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REVIEW

Phototropism in land plants: Molecules and mechanism from light perception to response

Johanna Morrow[1,2], Kyle T. Willenburg[1,2], Emmanuel Liscum (✉)[1,2]

[1] C.S. Bond Life Sciences Center, University of Missouri, Columbia, MO, USA
[2] Division of Biological Sciences, University of Missouri, Columbia, MO, USA

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BACKGROUND: Phototropism is the response a plant exhibits when it is faced with a directional blue light stimulus. Though a seemingly simple differential cell elongation response within a responding tissue that results in organ curvature, phototropism is regulated through a complex set of signal perception and transduction events that move from the plasma membrane to the nucleus. In nature phototropism is one of several plant responses that have evolved to optimize photosynthesis and growth.
OBJECTIVE: In the present work we will review the state of the field with respect to the molecules and mechanisms associated with phototropism in land plants.
METHODS: A systematic literature search was done to identify relevant advances in the field. Though we tried to focus on literature within the past decade (1998-present), we have discussed and cited older literature where appropriate because of context or its significant impact to the present field. Several previous review articles are also cited where appropriate and readers should seek those out.
RESULTS: A total of 199 articles are cited that fulfill the criteria listed above.
CONCLUSIONS: Though important numerous and significant advances have been made in our understanding of the molecular, biochemical, cell biological and physiologic mechanisms underlying phototropism in land plants over the past decade, there are many remaining unanswered questions. The future is indeed bright for researchers in the field and we look forward to the next decade worth of discoveries.

Keywords phototropism, phototropin, phytochrome, crytochrome, auxin, auxin response factor, phosphorylation, ubiquitination, transcriptional control, cell elongation, growth, non-phototropic hypocotyl 3, NPH3/RPT2-like, protein kinase, calcium

Introduction

Plants, being sessile, are rooted in the ground and must make the most out of the environment they find themselves in. As such, plants have evolved multiple mechanisms to optimize their photosynthetic light-capture. One of these mechanisms is phototropism, or a plants ability to bend toward (positive) or away (negative) from a directional blue light (BL) source (Holland et al., 2009; Liscum et al., 2014). In brief, BL perception by the phot (phototropin) photoreceptors (Christie et al., 1998) stimulates the establishment of an asymmetric gradient of the plant hormone auxin within the responsive tissue/organ (Esmon et al., 2006; Went and Thimann, 1937), which in turn leads to a directional growth (Liscum et al., 2014). Here we describe the current state of the field, much of which is derived from work in the model plant *Arabidopsis thaliana*. We will begin our discussion with BL perception; then continue with a discussion of signal transduction, as well as the role of auxin transport, perception and response; and finally end with a discussion of additional modulatory components of the phototropic signal-response pathway.

Phototropin 1 and 2 mediate perception of directional BL

There are two phototropin photoreceptors in land plants; phot1 and phot2. While in *Arabidopsis* each is represented by a single gene (Briggs and Huala, 1999), there has been

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Correspondence: Emmanuel Liscum
E-mail: liscume@missouri.edu

duplication of these genes in some species (Li et al., 2015). In the context of phototropic function, phot1 has been shown to be the primary photoreceptor under low fluence rate (intensity) light, while both phot1 and phot2 act redundantly under moderate to high intensity conditions (Khurana and Poff, 1989; Liscum and Briggs, 1995; Sakai et al., 2001). In addition to the phototropic pathway, the phots act redundantly in a variety of other functions that impact optimization of photosynthesis. These functions include: stomatal opening, chloroplast accumulation and avoidance, cotyledon and leaf movement, as well as leaf flattening and expansion (Jarillo et al., 2001; Kagawa et al., 2001; Kinoshita et al., 2001; Sakai et al., 2001; Ohgishi et al., 2004; Takemiya et al., 2005; Inoue et al., 2008; Han et al., 2013).

The phots undergo a conformational change upon blue light perception that leads to trans/autophosphorylation

Phots contain an N-terminal sensory region and carboxyl-terminal output region (Christie et al., 1998). The sensory region contains two LOV (light, oxygen, and voltage) domains, which in darkness each noncovalently bind a flavin mononucleotide (FMN) cofactor as a chromophore (Christie et al., 1998; Huala et al., 1997); while the output region contains a serine/threonine protein kinase domain (PKD) of the AGCVII subfamily family of protein kinases (Huala et al., 1997; Bögre et al., 2003; Rademacher and Offringa, 2012). The LOV domains represent a subclass of the PAS (Per-Arnt-Sim) domains that are present in proteins of diverse function across a large number of taxa (Crosson et al., 2003; Rojas-Pirela et al., 2018). Within the phots each LOV domain has been shown to have a distinct function: LOV1 has been proposed to be involved in protein di-/multimerization, while LOV2 functions as a molecular light activated switch for repression/de-repression of the PKD (Harper et al., 2004; Salomon et al., 2004; Jones et al., 2007; Nakasako et al., 2008; Sullivan et al., 2008; Tokutomi et al., 2008).

Upon BL absorption, the FMN chromophores becomes covalently attached to a cysteine residue within each LOV domain. Studies of phot proteins lacking the PKD have shown that FMN-cysteinyl adduct formation leads to a progressive conformational change in the protein that moves from the chromophore binding pocket out to an alpha-helix (the Jα-helix, located in the linker region between LOV2 and PKD). In darkness the protein folds in a way to keep the PKD in a repressed/inactive state, whereas conformational changes occurring in response to BL-induced adduct formation leads to de-repression of the PKD and allows for protein trans-/autophosphorylation of the receptor (Christie et al., 1999; Salomon et al., 2000; Inoue et al., 2008; Sullivan et al., 2008). Phot phosphorylation is critical for phototropic signaling (Inoue et al., 2008; Tseng and Briggs, 2010). Though phots can be phosphorylated on multiple Ser/Thr residues, a pair of Ser residues (Ser849 and Ser851 in phot1; Ser761 and Ser763 in phot2) appear most critical with respect to phototropic light perception and signaling (Inoue et al., 2008; Inoue et al., 2011). In the case of phot1, phosphorylation of Ser851 appears essential for phototropic signaling (Inoue et al., 2008). Loss of phosphorylation at either, or both, of the conserved serines in phot2 does not lead to abrogation of phototropism indicating that there are likely additional critical phosphorylation site(s) within phot2 (Inoue et al., 2011).

Trans/autophosphorylation of phot1 leads to receptor internalization

Though phots contain no transmembrane-spanning or membrane insertion domain both are associated with the plasma membrane in darkness, with the carboxyl-terminal portion of the PKD being required for membrane association (Kong et al., 2007; Kong et al., 2013a; Kong et al., 2013b). However, upon BL activation, a portion of the total pool of phot protein becomes internalized from the plasma membrane to cytoplasm (Sakamoto and Briggs, 2002; Kong et al., 2006; Han et al., 2008; Wan et al., 2008). In the case of phot1, it has been shown that this internalization is dependent upon trans-/autophosphorylation (Kaiserli et al., 2009; Sullivan et al., 2010). Interestingly, though phot2 is also internalized in response to BL, trans-/autophosphorylation does not appear necessary (Kong et al., 2006; Aggarwal et al., 2014).

Phototropin internalization: red herring or functionally relevant?

Many plasma membrane proteins, including receptor proteins, are often internalized via a clathrin-dependent endocytic pathway (Doherty and McMahon, 2009). Indeed, phot1 and phot2 interact with heavy and light chain clathrins, respectively (Kong et al., 2006; Kaiserli et al., 2009; Roberts et al., 2011). While it is still unknown precisely where phot1 relocates upon internalization, phot2 has been shown to move from the plasma membrane/cytoplasm to the Golgi (Kong et al., 2006; Aggarwal et al., 2014). It is worth noting that, though a direct connection between the cytoskeleton and phot internalization has yet to be described, BL-induces the formation of new microtubules in hypocotyl cells and that this response is phot-dependent (Lindeboom et al., 2013). Interestingly, phototropism is impaired in plants deficient in Katanin1, a microtubule-servering protein necessary for growth of microtubules (Lindeboom et al., 2013).

Though phots can move from the plasma membrane, it is important to ask: from what compartment does phot signaling occur? Studies of phototropic responsivess have shown that *Arabidopsis* seedlings treated with red light (RL) prior to, or concominant with, stimulation with directional BL exhibit enhanced curvatures relative to seedlings exposed to BL

alone (Janoudi et al., 1992; Janoudi and Poff, 1993; Parks et al., 1996; Janoudi et al., 1997; Stowe-Evans et al., 2001). Han and colleagues (2008) demonstrated that phot1 is retained at the plasma membrane in seedlings pretreated with RL, suggesting that enhanced phototropic responsiveness results from enhanced phot1 signaling from the plasma membrane. More support for plasma membrane-associated phot representing the "functional" receptor comes from a study in which phot1 was irreversibly anchored to the plasma membrane via a myristylation/farnestylation tag (Preuten et al., 2015). When such irreversibly-anchored phot1 was expressed in a *phot1phot2* double mutant the resultant seedlings exhibited a normal phototropic response, implying that internalization may not be necessary for primary signaling; though it might be involved in receptor turnover or recycling (Kong et al., 2006; Aggarwal et al., 2014; Liscum, 2016; Preuten et al., 2015). Indeed, both phots have been shown to be degraded by the 26S proteasome in response to prolonged BL exposure (Roberts et al., 2011; Aggarwal et al., 2014). A recent study by Xue and colleagues (2018) suggests that phot1 signaling may occur within sterol-rich microdomains after BL-induced receptor dimerization and lateral diffusion within the plasma membrane. These observed intra-membrane dynamics are consistent with previous findings (Askinosie, 2016).

NPH3, a phot-interacting protein necessary for the phototropic response

NPH3 (*NON-PHOTOTROPIC HYPOCOTYL 3*) was identified in a screen for non-phototropic mutants and has been shown to be critical for the phototropic bending response (Liscum and Briggs, 1995; Liscum and Briggs, 1996; Motchoulski and Liscum, 1999; Okada and Shimura, 1992). The NPH3 protein is characterized by an N-terminal BTB (*broad complex, tamtrack, and bric a brac*) domain (Stogios et al., 2005), a central 'NPH3 domain' (Pfam, PF03000), and a carboxyl-terminal coiled-coil domain (Motchoulski and Liscum, 1999). The coiled-coil domain of NPH3 has been shown to facilitate interaction with phot1 (Motchoulski and Liscum, 1999) and phot2 (de Carbonnel et al., 2010). In addition to its role in phot-dependent phototropism, NPH3 has been shown to be involved in phot-mediated leaf flattening and petiole positioning (Inada et al., 2004; Inoue et al., 2008;de Carbonnel et al., 2010).

NPH3 is a phosphoprotein in darkness and is rapidly dephosphorylated upon exposure to BL

NPH3 isolated from BL-treated seedlings exhibits an enhanced mobility on SDS-PAGE, relative to protein from seedlings kept in darkness (Motchoulski and Liscum, 1999). Pedmale and Liscum (2007) demonstrated that this BL-dependent mobility shift results from dephosphorylation. The dephosphorylation of NPH3, which appears to occur as the result of a yet unidentified type 1 protein phosphatase, has also been shown to be dependent upon the presence of phot1 (Pedmale and Liscum, 2007). Moveover, blocking dephosphorylation of NPH3 with phosphatase inhibitors also abrogates phototropism under low intensity BL, suggesting that the active signaling state of NPH3 is the dephosphorylated form (Pedmale and Liscum, 2007). However, Haga and colleagues (2015) have provided compelling evidence that the phosphorylated form of NPH3 is necessary for signaling under prolonged high intensity BL conditions.

Tsuchita-Mayama and colleagues (2008) identified 21 potential phosphorylation sites within NPH3 by *in silico* prediction. Unfortunately, no alteration in phototropic responsiveness was observed when any of these predicted phosphorylation sites (serine, threonine, or tyrosine) were mutated rendering them phosphorylation incompetent (Tsuchita-Mayama et al., 2008). If these predicted phosphorylation sits are indeed the native *in vivo* phosphorylation sites these results are consistent with the hypothesis that the dephosphorylated form of NPH3 is the active form. Alternatively, the sites identified *in silico* may not represent the native phosphorylation sites, thus complicating any interpretation of the observed phenotypes.

NPH3 as a substrate adaptor in an E3 ubiquitin ligase complex

Previous studies have shown BTB domain-containing proteins can interact with CUL3 (CULLIN 3) proteins (Stogios et al., 2005; Genschik et al., 2013). *Arabidopsis* contains two CUL3 proteins, CUL3A and CUL3B, which are functionally redundant and a loss-of-function of both proteins results in lethality (Figueroa et al., 2005). However, a *cullin3* hypomorph (designated, $cul3^{hyp}$), which results from a knockout of *CUL3B* and a knockdown of *CUL3A,* is viable and can be used to assess CUL3 function *in planta* (Thomann et al., 2009). Roberts and colleagues (2011) found that $cul3^{hyp}$ seedlings showed a significant reduction in phototropic curvature, while retaining normal gravitropic responsiveness. These findings indicate that CUL3 proteins are not only involved in the phototropic pathway, but that they likely function early in the pathway because the $cul3^{hyp}$ mutations did not impact differential growth generally (Roberts et al., 2011). The authors further showed CUL3 co-localizes and interacts with NPH3 at the plasma membrane (Roberts et al., 2011).

CUL3 constitutes one component of a CRL3 (CULLIN3-RING-LIGASE) complex, a class of E3 ubiquitin ligases (Haglund and Dikic, 2005; Hotton and Callis, 2008; Deshaies and Joazeiro, 2009). Roberts and colleagues (2011) were able to show that phot1 is ubiquitinated and this ubiquitination occurs in a NPH3- and BL-dependent fashion. Given that NPH3 interacts with CUL3 and phot1, the authors concluded

that NPH3 functions as a substrate adapter in a CRL3 complex, $CRL3^{NPH3}$, that targets phot1 for ubiquitination (Roberts et al., 2011). A single ubiquitin at one or more sites, or a chain of polyubiquitin molecules, may be transferred to proteins in the ubiquitination process (Haglund and Dikic, 2005). Intrerstingly, phot1 exhibits both types of ubiquitination but the type depends on the intensity of BL, with phot1 being poly-ubiquitinated in high intensity conditions ($> 1 \mu mol\ m^{-2}s^{-1}$), but mono/multi-ubiquitinated under low intensity conditions ($< 1 \mu mol\ m^{-2}s^{-1}$) (Roberts et al., 2011). Polyubiquitination of phot1 stimulates its 26S proteasome-dependent degradation, likely as a means of response attenuation (Roberts et al., 2011). While the precise mechanistic role of phot1 mono/multiubiquitination remains unknown, it appears that this posttranslational modification may be essential for phototropic responsiveness (Roberts et al., 2011). Recent data suggests that mono/multiubiquitination of phot1 may keep it at the plasma membrane as a signaling competent receptor (Askinosie, 2016).

NPH3 and RPT2 are founding members of a 33-member protein family

Like NPH3, RPT2 (ROOT PHOTOTROPISM 2) was identified by mutant phenotype, though the phenotype is distinguished from that of *nph3* mutants because *rpt2* mutants exhibit diminished phototropism specifically when exposed to moderate to high intenisity ($> 1\ \mu mol\ m^{-2}s^{-1}$) BL (Okada and Shimura, 1992; Sakai et al., 2000; Inada et al., 2004). RPT2 contains an N-terminal BTB domain, a central 'NPH3 domain,' and a carboxyl-terminal coiled-coil similar to NPH3, and together with NPH3 represents a founding member of the NRL (NPH3/RPT2-Like) family of proteins (Pedmale et al., 2010). Of the 33 members of the NRL proteins in *Arabidopsis*, all contain a central 'NPH3 domain,' while some lack the coiled-coil and two do not have a BTB domain (Pedmale et al., 2010). All land plants contain at least one *NRL* gene (Suetsugu et al., 2016; Christie et al., 2017). A NPH3 ortholog in rice, named CPT1 (COLEOPTILE PHOTOTROPISM 1) which contains all three NRL domains, has been identified by mutation and found to exhibit a non-phototropic phenotype of the coleoptile similar to that observed in the *Arabidopsis* hypocotyl (Haga et al., 2005).

While the primary sequence and predicted secondary structures of NRL proteins are similar, their functions vary

As already mentioned RPT2 has been shown to play a role in moderate to high intensity BL-induced phototropism (Sakai et al., 2000). Interestingly, RPT2 appears to regulate the phosphorylation status and membrane association of NPH3 to promote phototropism under high intensity BL condtions (Haga et al., 2015). RPT2 also interacts with phot1, though through its BTB domain rather than coiled-coil (Inada et al., 2004), and has been shown to be involved in leaf flattening, stomatal opening, and chloroplast accumulation responses (Harada et al., 2013; Kozuka et al., 2013; Suetsugu et al., 2016).

Recently, another NRL member, NRL31/NCH1 (NRL PROTEIN FOR CHLOROPLAST MOVEMENT 1), was shown to be involved in phot-mediated chloroplast accumulation (Suetsugu et al., 2016). Quite independently, NRL31 was identified as SR1IP1 (AtSR1Interaction Protein 1) and shown to play a role in plant immunity (Zhang et al., 2014). Interestingly, NRL31/NCH1/SR1IP1 was shown to interact with CUL3A through its BTB domain and act as a substrate adapter in a $CRL3^{NRL31/NCH1/SR1IP1}$ complex involved in ubiquitination of AtSR1 in the pathogenesis response (Zhang et al., 2014). Suetsugu and colleagues (2016) also demonstrated that NRL31/NCH1/SR1IP1 interacts with phot1 through its coiled-coil domain, much as NPH3 does (Motchoulski and Liscum, 1999).

A third member of the NRL family, NRL3/BPH1 (BTB/POZ PROTEIN HYPERSENSITIVE TO ABA 1) has recently been shown to interact with CUL3A through its BTB domain, and appears to negatively regulate the cellular response to the plant hormone abscisic acid (Woo et al., 2018). Woo and colleagues (2018) speculate NRL3/BPH1 may also function in BL responses by the mere presence of the 'NPH3 domain' in this NRL protein. At present there is however no evidence that the 'NPH3 domain' is critical for BL responsivess of NPH3, RPT2 or NRL31/NCH1/SR1IP1.

NRL20 has been characterized to function in organ development and was independently named NPY1 (NAKED PINS IN YUCCA 1), ENP1 (ENHANCER OF PINOID 1), and MAB4 (MACCHI-BOU 4) to reflect its mutant phenotypes (Treml et al., 2005; Cheng et al., 2007; Furutani et al., 2007). NRL2/NPY1/ENP1/MAB4 and four additional NRL proteins (NRL6, NRL7, NRL21, and NRL30) form the NPY sub-clade of the NRL family (Cheng et al., 2008). The genes encoding these proteins have been shown to have overlapping expression patterns, and NRL20/NPY1/ENP1/MAB4, NRL7/NPY3, and NRL30/NPY5 have each been implicated in organogenesis (Cheng et al., 2008). Interestingly, the AGCVIII kinases PID (PINOID), PID2, WAG1 (WAVY ROOT GROWTH) and WAG2, which are in the same sub-family as phot1 and phot2 (Rademacher and Offringa, 2012), have been shown to be involved in NRL/NPY-regulated organogenesis (Bennett et al., 1995; Christensen et al., 2000; Cheng et al., 2008). More recently, the NPY's have been shown to be involved in yet another response mediated by auxin; namely, root gravitropism (Li et al., 2011).

Two other NRL members have been shown to regulate functions linked to auxin. First, auxin is known to be a key regulator in vascular development (Zhao, 2010) and NRL23/DOT3 (DEFECTIVELY ORGANIZED TRIBUTARIES 3) was identified in a mutant screen for seedlings defective in

vein patterning (Petricka et al., 2008). Second, NRL8/SETH6 (named after the brother and murderer of the Egyptian fertility god Osiris) was also identified in a screen for mutants with altered pollen germination (Lalanne et al., 2004), which can also be regulated by auxin (Zhang and ONeill, 1993). Each of thse auxin- and NRL-dependent responses may or may not involve AGCVIII Kinases (Cheng et al., 2008; Rademacher and Offringa, 2012).

PKS proteins are important regulators of phototropsim

PKS1 (PHYTOCHROME KINASE SUBSTRATE 1) was initially identified as a protein that interacts with both the red (P_r) and far-red absorbing (P_{fr}) forms of phytochrome, and can be directly phosphorylated by phyA (phytochrome A) to negatively regulate signaling (Fankhauser et al., 1999). Two additional members of the four member of the PKS protein family, PKS2 and PKS4, also interact with phyA (Lariguet et al., 2003; Lariguet and Dunand, 2005; Schepens et al., 2008).

PKS1, PKS2, and PKS4 have all been shown to be important for phototropic signaling. For example, plants lacking these PKS proteins exhibit a loss of phototropic responsiveness, with the strength of the phenotype being correlated with the number of genes simultaneously mutated (Lariguet et al., 2006). Morover, studies by Demarsey and colleagues (2012) have shown that PKS4 is a direct substrate of the phot1 PKD. While phosphorylation of PKS4 is not a prerequisite for phototropic responsiveness, it does appear to be important in response attenuation (Demarsy et al., 2012). Indeed, a recent study by Schumacher and colleagues (2018) has shown that while unphosphorylated PKS4 functions as a positive regulator of phototropism under low intensity BL conditions, in response to high intensity BL phot1-mediated phosphorylation of PKS4 represses responsiveness. PKS1 is a plasma membrane-associated protein in both dark and light conditions, and it physically interacts with both phot1 and NPH3, suggesting that these three proteins might form a complex (Lariguet et al., 2006). Interestingly, PKS2 also functions in phot- and NPH3-dependent leaf flattening and positioning responses (de Carbonnel et al., 2010).

Cytosolic calcium is a possible intermediary signal within the phototropic pathway

Baum and colleagues (1999) described a phot-dependent cytosolic calcium influx in response to BL. While this calcium influx occurs coincident with phototropism (Babourina et al., 2004), pharmacological studies failed to link the two responses (Folta et al., 2003). Instead the calcium influx is likely important for phot1-dependent hypocotyl growth inhibition (Folta et al., 2003). More recently, it has been shown that the influx of calcium is necessary for phot2-dependent phototropism in high intensity BL (Zhao et al., 2013).

An increase in cytosolic calcium can come from either the extracellular space or from intracellular compartments such as the vacuole (Sanders et al., 2002). Harada and colleagues (2003) have shown that action of both phot1 and phot2 is needed for BL-induced increase of cytosolic calcium. Under low intensity BL where only phot1 is active, calcium enters the cell from the extracellular space by means of plasma membrane-localized calcium channels, while in higher intensity BL where both phot1 and phot2 are active, there is additional influx of calcium to the cytoplasm from internal stores (Harada and Shimazaki, 2007).

As will be discussed later, the plant hormone auxin is critical for plant development (Zhao, 2010). It has been shown that upon BL exposure, a lateral redistribution of auxin occurs, leading to the bending response (Esmon et al., 2006). One of the auxin transporters involved in this redistribution is PIN1 (PIN-FORMED 1), which is regulated by the AGCVIII protein kinase PID (Blakeslee et al., 2004; Friml et al., 2004). Benjamins and colleagues (2003) found that PID can physically interact with two proteins involved in calcium binding: TCH3 (TOUCH3), a calmodulin-related protein, and AtPBP1 (PID-BINDING PROTEIN 1), a calcium binding protein. These findings are consistent with a hypothesis that increases in cytosolic calcium play a role in the phototropic response. Previous work had already identified the crosstalk between auxin and calcium signaling. In maize a differential gradient of calcium is established across the coleoptile in response to BL exposure, similar to what has been observed for auxin (Felle, 1988; Gehring et al., 1990). An interaction between PKS1 and CAM4 (Calmodulin 4) has been suggested by Zhao and colleagues (2013) as a possible link between auxin, calcium, and phot signaling.

EHB1 and ADG12 are NPH3-interacting proteins involved in the phototropic response

EHB1 (ENHANCED BENDING 1) was identified as an NPH3-interacting protein via a yeast three-hybrid assay and confirmed by co-immunoprecipitation (Knauer et al., 2011). Interestingly, loss-of-function *ehb1* mutants show an increased phototropic and gravitropic responses. EHB1 was shown to preferentially interact with the BTB domain containing N-terminal of NPH3. This suggests that EHB1 may compete with CUL3 for binding to the NPH3 BTB domain.

EHB1 contains an N-terminal C2/CaLB (calcium-dependent lipid-binding) domain, while the carboxyl terminal region shows homology to the ARF-GAP (ADP-RIBOSYLATION FACTOR GTPase-ACTIVATING PROTEIN) family but lacks the GTPase domain (Knauer et al., 2011; Rodriguez et al., 2014; Dummer et al., 2016). Interestingly,

loss-of-function alleles in a *ADG12*, a member of the ARF-GAP family that shows high sequence similarity to EHB1, exhibit reduced, rather than enhanced, phototropic and gravitropic responses (Knauer et al., 2011; Dummer et al., 2016; Michalski et al., 2017). Like EHB1, ADG12 has been shown to physically interact with NPH3 (Dummer et al., 2016; Michalski et al., 2017).

Since EHB1 and ADG12 both contain a C2/CaLB calcium binding domain, it was important to determine what, if any, connection exists between these proteins and calcium in the regulation of both gravitropic and phototropic responses. Though exogenous addition of calcium affected both gravitropic and phototropic responses in wild-type seedlings, only the gravitropic response was impacted by addition of exogenous calcium to *ehb1* and *adg12* mutants (Dummer et al., 2016; Michalski et al., 2017). This led the researchers to conclude that phototropic signaling through EHB1 and ADG12 is not mediated by calcium (Dummer et al., 2016; Michalski et al., 2017).

A potential role for heterotrimeric G proteins in phototropism

Heterotrimeric G protein complexes are found in a variety of eukaryotic organisms and consist of three subunit proteins: Gα, Gβ, and Gγ (Urano et al., 2013). An *Arabidopsis* Gβ (AGB1) has been shown to physically interact with the N-terminal region of NPH3 (Kansup et al., 2014). Interestingly, an *agb1* loss-of-function mutant shows a reduction in phototropic response (Kansup et al., 2014), though further studies are necessary to connect G proteins to the overall phot-dependent signaling pathway discussed here.

Protein phosphatases have a variety of functions in phototropism

As mentioned earlier, an as yet identified type 1 protein phosphatase (PP1) appears responsible for the BL-induced phot-dependent dephosphorylation of NPH3 (Pedmale and Liscum, 2007). Interestingly, mutants defective in RCN1 (ROOT CURLING IN N-NAPHTHYLPHTHALAMIC ACID 1), a subunit of type 2A protein phosphatase (PP2A), have been shown to exhibit enhanced phototropic bending, as well as increased stomatal opening response (Tseng and Briggs, 2010). RCN1 has been shown to interact with the N-terminal portion of phot2 and dephosphorylate phot2. In contrast, *rcn1* mutations have no impact on phot1-mediated responses (Tseng and Briggs, 2010).

Auxin and auxin response: Sites of signal integration

As previously mentioned, the plant hormone auxin is a critical regulator of plant development and is involved in many different growth responses, including tropic responses. In the absence of tropic stimulation auxin synthesized at the tip of the hypocotyl/coleoptile is transported by several different proteins in a polar manner. However, upon tropic stimulation, polar auxin transport is supplemented by new lateral transport across the seedlings (Ha et al., 2010; McSteen, 2010; Peer et al., 2011), which in turn mediates differential growth as has been described by the Chlodony-Went hypothesis (Went and Thimann, 1937; Liscum et al., 2014).

The predominat naturally-occurring auxin, indole-3-acetic acid (IAA), exists in one of two ionization states depending upon where it is found in the cell: a deprotonated form (IAA^-) is found in the neutral cytoplasm, while a protonated form (IAAH) is found in the more acidic inter-cellular cell wall space. This differential ionization means that IAA can enter a cell by either passive diffusion or facilitated transport, but can only leave the cell through active transport. Facilitated influx of auxin is mediated by the AUX1/LAX (AUXIN RESISTANT 1/LIKE AUX1) proteins (Bennett et al., 1996; Zazímalová et al., 2010), whereas auxin efflux is mediated by two classes of protein transporters, the PIN (PIN-FORMED) and ABCB (ATP-BINDING CASSETTE, B-TYPE)/MDR (MULTI-DRUG RESISTANCE)/PGP (P-GLYCOPROTEIN) (Zazímalová et al., 2010).

Facilitated auxin influx and phototropism

While *aux1/lax* mutants exhibit clear defects in gravitropism, phototropic responses have generally been reported to be normal (Bennett et al., 1996; Parry et al., 2001). However, Stone and colleagues (2008) demonstrated that AUX1-facilitated auxin influx is required for phototropism when plants are compromised in auxin responsiveness through mutation of the ARF7 (AUXIN RESPONSE FACTOR 7)/NPH4 (NON-PHOTOTROPIC HYPOCOTYL 4) transcriptional regulator (see later discussion).

Active auxin efflux and phototropism

As already introduced, auxin efflux from a cell requires the action of PIN and ABCB transporters. The PIN family in *Arabidopsis* is comprised of eight members that form two classes of proteins: the long PINs (PIN1, PIN2, PIN3, PIN4 and PIN7) and the short PINs (PIN5, PIN6 an PIN8). The short PINs have been shown to localize to the ER membrane, whereas the long PINs are found in the plasma membrane (Bennett, 2015). PIN1 is primarily polar-localized within the cell and is critical for auxin efflux in shoots, while PIN2 shows similar intracellular localization patterns but functions primarily in roots (Grunewald and Friml, 2010). The PINs have been shown to function in many plant growth and developmental responses (Bennett, 2015). Relative to phototropism, PIN3 appears critical for responsiveness of shoot tissues since *pin3* mutants exhibit a moderate loss-of-function

phenotype (Friml et al., 2002). Interestingly, BL induces a phot1-dependent lateral relocalization of PIN3 protein that precedes the phototropic response (Friml et al., 2002; Ding et al., 2011). Wan and colleagues (2012) have shown that BL-induced phot1-dependent relocalization of PIN2 is important for phototropism in roots.

Unlike the PIN proteins involved in tropic responses, ABCB transporters appear not to be polarly localized (Cho et al., 2007; Lewis et al., 2007). Only mutants deficient in ABCB19 exhibit a phototropic phenotype that differs from wild-type seedlings; namely an enhanced response (Noh et al., 2003; Nagashima et al., 2008). Christie and colleagues (2011) found that ABCB19 is a target of the phot1 PKD and that phosphorylation of ABCB19 inhibits its auxin efflux activity. Additionally, in etiolated seedlings it has been shown that ABCB19 inhibits PIN1 cycling, thus keeping PIN1 polarly localized (Titapiwatanakun et al., 2009). Additional research is necessary to clarify the role of ABCB19 in phot-dependent phototropism.

Regulation of PIN proteins involves intracellular cycling, phosphorylation and members of the AGCVIII protein kinase family

D6PK (D6PROTEIN KINASE), a member of the AGCVIII protein kinase family, has been shown to be polarly localized and necessary for polar auxin transport (Zourelidou et al., 2009). Interestingly, D6PK can phosphorylate long PINs, resulting in increased PIN activity at the plasma membrane (Zourelidou et al., 2009). D6PK has also been implicated in phototropic signal transduction as seedlings lacking this protein exhibit reduced phototropic responsiveness (Willige et al., 2013). Whereas D6PK appears necessary for both pulse-induced (first positive) and time-dependent (second positive) phototropic responses, another previously uncharacterized AGCVIII member, AGC1-12, appears necessary only for pulse-induced phototropism (Haga et al., 2018). Like D6PK, AGC1-12 can directly phosphorylate PIN1, and does so with the same phosphorylation site preference (Haga et al., 2018).

PID, another member of the AGCVIII family, has been shown to regulate cycling of PIN proteins between the apical and basal locations within cells (Friml et al., 2004). PID directly phosphorylates PIN1, and may phosphorylate other long PINs, providing a switch for polar relocalization within the cell (Huang et al., 2010). Ding and colleagues (2011) have shown that in seedlings lacking PID, as well as WAG1 and WAG2 (two related AGCVIII members; Santer and Watson, 2006), PIN3 fails to relocalize in response to BL exposure. Furthermore, the *pidwag1wag2* triple mutant seedlings also exhibited a lack of phototropic response, implicating the involvement of these protein kinases along with PIN proteins in the lateral redistribution of auxin leading to the phototropic response (Ding et al., 2011).

In addition to cycling between the apical and basal locations within the cell, PIN proteins have also been shown to be recycled from the plasma membrane to the Golgi by the action of GNOM, an ARF-GEF (ADP RIBOSYLATION FACTOR-GUANINE EXCHANGE FACTOR) (Geldner et al., 2003b). Interestingly, seedlings homozygous for *gnom*^{R5}, a partial loss-of-function allele, display a defect in their phototropic responsiveness (Gelder et al., 2003a), implying that GNOM-dependent recycling of PIN proteins is necessary for the auxin redistribution that precedes phototropic bending (Ding et al., 2011).

Auxin perception and response in phototropism

As described above, phot1 initiates a set of molecular signaling events that lead to the formation of an auxin gradient within the responding organ, which is prerequisite to phototropism. Auxin perception is necessary to transduce the BL-induced auxin gradient into differential growth—phototropic curvature. Of the systems of auxin perception that have been described to date, the nuclear-localized SCF$^{TIR1/AFB}$-Aux/IAA co-receptor complex is by far the most well understood and thus far only one clearly linked to phototropism (Harper et al., 2000; Grones and Friml, 2015; Dezfulian et al., 2016; Lavy and Estelle, 2016; Strader and Zhao, 2016).

Like the CRL3 complexes we have already discussed, the SCF$^{TIRT1/AFB}$ portion of the auxin co-receptor is an E3 ubiquitin ligase (Chen and Hellmann, 2013). However, unlike the CRL3′s which are comprised of a CUL3, a RING protein (RBX1, RING-BOX PROTEIN 1), an E2 subunit and a BTB protein as the CULLIN-interacting protein and substrate adaptor, the SCF$^{TIR1/AFB}$ complex substitutes CUL1 for CUL3, and replaces the BTB protein with two proteins: SKP1 (S-PHASE KINASE-ASSOCIATED PROTEIN 1)/ASK1 (Arabidopsis SKP1-LIKE 1) as the CULLIN-interacting protein, and a TIR1 (TRANSPORT INHIBITOR RESISTANT 1)/AFB (AUXIN SIGNALING F-BOX) as a substrate adapter and auxin-interacting protein. Auxin 'perception' occurs when auxin forms a kind of molecular glue between an Aux/IAA (Auxin/Indole-3-Acetic Acid) protein and TIR1/AFB portions of the SCF$^{TIR1/AFB}$-Aux/IAA co-receptor complex (Chen and Hellmann, 2013; Lavy and Estelle, 2016). As such, auxin binding facilitates the interaction of the SCF$^{TIR1/AFB}$ and Aux/IAA proteins, leading to ubiquitination of the Aux/IAA protein and its subsequent 26S proteasome-dependent degradation (Dezfulian et al., 2016; Lavy and Estelle, 2016; Strader and Zhao, 2016).

In the absence of bound auxin the Aux/IAA proteins function as transcriptional repressors, by interacting with and inhibiting the action of a class of transcription factors, the ARFs (AUXIN RESPONSE FACTOR) (Liscum and Reed, 2002; Guilfoyle, 2015). ARFs are found bound to promoters of genes containing one or more AuxRE (auxin response

element; typically TGTCTC) (Ulmasov et al., 1997) via an N-terminal DNA binding domain (Boer et al., 2014; Guilfoyle, 2015). In *Arabidopsis* there are 29 Aux/IAAs (Kim et al., 1997; Liscum and Reed, 2002;Guilfoyle, 2015) and 23 ARFs (Okushima et al., 2005), and these two classes of proteins can form both hetero- (ARF-Aux/IAA) and homo- (ARF-ARF and Aux/IAA-Aux/IAA) di/multimers through electrostatic interactions of their shared carboxyl-terminal located PB1 domain, historically referred to as domain III/IV (Han et al., 2014; Korasick et al., 2014; Guilfoyle, 2015). The sensitive $SCF^{TIR1/AFRB}$-dependent auxin-regulation of Aux/IAA protein abundance, together with the multitude of potential interactions between Aux/IAA and ARF proteins, provides a dynamic range of control over auxin-regulated gene expression.

Relative to phototropism, one ARF appears to have the predominate role, namely ARF7/NPH4 (Liscum et al., 2015). ARF7/NPH4 was first associated with phototropism through a forward-genetic screen for aphototropic mutants; the same screen that identified critical alleles of *phot1* and *nph3* (Liscum and Briggs, 1995; Liscum and Briggs, 1996). Unlike *phot1* and *nph3* loss-of-function mutants that are deficient in phototropism but retain normal gravitropic responsiveness (Liscum and Briggs, 1995; Liscum and Briggs, 1996), *arf7/nph4* mutants are defective in both tropic responses (Liscum and Briggs, 1996; Stowe-Evans et al., 1998). These initial findings are now consistent with what we know about the function of the encoded wild-type proteins: phot1 and NPH3 function in the perception and early transduction of BL signals leading specifically to phototropism, while ARF7/NPH4 regulates the transcriptional response to differential auxin accumulation established upon tropic stimulation, be that photo- or gravitropic stimulation (Liscum et al., 2015). Not surprisingly, additional *arf7* alleles were independently identified in screens for mutants lacking curvature in response to exogenously-applied auxin (the *msg1*, or *massugu1* mutants; Watahiki and Yamamoto, 1997), as well as in screens for mutants resistant to auxin transport inhibitors (the *tir5*, or *transport inhibitor resistant5* mutants; Ruegger et al., 1997).

Not surprisingly given the large number of ARF proteins encoded by the *Arabidopsis* genome, ARF7/NPH4 is not the only ARF involved in phototropism. Null alleles of *arf7/nph4* are conditional; if seedlings are grown in the presence of ethylene or pre-treated with RL prior to exposure to unilateral BL a partial phototropic response is observed (Liscum and Briggs, 1996; Harper et al., 2000; Stowe-Evans et al., 2001). It appears that ARF19, whose expression is transcriptionally upregulated by ethylene (Li et al., 2006), is the redundant ARF operating when ethylene suppresses the *arf7/nph4* aphototropic phenotype (Stone et al., 2008). Though no redundant ARF has yet to be reported for the RL-induced recovery of phototropism in *arf7/nph4* null mutants, Stone and colleagues (2008) reported the identification of a locus, *MAP2* (*MODIFIER OF ARF7 PHENOTYPES 2*) that may encode this ARF.

As introduced above, it is the auxin-induced degradation of an Aux/IAA protein that truly links ARF activity to environmental cues; cues like unilateral BL that lead to the differential accumulation of auxin (Liscum et al., 2014). The primary Aux/IAA protein involved in ARF-dependent regulation of phototropism is IAA19/MSG2 (MASSUGU 2) (Tatematsu et al., 2004). IAA19/MSG2 and ARF7/NPH4 directly interact and dominant *iaa19/msg2* mutations that stabilize the IAA19/MSG2 protein, even in the presence of auxin, result in a aphototropic phenotype similar to loss-of-function *arf7/nph4* null mutants (Tatematsu et al., 2004). As is the case with the ARFs, there appear to be partially redundant Aux/IAA proteins that can also function in phototropic regulation. To date, two additional Aux/IAA proteins have been associated with ARF-dependent phototropism; namely, IAA1/AXR5 (AUXIN RESISTANT 5) (Park et al., 2002) and IAA29 (Sun et al., 2013). Interestingly, both IAA19/MSG2 and IAA29 expression is upregulated by the action of two phytochrome-responsive transcription factors, PIF4 (PHYTOCHROME-INTERACTING FACTOR 4) and PIF5 (Sun et al., 2013). We will discuss phytochromes as modulators of phot-dependent phototropism in the following section.

While much has been learned about how perceived directional light cues lead to differential auxin accumulation in the responding organ, much less is known about the specific genes induced in response to ARF action that encode proteins causative for the differential cell elongation leading to phototropic curvature. What is known comes largely from the work of Esmon and colleagues (2006) who utilized a *Brassica oleracea* split-hypocotyl system to identify eight *TSI* (*TROPIC STIMULUS-INDUCED*) genes: *EXP1 (EXPANSIN 1)* and *EXP8* (Sampedro and Cosgrove, 2005); *GH3.5 (*for *Glycine max hypocotyl 3.5)/WES1 (WESO 1)* (Park et al., 2007) and *GH3.6/DFL1 (DWARF IN LIGHT 1)* (Nakazawa et al., 2001); *SAUR50 (SMALL AUXIN UPREGUATED RNA 50)* (Ren and Gray, 2015); *HAT2 (HOMEOBOX-LEUCINE ZIPPER of Arabidopsis thaliana 2)* (Sawa et al., 2002); *SKS1 (SKU5 SIMILAR 1)* (Borner et al., 2003); and *BHLH134 (BASIC HELIX-LOOP-HELIX 134)/PRE1 (PACLOBUTRAZOL RESISTANCE 1)/BNQ2 (BANQUO 2)* (Lee et al., 2006; Carretero-Paulet et al., 2010; Pires and Dolan, 2010; Mara et al., 2010). Each of these *TSI* genes exhibits four traits consistent with them being auxin and ARF-induced, and involved in the regulation of phototropic responsiveness: First, their mRNAs accumulate in the region of the hypocotyl where auxin accumulates upon phototropic stimulation. Second, mRNA accumulation occurs concomitant with, or prior to, the development of curvature. Third, each of these genes contains at least one AuxRE within its promoter and its expression in *Arabidopsis* is dependent upon auxin and ARF7/NPH4. Forth, each gene encodes a protein whose known function(s) fit with a model of auxin-regulated growth (Esmon et al., 2006; Liscum et al., 2014). Two pairs of

TSI genes, the *EXPs* and *GH3s*, are of particular interest relative to potential functional links to phototropism.

EXP1 and *EXP8* encode members of the α-EXPANSIN family that mediate cell wall extension at low pH (Sampedro and Cosgrove, 2005). Auxin accumulation in the flank of the hypocotyl opposite to the BL stimulus not only induces the accumulation of *EXP1* and *EXP8* mRNAs in that region (Esmon et al., 2006), but would be expected to activate plasma membrane–localized H^+-ATPase activity in that region as well (Rayle and Cleland, 1970; Rayle and Cleland, 1992; Sauer and Kleine-Vehn, 2011; Scherer, 2011). Thus, the region of increased EXP protein expression should overlap with localized cell wall acidification, precisely where elongation that causes curvature occurs. Consistent with this hypothesis mRNAs of both *EXP1* and *EXP8* exhibit appropriate differential accumulation well before any visible curvature occurs (Esmon et al., 2006).

Unlike the *EXPs*, *GH3.5/WES1* and *GH3.6/DFL1*, accumulate not prior to, but coincident with, establishment of curvature (Esmon et al., 2006). In fact, the mRNAs of these *GH3s* accumulate with a time course similar to the development of phototropic curvature and reach maximal levels at about the time the curvature ceases (Esmon et al., 2006). These patterns of expression suggest that GH3.5/WES1 and GH3.6/DFL1 aren't likely regulating the initiation of cell elongation, but rather may play a role in response attenuation. The fact that these *GH3*s encode IAA-amido synthetases that conjugate free IAA primarily into an IAA-Asp conjugate (an inactive auxin) (Staswick et al., 2005; Park et al., 2007), and their protein abundances would be expected to exhibit a similar temporal pattern, though trailing, of the mRNAs, is consistent with this hypothesis. Further studies are needed to directly test these aforementioned hypotheses.

Phytochromes as modulatory photoreceptors of phototropism

As discussed in detail above, the phots function as the primary photoreceptors responsible for perception of directional BL that initiates signaling events leading to phototropic curvature. Yet, phot-dependent phototropism can be modulated by the phy family of RL/FR (far-red light) photoreceptos (Liscum et al., 2014). In *Arabidopsis* there are five phys, phyA-E (Clack et al., 1994). These five phys form two 'pools' of phy protein: the light-labile phy, represented solely by phyA; and the light-stable phy, which are represented by the remaining phys (phyB-E) (Fankhauser, 2001). While each phy can modulate unique or shared responses, as a group they mediate many important responses, including: germination, de-etiolation, gravitropic growth orientation, shade avoidance, stomatal development, circadian clock entrainment, and photoperiodic flowering (Fankhauser, 2001; Franklin and Quail, 2010; Kami et al., 2010). Though both phyA and phyB can also modulate phot-dependent phototropism, we will focus our attention on phyA as it appears to be the dominant player (Janoudi et al., 1992; Janoudi and Poff, 1993; Parks et al., 1996;Janoudi et al., 1997; Stowe-Evans et al., 2001; DeBlasio et al., 2003; Lariguet and Fankhauser, 2004; Whippo and Hangarter, 2004;Rosler et al., 2007; Tsuchida-Mayama et al., 2010; Kami et al., 2012; Hughes, 2013).

Seedlings that are exposed to RL prior to, or concomitant with, unilateral BL, exhibit enhanced phot-dependent phototropism (Janoudi et al., 1992; Janoudi and Poff, 1993; Parks et al., 1996; Janoudi et al., 1997;Stowe-Evans et al., 2001). While this is clearly a phyA-dependent RL response the mechanistic underpinnings of this enhancement, and other phy-dependent modulatory effects on phot-dependent phototropism, remain largely unknown. Studies on the intracellular localization of phyA, and the development of genetic lines that influence phyA localization, have however provided some potential clues. phyA is abundant in the cytosol in darkness, and upon light perception quickly translocated into the nucleus (Fankhauser, 2001; Franklin and Quail, 2010; Kami et al., 2010). Rosler and colleagues (2007) have found that light-dependent translocation of phyA fails to occur in a double mutant lacking the *FHY1 (FAR-RED ELONGATED HYPOCOTYL 1)* and *FHL (FHY1-LIKE)* proteins. Though several phyA-dependent responses were impaired in the *fhy1fhl* double mutant, multiple others were normal, suggesting that both nuclear and cytoplasmic phyA have signaling capacity (Rosler et al., 2007). Kami and colleagues (2012) have concluded that nuclear-localized phyA is critical for phot-dependent phototropism, likely occurring through regulation of gene expression via PIF4 and PIF5. However, Rosler and colleagues (2007) have also provided evidence for a cytoplasmic function for phyA in the RL-induced enhancement of phot-dependent phototropism.

How might cytoplasmic phyA modulate phot-dependent phototropism? As mentioned earlier, Han and colleagues (2008) found that RL pulses given prior to low intensity unilateral BL not only results in enhancement of phototropism in dark-grown seedlings, but that is also prevents the movement of phot1 from the plasma membrane. Because both phyA and phot1 can interact with PKS1 (Fankhauser et al., 1999; Lariguet et al., 2006; Kami et al., 2014), it is possible the influences of phyA on phot1 are occurring directly at the plasma membrane. Intriguingly, phots and phys have been shown to directly interact in lower plants. For example, in the moss *Physcomitrella patens*, PHY4 (the phyA ortholog) was shown to interact with phots (Hughes, 2013). Phototropism in ferns and algae is mediated by a chimeric phot-phy photoreceptor known as neochrome (Nozue et al., 1998; Suetsugu, 2005). Though direct native phot-phyA interaction has yet to be demonstrated in land plants, Jaedicke and colleagues (2012) have shown that *Arabidopsis* phot1 and phyA can interact at the plasma membrane when transiently expressed in onion epidermal cells as split-YFP proteins. If phyA-dependent enhancement of phototropism

occurs through direct phyA-phot interaction, results from Sullivan and colleagues (2016) indicate that it must occur in tissues other than the epidermis.

Cryptochromes as modulatory photoreceptors of phototropism

Crys (cryptochromes) are an additional class of BL-absorbing flavoprotein photoreceptor belonging to the cry/photolyase superfamily found in all taxa from bacteria to plants to humans (Chaves et al., 2011; Liu et al., 2016; Sancar, 2014). The crys share sequence homology with the photolyases but have no photolyase activity. In *Arabidopsis* there are two well characterized crys, cry1 and cry2, that have been implicated in many developmental responses during the lifecycle of plants such BL-induced hypocotyl growth inhibition (Ahmad and Cashmore, 1993) and photoperiod-induced flowering time (Ahmad et al., 1998; Chaves et al., 2011; Liu et al., 2016).

A number of studies have demonstrated roles for crys in the modulation of phot-dependent phototropism (Lascève et al., 1999; Whippo and Hangarter, 2003; Ohgishi et al., 2004; Nagashima et al., 2008; Liu et al., 2016). Notably, Tsuchida-Mayama and colleagues (2010) found that *cry1, cry2, phyA* and *phyB* single and multiple mutants showed defects in high intensity BL-induced phototropism and transcriptional activation of *RPT2*. These results suggest that crys, together with phyA and phyB, may regulate phototropism by modulating *RPT2* expression, which is a known regulator of phot-dependent phototropism (Inada et al., 2004). The auxin efflux carrier ABCB19 has also been shown to be regulated by crys and phys (Nagashima et al., 2008), representing another route that these modulatory photoreceptors may influence phototropism. Though we have learned much there is still a lot to be discovered. The coming years should indeed be an exciting time to study a response that Darwin himself wrote extensively about (Darwin, 1880).

Concluding thoughts

As should now be clear, the phototropic response, though a relatively simple physiological differential growth response, is regulated in complex and interesting ways. Multiple photoreceptors are involved in regulating this response, from phots acting as primary detectors of directional BL, to phys and crys modulating responsiveness of phots under both BL and RL/FR conditions. Signaling from the photoreceptors involves small molecules (e.g., Ca^{2+}) and protein modulators, and considerable post-translational modifications to receptors and signaling molecules. The regulation of hormone (auxin) transport and response ultimately ties it all together to change cell elongation patterns resulting in organ curvatures.

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