOTOTROPIC HYPOCOTYL 3 (NPH3), an essential protein for phot-mediated phototropism but apparently not for UVR8-mediated stem bending (Fig. 2A) (Liscum et al. 2014, Vandenbussche et al. 2014, Fankhauser and Christie 2015, Christie et al. 2018, Sullivan et al. 2019). In darkness phosphorylated NPH3 localizes to the plasma membrane and interacts with the N-terminal portion of phot1 through its C-terminal region. De-phosphorylation of NPH3, which can be detected within 5 min after irradiation, inhibits its interaction with phot1 and promotes internalization of the protein to cytosolic aggregates which are already visible 15min after irradiation (Fig. 2A) (Haga et al. 2015, Sullivan et al. 2019). Recently, using GFP-tagged versions of NPH3 it was shown that upon unilateral B irradiation these NPH3 aggregates are more abundant in the lit than in the shaded side of Arabidopsis hypocotyls, pointing at the existence of a phot activation gradient (Fig. 2A) (Sullivan et al. 2019). In darkness or after long periods of irradiation NPH3 is re-phosphorylated by a still unknown kinase and re-localized to the membrane (Haga et al. 2015, Christie et al. 2018).

Intriguingly, while NPH3 dephosphorylation correlates with phototropism, sustained NPH3 de-phosphorylation and exclusion from the membrane correlate with lower phototropic response. So, a fast recovery of phosphorylated NPH3 levels at the membrane would be required to achieve maximal responses to light (Liscum et al. 2014, Haga et al. 2015, Hart et al. 2019, Sullivan et al. 2019). One fundamental factor

for this process is ROOT PHOTOTROPISM2 (RPT2) (Fig. 2A). RPT2 is the second founding member of the NPH3/RPT2-like (NRL) family, since it shares structural features with NPH3. It also localizes to the plasma membrane, interacts with phot1 and NPH3 and is required for normal hypocotyl phototropism. *rpt2* mutants respond to B intensities below 0.17μmol.$m^{-2}$.$s^{-1}$, but have impaired responses to higher irradiances (Haga et al. 2015). Also, in etiolated seedlings a pretreatment with red light (R) enhances phototropism in a process that involves RPT2. Moreover NPH3 phosphorylation and membrane localization are restored after a long exposure to B in an RPT2-dependent manner (Haga et al. 2015). These phenotypes can be explained by the promotion of RPT2 accumulation by light (Haga et al. 2015). Thus, the current model is that HB enhances NPH3 de-phosphorylation and internalization, but light-promoted accumulation of RPT2 counteracts this action allowing phototropism. NPH3 and RPT2 interact in yeast, so the effect of RPT2 on NPH3 activity could be direct (Christie et al. 2018). Nevertheless, in etiolated wild type seedlings NPH3 de-phosphorylation and internalization increase with higher irradiances of B even after long exposure times, hence RPT2 accumulation is insufficient to inhibit these processes (Haga et al. 2015, Sullivan et al. 2019). In addition, a recent report showed that in de-etiolated seedlings NPH3 de-phosphorylation is inhibited independently of RPT2 by factors related to other photoreceptor signaling mechanisms (discussed below) (Sullivan et al. 2019).

NPH3 and RPT2 contain an N-teminal BRIC-A-BRAC, TRAMTRACK AND BROAD COMPLEX (BTB) domain, an NPH3 domain and a C-terminal coiled coil domain (Liscum et al. 2014, Christie et al. 2018). The NPH3 domain characterizes NRL proteins (33 members in Arabidopsis), which have various roles in plant development and physiology (Christie et al. 2018). While the biochemical function of RPT2 is unknown NPH3 has been reported to form part of a CUL3 RING E3 UBIQUITIN LIGASE (CRL3) complex which targets phot1 for ubiquitination following light activation (Christie et al. 2018). phot1 mono-ubiquitination occurs in response to LB and has been related to phot1 internalization, which as discussed before, appears to be unrelated to phototropism. Multi and poly-ubiquitination of phot1 occurs in response to HB and triggers its degradation (Christie et al. 2018). Given the tight correlation between NPH3 phosphorylation levels and phototropism, it would be interesting to test the role of NPH3 phosphorylation on its activity as an E3 ligase and its potential effect on phot1 levels.

Apart from promoting their own phosphorylation, phot also phosphorylate other proteins. Among phot targets, PHYTOCHROME KINASE SUBSTRATE 4 (PKS4) and the auxin transporter ABCB19 have been related to phototropism (Fig. 2A) (Liscum et al. 2014, Christie et al. 2015, Okajima 2016). ABCB19 is phosphorylated by phot1 in vitro and phosphorylation inhibits its function. However, *abcb19* mutants have exaggerated phototropism, so it seems that this phosphorylation is not required to promote hypocotyl bending but rather to inhibit it. PKS4 belongs to a family of plant-specific proteins with 4 members in

Arabidopsis (PKS1-4) involved in various phot-mediated responses (de Carbonnel et al. 2010, Kami et al. 2014, Liscum et al. 2014, Christie et al. 2015). Although the biochemical function of PKS proteins is still unclear it may be related to auxin transport or signaling (de Carbonnel et al. 2010, Kami et al. 2014). PKS4 localizes to the plasma membrane, interacts with phot1 and NPH3 and is required for hypocotyl phototropism in LB (Kami et al. 2014, Fankhauser and Christie 2015). Upon B exposure it is phosphorylated in vivo by phot1 on S299. However, this phosphorylation is not required for phototropism towards LB in etiolated seedlings. On the contrary, phosphorylated PKS4 acts as an inhibitor of phototropism towards HB in de-etiolated seedlings (Schumacher et al. 2018). Thus, future research is required to link phot-mediated phosphorylation of signaling targets to positive phototropism. To date, the only phot phosphorylation target required for a phot-mediated response is the kinase Blue Light Signaling 1 (BLUS1), which is essential for blue light induced stomata opening (Christie et al. 2015).

While phot-triggered early signaling occurs at the plasma membrane, UVR8 signaling takes place in the nucleus where UVR8 monomers interact with COP1 (Fig. 2B) (Jenkins 2017, Lau et al. 2019, Liang et al. 2019). Together with SUPPRESSOR OF PHYA-105 (SPA) proteins, COP1 acts as a substrate adapter in a CUL4-DDB1 E3 ubiquitin ligase complexes which target many proteins involved in light signaling. ELONGATED HYPOCOTYL5 (HY5) is a transcription factor that promotes photomorphogenesis, is one of the most up-regulated genes in response to UVB, and is a COP1 target (Liang et al. 2019, Vanhaelewyn et al. 2019). Upon UVB irradiation UVR8 binding to COP1 reduces its association with the E3 ligase complex inhibiting COP1-mediated degradation of HY5 (Fig. 2B) (Podolec and Ulm 2018, Lau et al. 2019). This allows HY5 protein accumulation, which in turn promotes its own transcription, creating a feed forward loop which enhances photomorphogenic responses to UVB (Liang et al. 2019).

Early UVR8 signaling has been widely studied in the context of hypocotyl growth inhibition in response to UVB. However it was shown that upon unilateral UVB irradiation a UVR8 activity gradient is established in the hypocotyl and in the inflorescence stem, which allows phototropic bending. This causes accumulation of HY5 and expression of its targets in the lit side of the organ, presumably leading to site-specific growth inhibition (Vandenbussche and Van Der Straeten 2014, Vanhaelewyn et al. 2019). In inflorescence stems HY5 HOMOLOG (HYH) has a role in addition to HY5, and its expression is induced by UVB more prominently in the lit than in the shaded side (Fig. 2B) (Vanhaelewyn et al. 2019). Accordingly, HY5 and HYH targets are also differentially expressed across the stem (Vanhaelewyn et al. 2019).

Apart from COP1, UVR8 in the nucleus also interacts with transcription factors (TFs) such as WRKY DNA-BINDING PROTEIN 36 (WRKY36), BRI1-EMS-SUPRESSOR1 (BES1) and BES1-INTERACTING MYC-LIKE1 (BIM1) (Liang et al. 2019) (Fig. 2B). WRKY36 represses transcription of HY5, inhibiting photomorphogenesis downstream of UVR8. BES1 and BIM1 are brassinosteroid signaling

transcription factors which promote hypocotyl elongation promoting several growth-related genes. While interaction of UVR8 with these transcription factors is required for hypocotyl growth inhibition by UVB, their role in phototropism has not been studied.

**Late downstream signaling**

Growth reorientation towards the light source requires that the shaded side of the stem grows more than the lit side. Both in response to B and UVB this is achieved by the formation of an auxin gradient across the stem (Fig. 2). Although this has not been measured directly in Arabidopsis due to its small size, it has been found in other species such as Brassica and oat, and indirectly measured in Arabidopsis using auxin signaling reporters (Liscum et al. 2014, Fankhauser and Christie 2015). Auxin is mostly synthesized in developing tissues, such as young leaves and cotyledons, and moves basipetally through the phloem. Given that the epidermis has a major role regulating plant growth, control of auxin transport from the vasculature to the epidermal tissues is fundamental for phototropism (Savaldi-Goldstein et al. 2007).

In hypocotyls bending towards B phot require members of the PIN FORMED (PIN) family of auxin efflux carriers. High order PIN mutants have impaired hypocotyl bending (Liscum et al. 2014, Fankhauser and Christie 2015). This could reflect a general need of auxin transport from the site of production to the site of action, or a specific role of PINs in the bending site. In favor of the second alternative, in response to unilateral B PIN3 changes its localization in the endodermal cells promoting auxin transport from the vasculature to the shaded side of the hypocotyl in a process regulated by clathrin (Zhang et al. 2017). Although the mechanism linking photoreceptor activation with modulation of PIN activity is still unknown, kinases belonging to the same class as phot, the AGCVIII, regulate PIN activity via phosphorylation. Among these kinases, D6 PROTEIN KINASES (D6PKs) phosphorylate and activate PINs, and are essential for phototropism in many light conditions without affecting hypocotyl growth (Haga et al. 2018). PINOIDs (PIDs) were proposed as regulators of PIN activity in phototropism. However, the quadruple mutant lacking all four family members has normal phototropism towards B, ruling out a key role of these kinases in the process (Haga et al. 2014). Recently AGC1-12 was shown to phosphorylate PINs and is required for phototropism in response to B pulses. AGC1-12 and D6PKs also play a role in gravitropism suggesting that these kinases have a broad role in auxin-mediated tropic responses (Haga et al. 2018).

Interestingly, the role of PINs is not so prominent in phototropism towards UVB. *pin3* mutants have a full response to unilateral UVB, and overexpressing PID or inhibiting PINs with N-(1-naphtyl)phtalamic acid (NPA) has a smaller effect than in response to B (Vandenbussche et al. 2014). In inflorescence stems the role of PINs in UVB responses remains to be established. However, NPA treatment inhibits bending, and

PID, which is required for full bending, is upregulated in the lit side in a UVR8-dependent fashion, so probably regulation of PINs activity influences stem bending towards UVB (Vanhaelewyn et al. 2019).

As mentioned before ABCB19, another auxin transporter is phosphorylated by phot but mutants have increased hypocotyl phototropism so its role in phototropism is still unclear, and members of the AUX/LAX family of auxin importers have a very limited effect in hypocotyl phototropism towards B and no role in response to UVB (Liscum et al. 2014, Vandenbussche et al. 2014, Fankhauser and Christie 2015).

Once in the cell auxin is perceived by nuclear receptors, with members of the TRANSPORT INHIBITOR RESISTANT1/AUXIN BINDING F-BOX (TIR/AFB) having a clear role in phototropism (Liscum et al. 2014, Leyser 2018). These proteins act as substrate adaptors in a SCF-type ubiquitin ligase complex that targets transcriptional regulators to de-repress gene expression in response to auxin (Leyser 2018). Aux/IAA proteins, together with co-repressor proteins such as TOPLESS (TPL) inhibit transcription promoted by AUXIN RESPONSE FACTORs (ARFs). In response to auxin Aux/IAAs are degraded and ARFs promote transcription of auxin responsive genes. NPH4/ARF7 and IAA19 are among the most important auxin related factors for phototropism in response to B (Liscum et al. 2014). Interestingly NPH4, ARF19 and IAA19 are most likely dispensable for phototropism towards UVB (Vandenbussche et al. 2014, Vanhaelewyn et al. 2019). Nevertheless, stable versions of IAA7 (*axr2*) and IAA17 (*axr3*) have impaired phototropism in response to both B and UVB, suggesting that auxin signaling is required in both cases (Vandenbussche et al. 2014, Vanhaelewyn et al. 2019). However, *axr* mutants have pleiotropic effects, so the interpretation of these results is not straightforward. Indeed, inflorescences of *axr2* mutants show negative phototropism in response to B, pointing at a complex regulation of differential growth in these mutants (Sato et al. 2015). Auxin signaling also controls cell expansion regulating the orientation of microtubules (True and Shaw 2020). In addition, in hypocotyls it was shown that phot can also control microtubule orientation (Lindeboom et al. 2013). It will be interesting to know how these pathways interplay in the control of differential cell expansion in the stem in response to unilateral light stimulus.

Members of the SMALL AUXIN UP RNA (SAUR) are upregulated in response to auxin (Leyser 2018). In response to UVB SAUR are downregulated in a UVR8-dependent manner (Vandenbussche et al. 2014). SAUR19 was shown to have a role in phototropism towards B since hyperactive variants have impaired phototropic responses (Spartz et al. 2012). SAUR19 and SAUR24 localize to the plasma membrane, where they interact with and inhibit PP2C-D thereby inhibiting de-phosphorylation of the H+ATPase which in its active phosphorylated form acidifies the apoplast enhancing cell expansion (Leyser 2018). Activation of the H+ATPase is required for phototropism, but was proposed to initiate the formation of an auxin gradient (Hohm et al. 2014). Also, in stomata phot trigger H+ATPase activation presumably independently of auxin, in a process that requires the guard-cell specific phot1 target BLUS1 (Christie et al. 2015). Hence, while

the requirement of SAUR and H+ATPase for phototropism is clear, the mechanisms in which they are involved are not fully understood.

Stem phototropism towards UVB requires not only auxin but also gibberellins (GA). In the lit side of the stem HY5 promotes expression of GA2-oxidases GA2OX1 and GA2OX8, two enzymes involved in GA inactivation by hydroxylation (Fig. 2B). This creates a gradient of bioactive GA abundance across the stem, which in addition to the auxin gradient is expected to control differential cell expansion controlling for example the abundance of REPRESSOR OF GA (RGA) (Fig. 2B). However, this GA gradient is not enough to promote bending, but is required for a full response (Vanhaelewyn et al. 2019). In contrast, GA is not necessary for phototropism towards B in etiolated seedlings but may be involved in the interaction between phot and other photoreceptor signaling pathways (Tsuchida-Mayama et al. 2010).

**Modulatory roles of other photoreceptors**

While phot and UVR8 are the only photoreceptors capable of triggering phototropism, the R and far-red light (FR) receptors phytochromes (phy) and the B receptors cryptochromes (cry) have a modulatory role which depends on the plant developmental stage (Fig. 3) (Liscum et al. 2014, Fankhauser and Christie 2015). One key developmental process in a plant's life cycle is de-etiolation, which happens when seedlings growing in the dark reach the soil surface, and transition from a heterotrophic metabolism to photo-autotrophy (Legris et al. 2019). Predictably, responses to light are very different between etiolated and de-etiolated plants, and in particular the mechanisms underlying phototropism vary significantly between these developmental states (Fig. 3). For example, phy and cry enhance phototropism in etiolated seedlings, but inhibit it in de-etiolated seedlings. In this section we will describe how photoreceptors modulate phototropism in etiolated and de-etiolated plants.

Etiolated seedlings grow below the soil and rely on the seed reserves to reach the surface. In these conditions, seedlings are highly sensitive to light, at least in part due to the accumulation of high levels of phot1 and phyA (Liscum et al. 2014, Legris et al. 2019). In etiolated seedlings, B or R perceived by cry or phyA respectively enhance hypocotyl curvature towards B (Fig. 3) (Whippo and Hangarter 2003, Tsuchida-Mayama et al. 2010). This can be explained by increased expression of genes related to phototropism such as *RPT2* and *PKS1* (Kami et al. 2012, Liscum et al. 2014, Fankhauser and Christie 2015, Haga et al. 2015). In addition, it was recently shown that phyA can also enhance hypocotyl phototropism towards LB in response to a B pre-treatment (Sullivan et al. 2016a). Interestingly, while *PHOT1* expression in the epidermis is enough to trigger phototropism, this interaction between phyA and phot1 occurs in another tissue, probably the cortex (Sullivan et al. 2016a). Hypocotyls have negative gravitropsim, and to bend they need to reorient growth in a direction opposed to the one set by the gravitropic stimulus. It has been

previously shown that phyA reinforces phototropism inhibiting gravitropism (Lariguet and Fankhauser 2004, Liscum et al. 2014). Interestingly, epidermal or cortical phyB inhibits gravitropism in de-etiolated seedlings, promoting degradation of amyloplasts in the endodermis (Legris 2019). Whether this is the case in phyA-mediated inhibition of gravitropism, or if phyB-mediated inhibition of gravitropism has an effect on phototropism remains to be established.

Once the seedling reaches the soil surface, phy, cry and UVR8 promote de-etiolation, which is characterized by inhibition of hypocotyl elongation among other responses. In these growth-inhibiting conditions seedlings are not too sensitive to the phototropic stimulus, suggesting that when photosynthetic organs are exposed to optimal light conditions, the re-orientation is not a priority (Fig. 3) (Whippo and Hangarter 2003, Goyal et al. 2016). Nevertheless, when light is scarce positioning of the photosynthetic organs towards the light would be advantageous. Indeed, in the presence of surrounding plants inhibition of phyB promotes phototropism (Goyal et al. 2016). In the proximity of plants, the light spectrum presents a reduced red to far-red ratio (R:FR), since the photosynthetic pigments absorb mainly R and B and reflect and transmit FR. In these conditions, inactivation of phyB allows the accumulation of auxin through the transcriptional activation of auxin synthesis genes by PHYTOCHROME INTERACTING FACTORS (PIF) in the cotyledons (Goyal et al. 2016, Legris et al. 2019). When low R:FR is combined with a directional B cue, this newly synthesized auxin is transported to the shaded side of the hypocotyl enhancing phototropic bending (Goyal et al. 2016). Remarkably, auxin biosynthesis is not required for etiolated seedlings. Mutants for auxin biosynthesis show reduced phototropism in light-grown seedlings, but not in dark-grown seedlings (Goyal et al. 2016) This is in agreement with previous data showing that the absence of cotyledons (where most auxin is synthesized in response to shade) does not affect phototropism in etiolated seedlings, while it inhibits the bending in de-etiolated seedlings (Preuten et al. 2013). As mentioned above, green tissues also absorb B so, below a green canopy cry and phot are also inactivated. Future research is required to understand how these signals are integrated to control phototropism in shaded environments.

While fully de-etiolated seedlings growing in the light have a reduced phototropic response, a recent report showed that dark-adapted de-etiolated seedlings are more responsive to unilateral B than etiolated seedlings (Sullivan et al. 2019). In this particular case, enhanced phototropic bending correlates with reduced NPH3 dephosphorylation but in a RPT2-independent manner, and cannot be explained by increased auxin sensitivity, suggesting the existence of an alternative mechanism to the previously reported (Sullivan et al. 2019).

So far there is no data regarding the interaction of other photoreceptors with phot and UVR8 in the control of phototropism in inflorescence stems (Fig. 3). However, it is tempting to speculate that COP1 may represent a signaling hub in this process. In addition to UVR8, phy and cry also inhibit COP1 (Podolec and

Ulm 2018). Two recent papers showed that UVR8 and cry compete with other transcription factors, such as HY5, for the binding to COP1 thereby impeding their degradation (Lau et al. 2019, Ponnu et al. 2019). Considering the importance of HY5 distribution for asymmetrical growth of the stem, it is reasonable to speculate that the modulation of the HY5-COP1 interaction by different photoreceptors may be critical for stem curvature in different light scenarios (Vanhaelewyn et al. 2019). In addition, UVR8 was shown to inhibit accumulation of PIF4 and PIF5 in de-etiolated seedlings (Sharma et al. 2019, Tavridou et al. 2019). Given that PIF activity can also be regulated by phy and cry, this may also represent a signaling hub.

**Conclusions**

Phototropism has fascinated scientists as early as Darwin's observations in the late 19$^{th}$ century. Since the discovery of phot in Arabidopsis in the 1990's by Winslow Briggs' group we have advanced in our knowledge about phot structure and signaling mechanisms, showing that plants developed complex mechanisms to accurately regulate phototropism in a large range of environmental conditions. The recent discovery of the UVB receptor UVR8, and its role in phototropism makes the system even more complex and intriguing.

While phot are the main receptors involved in hypocotyl phototropism, inflorescence stem phototropism towards unilateral UVB is controlled by UVR8. It would be interesting to study the interplay of these receptors in natural conditions, where B and UVB will jointly provide information about the heterogeneity of the light environment, and where other factors such as temperature, day length and the activity of other photoreceptors could modulate phototropism. Also, since Arabidopsis is a rosette plant, bending of the inflorescence stem towards UVB could be directly related to positioning the flowers rather than the leaves. Studying phototropism in species with a different architecture might help us distinguish between the mechanisms controlling inflorescence positioning and leaf positioning, which could reveal the relative contributions of phot and UVR8 to phototropism. In addition, hypocotyl phototropism towards UVB was studied in etiolated seedlings. It would be interesting to evaluate the role of UVR8 triggering phototropism in de-etiolated seedlings.

In the previous paragraphs we listed unresolved issues regarding the molecular mechanisms of phot and UVR8 signaling. In general, UVR8 signaling has been studied in the context of hypocotyl growth inhibition. Now, we should evaluate whether these mechanisms are conserved for phototropism. While our knowledge about phot is more complete than for UVR8, key questions remain unsolved in all the steps leading from phot activation to stem bending. First, phot have a role at the membrane, but how they are associated with it is still unknown. The same is true for key signaling factors such as NPH3, RPT2 and PKS proteins. NPH3 phosphorylation status is clearly a determinant for phototropism, but we still ignore which are the kinases

and phosphatases required for this regulation. Finally, both for UVR8 and phot the establishment of an auxin gradient is required to trigger bending, but the molecular link between photoreceptor activation and auxin transport or signaling remains elusive. Given the site-specificity of these processes biochemical approaches face strong difficulties. However, as recent examples have shown, the use of fluorescence microscopy will be instrumental to study phototropism.

**Author contributions**

Martina Legris and Alessandra Boccaccini wrote the article.

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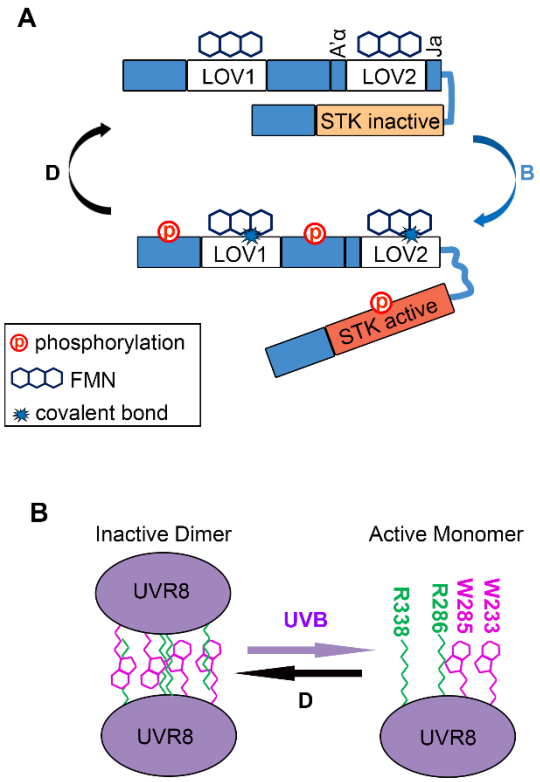
**Figure legends**

**Figure 1. Photoreversible activation by blue and UVB light of phot1 and UVR8**. A- Phot consist of two N-terminal light sensing LOV domains and a C-terminal serine-threonine kinase domain (STK). In the dark, LOV2 interacts with the STK inhibiting its kinase activity. Light induces covalent binding of FMN to the LOV domains, triggering conformational changes and eventually de-repressing the STK, which promotes phot autophosphorylation and phosphorylation of their targets. In the absence of blue light this process is reverted and phot return to the inactive state. B- UVR8 exists as a dimer in the dark, and in response to UVB monomerizes allowing interaction with its signaling partners. Light is perceived by tryptophan residues in the protein. In particular, W233 and W285 located at the interface between both monomers regulate dimerization through interaction with certain residues in the complementary monomer, with R286 and R338 having a major role. In the absence of UVB the monomer returns to the inactive dimeric state.

**Figure 2. Hypocotyl and inflorescence stem curvature mediated by phot1 and UVR8.** A- In Arabidopsis young seedlings, unilateral B irradiation drives hypocotyl curvature, which is the result of an increase in cell elongation in the shaded part of the hypocotyl compared to the lit side. This asymmetrical growth is accomplished by differential auxin distribution and phot1 activity across the hypocotyl. In blue light-irradiated cells, phot1 is activated and it starts a cascade of molecular events, which includes: NPH3 de-phosphorylation and internalization, phosphorylation of PKS4 and ABCB19. B- In adult Arabidopsis plants, unilateral UVB irradiation drives the curvature of the inflorescence stem, which is mainly regulated by UVR8. In UVB-irradiated cells, the monomeric and active UVR8 form is accumulated in the nucleus, where it modules the transcription of several genes by sequestration and release of different transcription factors (TFs). This differential gene expression across the stem generates the asymmetrical distribution of auxin and GA, which promotes stem bending. nu: nucleus.

**Figure 3. Photoreceptors action in stem phototropism at different developmental stages of *Arabidopsis thaliana*.** phot1, phot2 and UVR8 are the main photoreceptors involved in the perception of B and UVB triggering phototropism. Cry and phy have a modulatory role, which would be important for the integration of different environmental stimuli. n.t.: not tested. n.d.: no genetic evidence supporting the involvement of the photoreceptor in the process. 1- Reviewed in Liscum et al 2014. 2- Vandenbussche et al. 2014. 3- Vanhaelewyn et al. 2016. 4- Goyal et al. 2016. 5- Schumacher et al. 2018. 6- Kagawa et al. 2009. 7- Vanhaelewyn et al. 2019. 9- Whippo and Hangarter 2003. 10- Lariguet and Fankhauser 2004.

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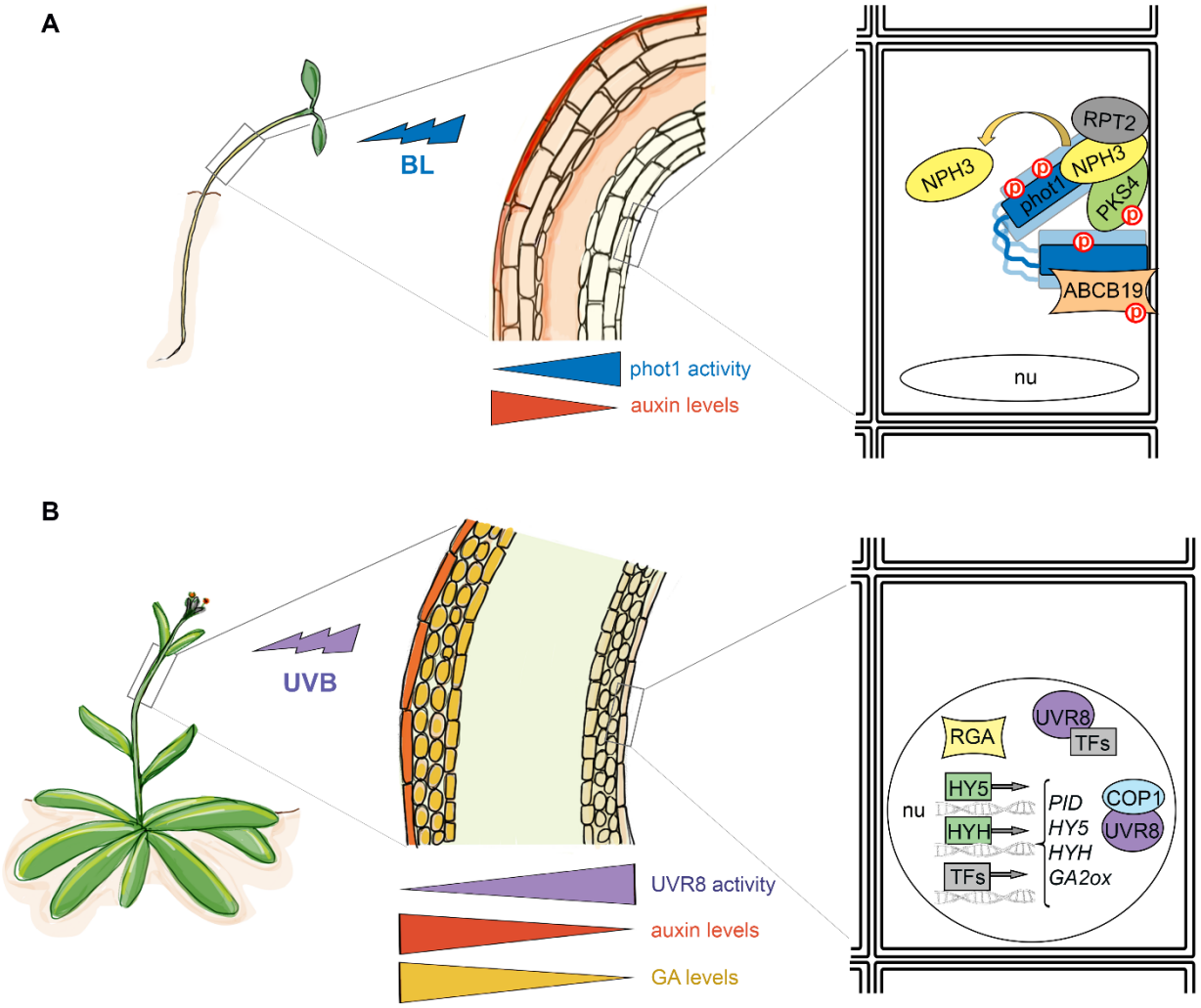


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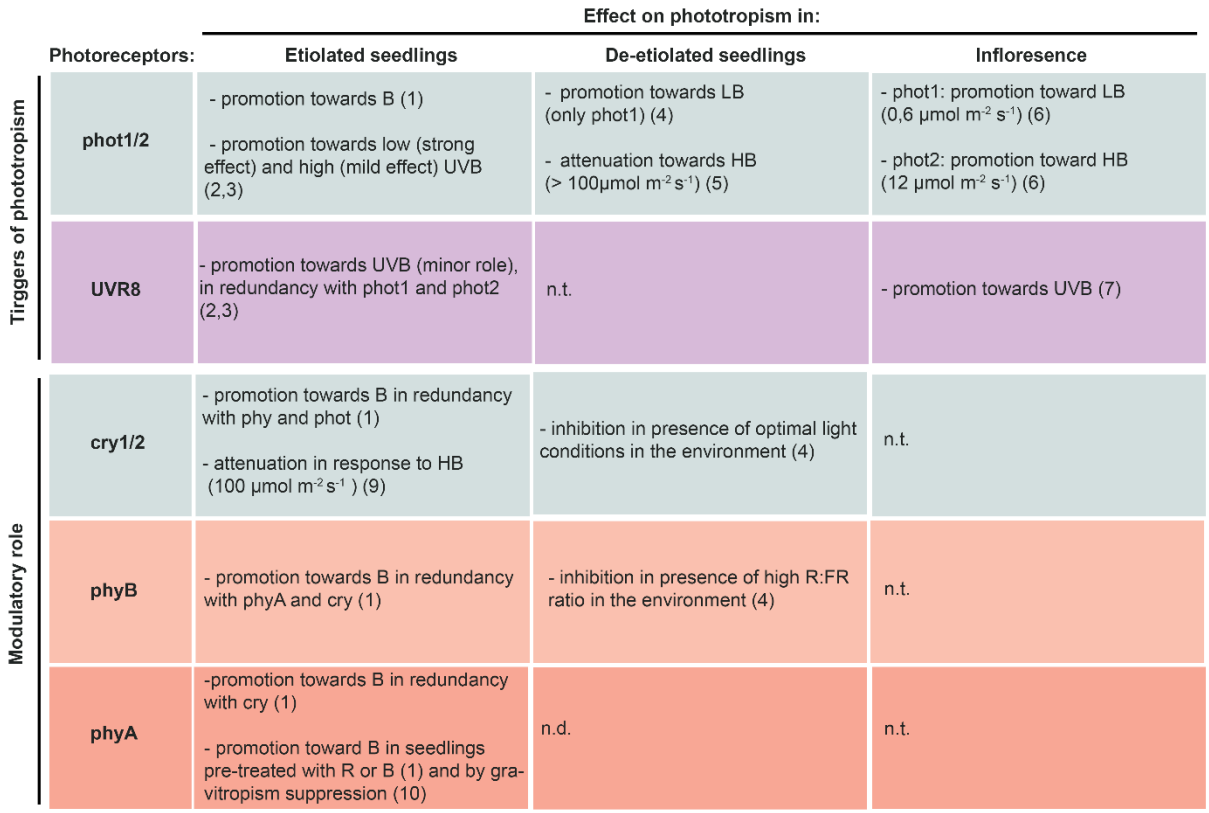


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