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Phototropism: Translating Light into Directional Growth

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Abstract page

Phototropism allows plants to align their photosynthetic tissues with the incoming light. The direction of incident light is sensed by the phototropin family of blue light photoreceptors (phot1 and phot2 in *Arabidopsis*) which are light activated protein kinases. The kinase activity of the phototropins and phosphorylation of residues in the activation loop of their kinase domain are essential steps for the phototropic response. Nevertheless, it remains rather poorly understood how these initial steps are connected to the formation of an auxin gradient across the hypocotyl which, once established, results in asymmetric growth through a series of steps that are starting to be elucidated.

In this review we cover the major steps leading from light perception to the directional growth response concentrating on *Arabidopsis*. In addition we highlight links connecting the different steps.

Key words: *Arabidopsis thaliana*, phototropism, phototropin 1, auxin transport, auxin receptors, phosphorylation, asymmetric growth.

Introduction

Plants are sensitive to different environmental stimuli including light related cues. Amongst these and fundamental to optimize the positioning of its photoactive tissue plants perceive the direction of incoming blue light and align their growth accordingly. This so called phototropic response was already noticed in the antique but only in the 19th century Darwin proposed that it is a light-mediated active response of the plant involving a transmissible substance. This substance was later on identified as the phytohormone auxin. According to the still prevailing hypothesis formulated by Cholodny and Went in the late 1920s, auxin forms a lateral gradient causing this differential growth response (see Whippo and Hangarter, 2006 for a comprehensive review on the history of phototropism research).

The current understanding of phototropism suggests that the response is mediated by the following chain of events: (i) Incoming blue light is perceived by membrane associated photoreceptors (phototropins), (ii) light perception triggers a signal transduction chain that (iii) leads to the formation of a lateral auxin gradient, (iv) auxin is perceived and (v) triggers signaling networks that (vi) control asymmetrical cell elongation and cell growth, ultimately leading to bending of the hypocotyl towards a light source (Fig.1).

In the following we are going to give a detailed overview on the current state of research for these steps. We thereby focus on phototropism in *Arabidopsis* *thaliana* and disregard other aspects of photomorphogenesis as well as other phototropin-mediated responses such as stomatal opening or chloroplast movements (Christie, 2007; Kami et al., 2010). We aim at highlighting the connection between the different steps and thereby show the connection between fields covering different aspects of the phototropic response.

Fig. 1: Schematic view on the phototropic response from light perception to organ bending. Factors that have been shown to be involved in the establishment of phototropic curvature (bold face) and those which have been proposed to modulate phototropism (regular face) are listed for each step.

Blue Light Perception

As pointed out above, perceiving changes in light direction, quality, quantity, and duration is of great importance to plants as sessile organisms in order to adjust their growth, development and physiology. To this end, plants have evolved at least five classes of photoreceptors that are able to absorb light in different regions of the spectrum. Whereas the phytochromes (phys) mainly mediate responses to red/far-red light (Franklin and Quail, 2010; Chen and Chory, 2011), and UVR8 functions as a UV-B receptor (Rizzini et al., 2011; Christie et al., 2012; Hu et al., 2012) the remaining three families of photoreceptors are activated specifically by UV-A/blue light: the phototropins (phots), cryptochromes (crys) and members of the ZTL/FKF1/LKP2 family (Briggs, 2007; Christie, 2007; Demarsy and Fankhauser, 2009; Chaves et al., 2011; Ito et al., 2012).

Directional blue light leading to phototropism is detected by the phototropins (Liscum and Briggs, 1995; Sakai et al., 2001), which additionally mediate a variety of responses that generally serve to optimize photosynthetic performance and help the plant to adapt to changing environments (Whippo and Hangarter, 2006; Christie, 2007; Demarsy and Fankhauser, 2009; Holland et al., 2009). In *Arabidopsis* there are two phototropins, designated phot1 and phot2 (Briggs et al., 2001) that are very similar in sequence and structure and share an overall 58% identity (Jarillo et al., 2001; Sakai et al., 2001). Both proteins play overlapping roles in the phototropic response to high light conditions while phot1 solely mediates the response to low-fluence light (Sakai et al., 2001; Christie, 2007).

In recent years the photoreceptor itself, its structure and mode of activation upon blue light perception, have been studied in great detail. The comprehensive reviews of Christie (2007), Tokutomi et al. (2008), Möglich et al. (2010) and Demarsy & Fankhauser (2009) summarize our knowledge on these topics. In short, phototropins are composed of an N-terminal photosensory region and a C-terminal serine/threonine kinase domain. The photosensory half contains two LOV (light-, oxygen- or voltage-sensing) domains that each non-covalently bind a flavin mononucleotide (FMN) as a chromophore. Upon blue-light perception, the FMN forms a covalent adduct with a conserved cysteine residue within the LOV domains (Salomon et al., 2000). LOV2 in the dark binds to the kinase domain thereby repressing kinase activity. Blue-light perception leads to its dissociation and enhancement of kinase activity (Christie et al., 2002; Matsuoka and Tokutomi, 2005). Hence, LOV2 acts as a primary light-sensing domain, whereas the function of LOV1 remains largely elusive. It has been proposed that it serves as an attenuator of LOV2-induced kinase activity and implicated in dimerization processes (Salomon et al., 2004; Tokutomi et al., 2008). Activation of the kinase domain eventually leads to auto-phosphorylation (Christie et al., 1998; Sakai et al., 2001) on conserved serine residues (Inoue et al., 2008, 2011; Sullivan et al., 2008), an essential step in phototropin signaling, as loss of function of the kinase activity leads to an absence of both autophosphorylation and phot-mediated responses (Christie et al., 2002; Kong et al., 2007; Inoue et al., 2008). Among the numerous phot1 phosphorylation sites Ser^{851} and to a lesser extent Ser^{849} both located within the activation loop of the kinase domain are essential for all tested phot1-mediated responses (Inoue et al., 2008). Alignment of the activation loops of multiple phototropins furthermore showed that Ser^{851} is conserved in dicots, monocots, ferns, mosses and green algae, suggesting its importance (Inoue et al., 2008). Indeed, mutating the corresponding Ser^{763} in the activation loop of phot2 to alanine also leads to largely impaired phot2-mediated responses (Inoue et al., 2011). However, the roles of other phot1 and phot2 phosphorylation sites in modulating phot activity remain elusive (Inoue et al., 2008, 2011; Kaiserli et al., 2009).

Considering the general importance of phosphorylation processes in many signal transduction cascades, it is reasonable to assume that intermolecular phosphorylation substrates play a role in phototropin-mediated signaling pathways. The phot2 kinase domain phosphorylates the artificial substrate casein *in vitro* (Matsuoka and Tokutomi, 2005) and the phot1 kinase domain effectively phosphorylates serine residues on the phot1 N-terminus *in trans* (Okajima et al., 2011). Moreover, the auxin efflux transporter P-GLYCOPROTEIN 19 (PGP19) is phosphorylated by phot1 *in vitro* (Christie et al., 2011), an event that will be discussed in more detail in the chapter "Links between phototropin and Auxin Redirection". Furthermore, active phot1 trans-phosphorylates an inactive (kinase-dead) phot1 (Kaiserli et al., 2009) and phot2 cross-phosphorylates inactive phot1 *in vitro* (Cho et al., 2006). Apart from that, however, no direct substrates of phot kinases have been identified to date. In conclusion, light-regulated phot kinase activity is the first essential biochemical step from light perception to physiological responses but much remains to be discovered regarding the substrates of this activity (Christie, 2007; Matsuoka et al., 2007; Inoue et al., 2008, 2011; Tokutomi et al., 2008). Another important question is how the activated phototropins return to their inactive state and specifically how the phosphorylation of their activation loop is regulated. Ser^{851} in the phot1 activation loop is de-phosphorylated within ten minutes in the dark (Inoue et al., 2008). Interestingly, Tseng and Briggs (2010) recently reported that a PP2A phosphatase in *Arabidopsis* is potentially involved in the de-phosphorylation of phot2, thereby playing a role in its inactivation. Indeed, in a mutant with lower PP2A activity the sensitivity and rate of phot2 dependent phototropism were increased (Tseng and Briggs, 2010). However, we still know very little about the mechanisms leading to phot inactivation.

Early Signaling Events and Auxin Gradient Formation

Although the blue light receptors of the phototropin family are well investigated, signaling processes that take place further downstream and connect light sensing to the physiological response are much less understood. Nevertheless, several proteins have been found to act upstream of the formation of a lateral gradient in auxin distribution that according to the Cholodny-Went Hypothesis (Thimann and Went, 1937) ultimately causes phototropic bending. The existence of such an auxin gradient has been shown in several species and appears to be established by transferring auxin from the lit to the shaded side (Briggs et al., 1957; Briggs, 1963; Pickard and Thimann, 1964; Esmon et al., 2006; Holland et al., 2009). To date it seems clear that up to seven photoreceptors, several signal transducers, several auxin transporters, calcium as a second messenger, and an additional phytohormone, gibberellin (GA), are potentially involved in the astonishingly complex process of establishing a lateral auxin gradient in response to directed light stimuli. Their respective roles are discussed in the following.

NPH3 Phosphorylation

In 1999, Motchoulski and Liscum cloned the *Arabidopsis NPH3* gene (Motchoulski and Liscum, 1999), a locus found in the original screen for mutants impaired in the phototropic response that also led to the identification of phot1 (originally designated NPH1; Liscum and Briggs, 1995). It was found to encode a protein belonging to a novel, plant-specific family designated NRL (<u>N</u>PH3/<u>R</u>PT2-<u>L</u>ike; Pedmale et al., 2010) which is necessary for both phot1- and phot2-mediated hypocotyl phototropism (Inada et al., 2004). Since an *nph3* mutant is aphototropic without affecting (auto-) phosphorylation of phot1, NPH3 is thought to function downstream of the photoreceptor (Liscum and Briggs, 1995, 1996; Motchoulski and Liscum, 1999). Moreover, like the phots NPH3 is located at the plasma membrane (Lariguet et al., 2006; Pedmale and Liscum, 2007) and has been shown to interact physically with phot1 *in vitro*, in yeast, and *in vivo* (Motchoulski and Liscum, 1999; Lariguet et al., 2006).

A number of studies suggest that NPH3 acts upstream of the formation of an auxin gradient across the hypocotyl although this has not been directly demonstrated in *Arabidopsis*. Supporting evidence for this hypothesis comes from studies on maize coleoptiles where Matsuda and colleagues (2011) demonstrated that perception of a phototropism-inducing light stimulus, formation of a lateral auxin gradient, and expression of *NPH3-like* genes overlap in the tip of the coleoptiles (Matsuda et al., 2011). In addition, Haga and co-workers (2005) showed that CPT1, a NPH3 homolog in rice, is crucial for both coleoptile phototropism and lateral translocation of auxin (Haga et al., 2005). It is therefore likely that NPH3 acts upstream of differential auxin distribution.

In the dark, NPH3 exists in a phosphorylated form and it is de-phosphorylated quickly upon blue-light perception, a process that depends on phot1 but not on phot2 and is fully reversible (Pedmale and Liscum, 2007; Tsuchida-Mayama et al., 2008). It thus seems likely that phot1 is involved in this process at least indirectly although several studies have shown that NPH3 is phosphorylated even in the *phot1phot2* mutant, indicating that NPH3 is no direct target of either of the phot kinases (Pedmale and Liscum, 2007; Tsuchida-Mayama et al., 2008).

It is therefore tempting to speculate that the phosphatase de-phosphorylating NPH3 acts directly downstream of phot1. Nevertheless and despite some efforts, no such phosphatase has been identified to date. Despite these findings, there is still some controversy about the role of NPH3 de-phosphorylation for phototropism in *Arabidopsis*: Based on phototropism assays with different phosphatase inhibitors Pedmale and Liscum (2007) concluded that de-phosphorylation of NPH3 is necessary for a phototropic reaction (Pedmale and Liscum, 2007) while Tsuchida-Mayama and colleagues came to the opposite conclusion studying NPH3 protein variants mutated in potential phosphorylation sites (Tsuchida-Mayama et al., 2008). However, mutants lacking the ability to be de-phosphorylated and thereby being in a constitutive “dark-state” are still missing, thus the importance of the different phosphorylation states of NPH3 for its function remains to be determined.

NRL Family Interactions

Apart from its phosphorylation state, another potential role for NPH3 has been inferred from its sequence and structural properties. Like many members of the NRL family, NPH3 possesses two putative protein-protein interaction domains, namely a C-terminal coiled-coil domain and a N-terminal BTB/POZ (broad-complex, tramtrack, bric à brac/Pox virus and zinc finger) domain (Pedmale and Liscum, 2007). Protein-protein interactions may thus be a major biochemical feature of NPH3. Indeed, NPH3 directly interacts with at least three important components of the phototropism pathway: phot1 (dependent on the coiled-coil domain; Motchoulski and Liscum, 1999), ROOT PHOTOTROPISM 2 (RPT2) (via the BTB/POZ domain; Inada et al., 2004) and PHYTOCHROME KINASE SUBSTRATE 1 (PKS1) (Lariguet et al., 2006).

Interestingly, a variety of proteins containing BTB/POZ domains have been shown to act as substrate-specific adaptors in CULLIN3 (CUL3)-based E3 ubiquitin ligases (CRL3s), complexes that bind and catalyze the final step in the ubiquitination process of target proteins (Willems et al., 2004; Zimmerman et al., 2010). Following this lead, in a recent study Roberts and co-workers (2011) investigated the possible involvement of NPH3 in a $CRL3^{NPH3}$ complex and could show that NPH3 and CUL3 interact *in vitro* and *in planta* and that functional CUL3 is required for phototropic bending of *Arabidopsis* seedlings (Roberts et al., 2011). It appears that phot1 is ubiquitinated by a $CRL3^{NPH3}$ complex and that this ubiquitination state is fluence-rate dependent: under low-blue-light conditions phot1 is mono/multi-ubiquitinated, possibly leading to photoreceptor internalization into the cytoplasm, whereas under high-blue-light conditions it is additionally poly-ubiquitinated, presumably resulting in photoreceptor degradation by the 26S-proteasome (Roberts et al., 2011). It has been hypothesized that as a substrate adaptor in a $CRL3^{NPH3}$ complex, NPH3 influences auxin trafficking by controlling the availability of phot1 for downstream processes (Roberts et al., 2011).

In addition, BTB domain-containing proteins are often found as homo- or heterodimers (Stogios et al., 2005), suggesting that NPH3 could interact with other NRL family members and form $CRL3^{NPH3/NRL}$ complexes targeting numerous proteins. Such a complex could be formed with the aforementioned

RPT2, another plasma membrane-localized signal transducer in the phototropic response pathway that interacts with NPH3 and phot1 (Inada et al., 2004). However, while NPH3 is essential for phototropism at all fluence rates, RPT2 only functions under strong blue light (Sakai et al., 2000; Inada et al., 2004). Although it is currently unknown whether RPT2 interacts with CUL3, a model accounting for this data is that $\mathrm{CRL3}^{\mathrm{NPH3}}$ is essential for phototropism under low light while in high light a $\mathrm{CRL3}^{\mathrm{NPH3/RPT2}}$ complex partakes in signal transduction leading to differential auxin distribution.

Another group of proteins belonging to the NRL family, the NAKED PINS IN YUCCA MUTANTS (NPY) proteins have been shown to be essential for root gravitropism in *Arabidopsis* (Li et al., 2011), a process that also requires formation of a lateral auxin gradient (Morita, 2010). Intriguingly, both root gravitropism and phototropism seem to use similar pathways to achieve this gradient, involving serine/threonine kinases of the AGC superfamily, NRL proteins and AUXIN RESPONSE FACTOR (ARF) signaling components (Okushima et al., 2005; Santner and Watson, 2006; Sukumar et al., 2009; Li et al., 2011). This finding further promotes the view that NRL proteins commonly act as signal transducers in growth responses involving auxin redistribution.

Additional phot1 Interacting Proteins: PKS and 14-3-3 λ

Another primarily plasma membrane-located protein, PKS1, has been shown to interact with both phot1 and NPH3 (Lariguet et al., 2006). The small PKS (phytochrome kinase substrate) family in *Arabidopsis* consists of four members, PKS1-4 (Lariguet et al., 2003) and PKS1 was originally identified as a phyA interacting protein in a yeast-two-hybrid screen (Fankhauser et al., 1999). However, the blue light stimulated expression of *PKS1* suggested an additional role for PKS1 in blue light dependent signaling (Lariguet et al., 2006). Indeed, *pks1pks2pks4* triple mutants of *Arabidopsis* displayed severely reduced phototropism under low blue light conditions (Lariguet et al., 2006) indicating that the PKS proteins act positively and at least partially redundantly in the phot1 signaling pathway. In addition, PKS1 is involved in phot1-dependent negative (Boccalandro et al., 2008), as well as red light-induced, positive root phototropism (Molas and Kiss, 2008), while PKS4 is involved in red and far-red light-mediated randomization of hypocotyl growth orientation (Schepens et al., 2008). The notion of PKS proteins generally responding to light stimuli resulting in directional growth responses suggests that these proteins play a role in directing auxin fluxes. Consistent with this hypothesis both PKS1 and PKS2 can either promote auxin efflux or inhibit auxin influx in *Arabidopsis* mesophyll protoplasts (de Carbonnel et al., 2010). However, the biochemical mechanisms by which the PKS proteins might influence auxin fluxes remain elusive since PKS proteins do not contain any domains of known function (Lariguet et al., 2003, 2006).

In another recent yeast-two-hybrid screen Sullivan and colleagues identified a novel phot1-interacting protein, 14-3-3 λ (Sullivan et al., 2009) which later on was also shown to interact with phot2 (Tseng et al., 2012). In addition, a 14-3-3 protein interacts physically with phototropin in broad bean (Kinoshita et al., 2003). Although no functional role was demonstrated for its interaction with phot1, 14-3-3 λ in *Arabidopsis* was shown to be involved in stomatal opening mediated by phot2 (Tseng et al., 2012). However, it did not play a role in phot2-mediated phototropism (Tseng et al., 2012). The importance and role of its interaction with phot1 remains elusive, but it is intriguing to note that 14-3-3 proteins in barley were found to bind NPH3 and PIN1 (Schoonheim et al., 2007), two proteins known to be important players in the phototropic response (Blakeslee et al., 2004; Wisniewska et al., 2006). Furthermore, 14-3-3 proteins often act as scaffold proteins, allowing other proteins to bind (van Heusden, 2005). It is therefore tempting to speculate that 14-3-3 λ in *Arabidopsis* acts as a link between phot1 and downstream targets, such as NPH3 or auxin transporters.

Auxin Transporters and Gradient Formation

As pointed out before, formation of a lateral auxin gradient is a prerequisite for phototropism (Thimann and Went, 1937; Briggs et al., 1957; Briggs, 1963; Esmon et al., 2006; Tanaka et al., 2006; Peer et al., 2011). But how does perception of blue light by the phototropins influence auxin fluxes? In the following we review potential links between gradient formation and (i) auxin efflux as well as (ii) auxin influx.

With respect to (i) or the auxin efflux, at cytosolic pH (~7) indole-3-acetic acid (IAA), the principal naturally occurring auxin in plants, exists in its anionic state and requires active transport to exit the cell (Rubery and Sheldrake, 1974; Zazímalová et al., 2010). Two types of auxin efflux carriers have been described in the last decade: the plant-specific PIN-FORMED (PIN) family and members of the MULTIDRUG RESISTANCE (MDR)–p-glycoprotein (PGP) family (Noh et al., 2001; Paponov et al., 2005; Blakeslee et al., 2007).

In accordance with the chemiosmotic hypothesis (Rubery and Sheldrake, 1974), asymmetric localization of auxin efflux carriers alone can induce polar auxin transport (Wisniewska et al., 2006; Zhang et al., 2010) and thereby promote differential growth leading to phototropic bending. Indeed, application of the auxin efflux inhibitor 1-N-naphthylphthalamic acid (NPA) (Murphy et al., 2000) leads to a drastic reduction of phototropic curvature (Friml et al., 2002; Ding et al., 2011). Here, especially the PIN proteins (PIN1-4 and PIN7) are of potential interest since they show polar localization patterns on the plasma membrane (Zazímalová et al., 2010; Peer et al., 2011). Unfortunately, they function at least partially redundantly in many auxin-mediated processes, including phototropism (Friml et al., 2002; Vieten et al., 2005; Ding et al., 2011). However, PIN3 plays a significant role in phototropism as the *pin3* mutant has a pronounced defect in its phototropic response (Friml et al., 2002; Ding et al., 2011). PIN3 therefore is a good candidate for an efflux carrier promoting auxin gradient formation preceding phototropic bending. In accordance with that, Ding and colleagues (2011) reported a phot1-dependent polarization of PIN3 in the endodermis of unilaterally irradiated hypocotyls with a weak signal on the outer lateral membranes and a strong signal on the inner lateral membranes (Ding et al., 2011). This would localize PIN3 in a way preventing lateral transport of auxin towards the lit side thereby establishing a lateral auxin gradient. However, it is not clear if this relocalization precedes the establishment of an auxin gradient, as resolution and dynamic range of the microscopy were limiting (Ding et al., 2011).

In addition, in an earlier study changes in PIN3 localization upon phototropic stimulation were not observed (Blakeslee et al., 2004) and Christie et al. recently concluded from their data that lateral auxin fluxes promoting phototropic bending were not directly dependent on PIN3 (Christie et al., 2011). Yet, in support of a role for PIN3 in phototropism, the same study showed a decrease in PIN3-derived signal immediately below the region of phototropic curvature suggesting a role for PIN3 in the accumulation of auxin in the bending zone, thereby facilitating lateral transport (Christie et al., 2011).

A contribution of PIN1 to phototropism on the other hand appears likely but remains to be elucidated: In dark grown hypocotyls PIN1 is localized to the basal membranes of vascular and cortical cells (Blakeslee et al., 2004, 2007) and upon blue light irradiation it becomes delocalized on the shaded side of the bending region and immediately below. PIN1 was therefore proposed to promote auxin accumulation in this part of the hypocotyl (Blakeslee et al., 2004). PIN1 delocalization has been shown to be genetically dependent on phot1 since it does not occur in *phot1* mutants however the phototropic phenotype of *pin1* mutants remains to be described (Blakeslee et al., 2004).

In contrast to the PINs the efflux carriers of the MDR/PGP family are mainly homogeneously distributed at the plasma membrane. Nevertheless, they seem to play a role in the transduction process leading to phototropic bending: Mutants lacking PGP19 (a synonym for MDR1 and also designated ABCB19) show enhanced phototropism (Noh et al., 2003). Interestingly, the same mutants show a delocalization of PIN1 from basal ends of cells (Noh et al., 2003), mimicking the effect of blue light on the wild type (Blakeslee et al., 2004). It has furthermore been shown that PGP19 stabilizes PIN1 in specific membrane locations (Blakeslee et al., 2007; Titapiwatanakun et al., 2009). Together with the finding that a lack of PGP19 reduces the inhibitory effect of NPA on phototropism (Nagashima et al., 2008), these results indicate a role of PGP19 as a negative regulator of auxin fluxes underlying phototropic bending, most probably by interacting directly with PIN proteins and modifying their activity (Blakeslee et al., 2007; Nagashima et al., 2008). In accordance with that a recent study confirmed the enhanced phototropism phenotype of the *pgp19* mutant and showed that PGP19-dependent transport of auxin from the shoot apex to the root is inhibited upon blue light-induced activation of phot1, thereby pooling auxin in the region above the elongation zone. This may in turn facilitate lateral auxin distribution in the elongation zone ultimately leading to phototropic bending (Christie et al., 2011). Subsuming the above, the emerging picture is that independent, yet tightly coordinated action of auxin efflux carriers, mainly PIN3 and PGP19, restricts vertical flow of auxin from the shoot apex to the root in the vasculature (Friml et al., 2002; Blakeslee et al., 2007) while unilateral blue light leads to a lateral redistribution of auxin, presumably involving PIN proteins (Friml et al., 2002; Blakeslee et al., 2004, 2007; Christie et al., 2011; Ding et al., 2011).

With respect to auxin influx into cells, at apoplastic pH (~5.5) a significant fraction of auxin is protonated and therefore able to diffuse over the plasma membrane into the cells. In addition, members of the AUXIN-RESISTANT1/LIKE AUX1 (AUX1/LAX) family allow for active auxin uptake (Yang et al., 2006; Kerr and Bennett, 2007) and seem to play a role in the phototropic response. A recent study showed that hypocotyl phototropism was impaired in *aux1* mutants (Stone et al., 2008). This effect was only mild in single mutants, but more pronounced when seedlings were inhibited in basal auxin responsiveness, *i.e.* in the absence of the functional auxin responsive transcriptional activator, NPH4/ARF7 (Stone et al., 2008). The reduced phototropic phenotype of *nph4* mutants (Liscum and Briggs, 1996; Stowe-Evans et al., 1998; Harper et al., 2000) can be complemented by exposure to red light or treatment with ethylene (Harper et al., 2000; Stowe-Evans et al., 2001) and this complementation effect has been shown to be dependent on AUX1 activity (Stone et al., 2008). The underlying mechanisms have yet to be revealed; however, it seems plausible that AUX1 action in the phototropic response is dispensable when NPH4/ARF7 is active but becomes important under conditions in which another ARF system is mainly operating.

Links between phototropin and Auxin Redirection

Despite the above-mentioned links it remains largely elusive how the phototropins control the relocation of auxin. A possible piece of evidence comes from a recent study by Christie and colleagues: They show that phot1 can interact with PGP19 in yeast, *in vitro*, and *in vivo* and that this interaction is transient upon activation of phot1 (Christie et al., 2011). The authors of this study propose that blue-light-dependent inhibition of polar auxin transport and vertical growth are due to phot1 interaction with PGP19 in shoot apical tissues (Christie et al., 2011). As phot1 and PGP19 also co-localize at the plasma membrane and phot1 phosphorylates PGP19 *in vitro* (Christie et al., 2011) this provides evidence for a direct link between blue light perception and auxin transport.

A second model explaining a link between phot1 and auxin transport was recently proposed. PIN localization has been shown to be dependent on its phosphorylation state, which is mainly regulated by the PINOID (PID) kinase (Huang et al., 2010; Zhang et al., 2010). The phot-dependent regulation of *PID* expression was proposed as a mechanism for the phots to control PIN localization indirectly (Ding et al., 2011). PID activity on the other hand is regulated, amongst others, by intracellular calcium (Ca^{2+}) levels through interaction with Ca^{2+}-binding proteins, such as TOUCH3 (TCH3) and PID-BINDING PROTEIN1 (PBP1; Benjamins et al., 2003). Intriguingly, phot1 and phot2 have been shown to induce Ca^{2+} influx from the apoplastic space under low and high light conditions, respectively (Babourina et al., 2002; Harada et al., 2003; Stoelzle et al., 2003; Harada and Shimazaki, 2009; for a review, see Harada and Shimazaki, 2007). Therefore, regulation of intracellular Ca^{2+} levels by the phototropins might constitute a means to control auxin transport without directly interacting with the involved auxin efflux carriers.

Role of Further Photoreceptors

Although the phototropins are the only photoreceptors sensing the direction of incoming light (Sakai et al., 2001; Pedmale et al., 2010), it has become clear that other photoreceptors play important roles in the regulation of the phototropic response. The interaction network of photoreceptors that are involved in some of the processes discussed above has turned out to be quite complex and the degree of connectivity has still to be fully elucidated. Several studies have addressed the involvement of phytochromes (phys) and cryptochromes (crys) in the establishment of phototropic bending. Already in the 1990's it was shown that red light enhances the phototropic response via the action of multiple phytochromes, mainly phyA (Janoudi et al., 1992, 1997; Parks et al., 1996). The underlying mechanism remained elusive for many years. In 2004, Lariguet and Fankhauser proposed that phyA positively influenced phototropism by suppressing gravitropism in *Arabidopsis* seedlings (Lariguet and Fankhauser, 2004; Iino, 2006). This hypothesis is supported by a recent study of Kiss and coworkers that shows no enhancement of hypocotyl phototropism in response to blue light by pre-irradiation with red light in microgravity conditions (Kiss et al., 2012). In addition, in the same study the authors could show red light induced positive hypocotyl phototropism under the same microgravity conditions (Millar et al., 2010; Kiss et al., 2012), a feature that hints at an evolutionary conserved red light dependent regulative network known from lower plants .

More direct mechanisms by which phyA promotes the predominantly blue light dependent phototropism have also been identified, in particular the influence of phyA on the subcellular localization of phot1. In the dark, phot1 is tightly associated with the plasma membrane by currently unknown mechanisms (Liscum and Briggs, 1995; Sakamoto and Briggs, 2002). However, upon blue light irradiation a fraction is internalized into the cytoplasm (Sakamoto and Briggs, 2002; Wan et al., 2008; Kaiserli et al., 2009). The function of this internalization is still elusive; it might be a means of receptor desensitization or play a role in phot1 signaling and/or degradation (Wan et al., 2008; Kaiserli et al., 2009;

Roberts et al., 2011). Interestingly, Han and co-workers showed that pre-irradiation with red light prevents phot1 from being internalized in response to blue light while under the same conditions (pre-treatment with red light) phototropism is enhanced (Janoudi and Poff, 1992, 1993; Han et al., 2008). This led to the proposal that phyA-mediated retention of phot1 at the plasma membrane accounts (at least partially) for the enhanced phototropism seen in red light pre-treated seedlings (Han et al., 2008; Kaiserli et al., 2009). In accordance with this hypothesis data from Rösler et al. are consistent with the notion that phyA acts in the cytoplasm to promote phototropic bending (Rösler et al., 2007).

Modulation of auxin signaling through the action of phys and crys has been proposed by several authors (Stowe-Evans et al., 2001; Whippo and Hangarter, 2004). Indeed, both phys and crys can down-regulate transcription of the auxin efflux carrier gene *PGP19* thereby reducing PGP19 protein levels (Nagashima et al., 2008) and polar auxin transport which in turn enhances phototropism. These results were confirmed by a more recent study showing the particular involvement of phyB and cry1 in the alteration of PGP19 expression and auxin transport (Wu et al., 2010). *PGP19* is not the only phototropism-related gene whose expression is regulated by other photoreceptors than phot1. Expression of *RPT2* during phototropism in response to high light irradiation was shown to be induced by phys and crys (Tsuchida-Mayama et al., 2010). In addition, *PKS1* and *PKS4* are also regulated in a phy-dependent manner (Sakai et al., 2000; Tepperman et al., 2001; Lariguet et al., 2003; Schepens et al., 2008). In this context it is interesting to note that PKS1 protein accumulates in the elongation zone upon red-light irradiation (Lariguet et al., 2003). As phototropic curvature occurs in the same region and both processes are influenced by phyA it is conceivable that PKS1 acts as a link between phyA and phot1 signaling. Finally, it is worth noting that a prominent role in phyA-dependent gene regulation and therefore its impact on phototropism has recently been assigned to nuclear phyA activity (Kami et al., 2012). A conclusion from these studies is that the activity of phytochromes and phyA in particular is complex and that these photoreceptors may act at different levels (e.g. in the cytosol and by regulating gene expression) to modulate phototropism (Rösler et al., 2007; Han et al., 2008; Kami et al., 2012).

In addition to the above mentioned roles of secondary photoreceptors in the phototropic response a recent study revealed even more complexity: Depletion of GA complemented the phenotype of a *phyAcry1cry2* triple mutant that was severely affected in hypocotyl phototropism (Tsuchida-Mayama et al., 2010). Thus, GA seems to be responsible for the repression of phototropism in this mutant. Upon blue light irradiation, crys appear to suppress the inhibitory effect of GA by controlling GA levels as well as GA sensing and/or signaling, thereby enhancing phototropism (Tsuchida-Mayama et al., 2010). Moreover, Gallego-Bartolomé and colleagues uncovered a direct link between GA and auxin signaling through transcriptional regulation of a negative effector of auxin-induced gene expression. The authors suggest that GA attenuates hypocotyl gravitropism, mainly by generating a higher degree of variance in this response (Gallego-Bartolomé et al., 2011). It is therefore tempting to speculate that crys can enhance hypocotyl phototropism by modulating gravitropism through GA-dependent signaling.

Auxin Perception and Auxin Triggered Signaling

After a lateral auxin gradient is established this differential auxin distribution needs to be perceived in order to trigger a differential growth response. The current view on auxin perception postulates the existence of at least two different receptors, AUXIN BINDING PROTEIN 1 (ABP1; Löbler and Klämbt, 1985; Shi and Yang, 2011) and the auxin receptors of the F-box protein family called TRANSPORT INHIBITOR RESPONSE 1 (TIR1)/AUXIN SIGNALING F-BOX (AFB) proteins (Dharmasiri et al., 2005; Kepinski and Leyser, 2005).

Perception via ABP1

ABP1 was discovered due to its ability to bind auxin *in vitro* using membrane fractions of maize coleoptiles (Hertel et al., 1972). Nevertheless and despite considerable efforts in characterizing ABP1 function, whether ABP1 can indeed be considered an auxin receptor remained unclear throughout the following decades (Tromas et al., 2010; Shi and Yang, 2011). Starting with the identification of an *abp1* null allele (Chen et al., 2001) that proved ABP1's importance during early developmental stages this discussion gained new momentum. Unfortunately, the embryo lethality of a homozygous *abp1* allele prevented research on ABP1 function during later developmental stages, a problem that was solved by developing inducible *ABP1* knock-down lines (Braun et al., 2008; Tromas et al., 2009) as well as by characterizing a heterozygous *abp1/ABP1* line (Effendi et al., 2011). Nevertheless, embryo lethality of an *abp1* mutant is interesting since it brings *ABP1* in line with other genes that are crucial for embryo development and are implicated in tropic responses. Amongst these genes are the *PIN*s (a *pin1pin3pin4pin7* mutant (Blilou et al., 2005) and a PIN phosphorylation site mutant (Huang et al., 2010) are both embryo lethal) or genes related to the second auxin receptor complex formed together with TIR/AFBs (*axr6*, a *cul1* null allele is embryo lethal (Hellmann et al., 2003) and a *tir1afb1afb2afb3* mutant as well as an *iaa12* mutant have at least a dramatically decreased seedling viability (Dharmasiri et al., 2005)).

Experiments in maize have shown that ABP1 mostly localizes to the lumen or associates with the membrane of the endoplasmic reticulum (ER) (Shimomura et al., 1988; Jones et al., 1989) and is probably retained there by its carboxy-terminal tetrapeptide lysine-aspartic acid-glutamic acid-leucine (KDEL) signal (Inohara et al., 1989; Tillmann et al., 1989). Nevertheless, a small fraction appears to be secreted into the apoplast (Jones and Herman, 1993) where it associates with the plasma membrane by a yet to be identified mechanism and can interact with auxin (Hagen et al., 2010; Tromas et al., 2010).

Functionally, ABP1 can be related to H^+-ATPase activity that appears to be regulated from outside the plasma membrane (Rück et al., 1993; Napier et al., 2002) as well as potassium channel activity (Thiel et al., 1993; Fuchs et al., 2006). The fact that ABP1 plays a role while located outside of the plasma membrane fits with ABP1's auxin binding optimum that occurs at pH 5.5 corresponding to the expected apoplastic pH (Löbler and Klämbt, 1985). The function of ER localized ABP1 remains elusive (Napier et al., 2002; Hagen et al., 2010; Tromas et al., 2010). At cytosolic pH ABP1 is predicted to act as a low affinity auxin receptor leading to the suggestion that in the ER, ABP1 may have an auxin detoxifying function at high cytoplasmic auxin concentrations (LeClere et al., 2002; Tromas et al., 2010). This idea is supported by the fact that different auxin carriers are localized to the ER membrane as well, e.g. PIN5 (Mravec et al., 2009) or the recently discovered PILS proteins (Barbez et al., 2012). In addition, ABP1 appears to impact its own transcription, since in a heterozygous *abp1/ABP1* line ABP1 levels in response to auxin are reduced (Effendi et al., 2011), and thereby provides possibilities for self-reinforcement of an initial auxin response.

In terms of phototropism ABP1 functions are of interest since they link auxin perception to cell swelling (Steffens et al., 2001) as well as to changes in apoplastic pH and thereby to cell wall loosening (Cosgrove, 2000; Hager, 2003)– functions that are related to cell elongation and thereby possibly at the heart of the differential elongation process observed during phototropic bending. And indeed, heterozygous *abp1/ABP1* mutants show phototropic defects (Effendi et al., 2011) although the authors attribute this effect to an impact on PIN related auxin transport rather than the ABP1 functions at the plasma membrane described above. A more detailed view on the mechanisms related to elongation is given in the section ‘Physiological Response’.

Perception via F-Box Proteins

While ABP1 appears to affect mostly ion fluxes, auxin signaling is known to affect gene regulation as well (Abel and Theologis, 1996). In this regard molecular genetics experiments suggest that a major mode of auxin-based regulation of gene expression functions via protein degradation involving the ubiquitin-proteasome system (Gray and Estelle, 2000). Of central importance in this process are TIR1 and the AFB auxin receptors (see below) (Watahiki et al., 1999; del Pozo et al., 2002; Dharmasiri et al., 2005; Möller et al., 2010), which are known to be essential for a normal phototropic response (Möller et al., 2010).

Auxin influences transcription factors of the auxin response factor (ARF) family by leading to the degradation of AUXIN/INDOLE-3-ACETIC ACID (Aux/IAA) proteins which repress ARFs (Gray et al., 2001; Tiwari et al., 2001; Zenser et al., 2001; Tian et al., 2003). In brief, primary/early auxin response genes have been demonstrated to carry so-called auxin responsive elements (AuxREs) in their promoters that allow specific binding of certain ARF proteins (Kim et al., 1997; Ulmasov et al., 1999; Hagen and Guilfoyle, 2002). ARF proteins are thought to act as homodimers or heterodimers with other ARFs (Tiwari et al., 2001, 2003; Kepinski and Leyser, 2002; Liscum and Reed, 2002; Tatematsu et al., 2004; Esmon et al., 2006). However, given that at low auxin concentrations ARFs predominantly occur as heterodimers with Aux/IAA proteins, ARF activation requires the degradation of these Aux/IAA proteins in response to an increase in auxin levels (Tatematsu et al., 2004).

Ubiquitin-mediated degradation of these IAA proteins depend on TIR1/AFB auxin receptors (Dharmasiri, 2005; Kepinski and Leyser, 2005). TIR1/AFBs are a part of the SKP1, Cullin, and an F-box (SCF) type ubiquitin protein ligase (E3) with TIR1/AFB being responsible for the identification of specific substrates for ubiquitin conjugation while auxin plays the role of a 'molecular glue' (Calderon-Villalobos et al., 2010) increasing the binding affinity of the TIR/AFBs and the Aux/IAAs. The whole mechanism is reviewed in great detail for example by Calderon-Villalobos and colleagues as well as Hagen and colleagues (Calderon-Villalobos et al., 2010; Hagen et al., 2010).

Crosstalk between Auxin Receptors

ABP1 and the TIR1/AFBs appear to provide different means for crosstalk: in maize, potassium channel coding genes carry AuxREs (Christian et al., 2006) and thereby probably allow for an impact of TIR1/AFB mediated Aux/IAA ARF signaling on ABP1 mediated responses. On the other hand although ABP1's activity is typically believed to be restricted to early responses at the plasma membrane, there is evidence connecting APB1 to the modulation of *Aux/IAA* gene expression including members of this family that have been implicated in phototropism (Braun et al., 2008). ABP1 may thereby affect downstream signaling mediated by the SCF^{TIR1} complex. It is unlikely that this crosstalk involves direct interactions between the two classes of auxin receptors. ABP1 presumably initiates a signaling cascade at the cell surface ultimately leading to the modulation of nuclear events (Tromas et al., 2010).

Auxin Triggered Nuclear Signaling

With the regulatory machinery in place, in terms of phototropism one has to consider three questions: (i) which TIR1/AFBs are responsible for mediating auxin responses involved in phototropism, (ii) which ARFs and which Aux/IAAs are involved in transcriptional regulation of genes involved in phototropism, and lastly (iii) which genes undergo phototropism-specific regulation.

The *tir1afb1afb2afb3* quadruple mutant is strongly impaired in phototropism, (Möller et al., 2010). However, it should be pointed out that this *tir1afb1afb2afb3* quadruple mutant shows numerous morphological alterations (Dharmasiri et al., 2005) somewhat complicating the interpretation of its phototropic defect. Future studies will have to determine which one(s) of the 6 TIR1/AFBs are most important in mediating phototropism (Dharmasiri et al., 2005; Parry et al., 2009). All members of this gene family are rather broadly expressed rendering predictions difficult. Interestingly TIR1/AFBs vary in terms of Aux/IAA affinity as well as in their responsiveness to different auxins and auxin analogs (Vernoux et al., 2011; Calderon-Villalobos et al., 2012; Greenham et al., 2011). This may have important implications for the regulation of a process that relies on a rather shallow auxin gradient.

We have a better understanding regarding the ARFs and Aux/IAAs that are involved in gene regulation during phototropism. An early screen for mutants defective in hypocotyl phototropism led to the identification of *NPH4/ARF7* (Liscum and Briggs, 1995; Stowe-Evans et al., 1998; Harper et al., 2000). Moreover, the phototropicaly impaired *massugu1* (*msg1*) mutant (Watahiki and Yamamoto, 1997) turned out to be allelic to *nph4*/*arf7* (Tatematsu et al., 2004). The same screen identified the *msg2* mutant which codes for a dominant form of *Aux/IAA19* that is insensitive to auxin-induced degradation due to a mutation in its degron domain (Tatematsu et al., 2004). The physical interaction between

ARF7 and Aux/IAA19 suggests that phototropism crucially depends on the state of interaction between these two transcriptional regulators (Tatematsu et al., 2004). Nevertheless, since *aux/iaa19* loss of function mutants show no phenotype with respect to phototropism this suggests at least some redundancy among Aux/IAAs regulating tropic growth (Liscum and Reed, 2002; Hardtke et al., 2004; Tatematsu et al., 2004; Okushima et al., 2005). It should also be pointed out that ARF7 and IAA19 regulate both hypocotyl phototropism and gravitropism (Tatematsu et al., 2004). A few additional members of the Aux/IAA and ARF families have been implicated in phototropism. In the *arf8* mutant phototropic bending is reduced by about 20%, while a line with a stabilized IAA1 shows strongly reduced phototropic bending (Tian et al., 2004; Esmon et al., 2005; Yang et al., 2004). Further members of the Aux/IAA and ARF families are implicated in light-regulated auxin responses but have not been specifically linked to phototropism (Liscum and Reed, 2002).

With respect to (iii) or which genes undergo phototropism-specific regulation the report from Esmon and colleagues identified some candidates (Esmon et al., 2006). Because of the small size of *Arabidopsis*, these authors rather compared gene expression in the lit versus shaded flanks of *Brassica oleracea* seedlings that were treated with unilateral blue-light. In *Arabidopsis* the expression of the orthologous genes is auxin regulated in the wild type but not in *nph4/arf7* suggesting that they are implicated in phototropism (Esmon et al., 2006). This study identified: *EXPA1*, *EXPA8*, *SAUR50*, *HAT2*, *GH3.5*, and *GH3.6/DFL1*. From a physiological perspective especially the two α-expansins EXPA1 and EXPA8 are of particular interest since α-expansins are known to mediate cell wall extension

(Cosgrove, 2005; Esmon et al., 2006) and a more detailed view on the role of expansins during cell elongation is given in the section ‘Physiological Response’. The role of the *SAUR* (*Small Auxin Up RNAs*) genes remains poorly understood but they are transcriptionally induced by auxin and short-lived RNAs. SAUR proteins were proposed to act in auxin signal transduction involving calcium and calmodulin (Hagen and Guilfoyle, 2002). Two recent studies provide genetic evidence for a role of different SAURs in cell expansion (Chae et al., 2012; Spartz et al., 2012) and suggest that they might be involved in regulation of auxin transport (Spartz et al., 2012). HAT2 is a member of the HD-Zip class-II subfamily of transcription factors which is associated with increased hypocotyl length (Sawa et al., 2002) and therefore again might promote the differential cell elongation process during phototropism. GH3.5 and GH3.6 are IAA-amido synthetases that most probably play a role in auxin homeostasis by conjugating excess auxin (Staswick et al., 2005) and thereby could be part of a negative feedback loop preventing overshooting phototropic bending. In addition to this negative feedback, active ARF7 seems to promote expression of *Aux/IAA19* (Tatematsu et al., 2004) and thereby contributes to its own inactivation similar to transcription of most *Aux/IAA* genes that is promoted by auxin (Koshiba et al., 1995; Abel and Theologis, 1996).

Physiological Response

Ultimately, signaling during phototropism leads to an asymmetric cell elongation response induced by an asymmetric distribution of auxin causing increased cell elongation on the shaded side. In dicots, cell wall extension is documented to run through two different phases, an early but short extension peak followed by a decline in growth rate and transitioning into a second longer peak (Evans, 1985). Here, the first peak is caused by apoplastic acidification mediated by increased ATPase activity (Rayle and Cleland, 1992; Hager, 2003; Cosgrove, 2005) and ultimately requires balancing by K^+ uptake (Claussen et al., 1997; Hager, 2003) which in *Arabidopsis* is probably realized via KAT1 potassium channels (Thiel and Weise, 1999; Philippar et al., 2004). This early extension thereby probably results from increased activity of the pH sensitive α-expansins already located in the apoplast where α-expansins have the ability to modulate cell wall extensibility by cleaving one of at least three different types of wall stabilizing polymers, namely the hemicellulose cross-linked with cellulose (Cosgrove, 2005; Cho and Cosgrove, 2010; Cleland, 2010). The characteristics of this early response thereby perfectly fit ABP1 mediated auxin responses, especially since the first peak in growth rate appears to be independent of transcription (Schenck et al., 2010).

Sustained elongation on the other hand cannot be attributed to acidification and thereby ABP1 action alone (Yamagami et al., 2004; Christian et al., 2006; Schenck et al., 2010). The second growth peak probably relies on auxin induced transcription, e.g. of further expansins (Esmon et al., 2006) as well as newly synthesized ATPase and potassium channels (Claussen et al., 1997; Philippar et al., 2004; Fuchs et al., 2006) and probably involves synthesis of further cell wall material (Derbyshire et al., 200AD; Kutschera and Briggs, 1987; Cosgrove, 1997; Perrot-Rechenmann, 2010) and other events that might be downstream of the nuclear auxin signaling and thereby related to the action of the second auxin receptor of the TIR1/AFB family and thereby Aux/IAA ARF signaling.

Spatial Aspect of Phototropism

Finally, we would like to address spatial aspects of the phototropic response: the question of where the different steps take place. Starting with perception, there is still some debate as to where the directional stimulus is actually perceived. In a detailed study on maize coleoptiles Matsuda and colleagues showed that the coleoptile tip is not only the prime site for auxin synthesis but crucial for stimulus perception and formation of an auxin gradient which henceforward appears to be propagated downwards along the coleoptile (Matsuda et al., 2011). While for coleoptiles *PHOT1* as well as *NPH3* and *PGP-like* genes are expressed in that area as well (Matsuda et al., 2011), in dicots or at least *Arabidopsis* it appears to be different: Here, phot1 shows an expression maximum in cotyledons and the elongation zone (Knieb et al., 2004; Wan et al., 2008). Lateral gradient formation in *Arabidopsis* has recently been suggested to be initiated in and above the hypocotyl apex (Christie et al., 2011) leaving a potential role of phot1 in lower hypocotyl regions open. However, shading and amputation experiments in various dicots indicate that light perception occurs in the hypocotyl (Iino, 2001). And although shading experiments are not easy to interpret since plant tissue and especially hypocotyls have been shown to scatter and pipe light along the longitudinal axis (Mandoli and Briggs, 1982a; b), combined with the amputation experiments it seems safe to assume that phototropism in dicots at least does not strictly depend on the cotyledons.

Above all, it remains unclear how the plant is able to reliably perceive a shallow light intensity gradient with incoming light intensity varying over at least three orders of magnitude. In *Arabidopsis* hypocotyls phot1 is predominantly localized to cortical cells (Wan et al., 2008) and for a range of different monocots as well as dicots with larger diameters an internal light gradient has been measured (Iino, 2001). Interestingly this light gradient is reflected at the level of phot1 phosphorylation that is higher on the lit than the shaded side upon unilateral blue light irradiation of oat coleoptiles (Salomon et al., 1997). Importantly phototropic bending relies on an increased growth rate on the shaded side. How a potentially weaker activation of phot1 on the shaded side leads to enhanced growth remains to be understood. Most likely the establishment of phototropic curvature in response to a light cue implies communication between the partaking cells as well as propagation of the stimulus from lit to shaded side. In any case, blue light receptors like the phototropins are the most suitable candidates for gradient perceiving proteins since light gradients in plant tissue are more pronounced for the blue part compared to the rest of the solar spectrum (Iino, 2001).

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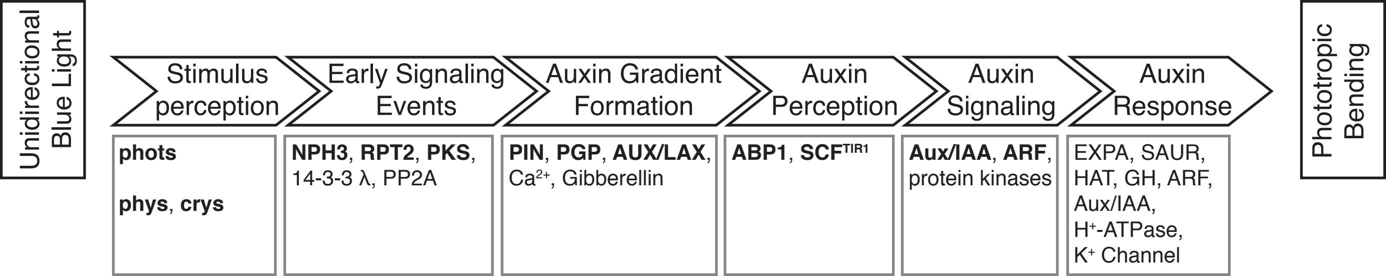
Unidirectional Blue Light
Stimulus perception
Early Signaling Events
Auxin Gradient Formation
Auxin Perception
Auxin Signaling
Auxin Response
Phototropic Bending
phots
phys, **crys**
NPH3, **RPT2**, **PKS**, 14-3-3 λ, PP2A
PIN, **PGP**, **AUX/LAX**, Ca2+, Gibberellin
ABP1, **SCFTIR1**
Aux/IAA, **ARF**, protein kinases
EXPA, SAUR, HAT, GH, ARF, Aux/IAA, H+-ATPase, K+ Channel