Phototropin Blue-Light Receptors

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Abstract

Phototropins are blue-light receptors controlling a range of responses that serve to optimize the photosynthetic efficiency of plants. These include phototropism, light-induced stomatal opening, and chloroplast movements in response to changes in light intensity. Since the isolation of the *Arabidopsis PHOT1* gene in 1997, phototropins have been identified in ferns and mosses where their physiological functions appear to be conserved. *Arabidopsis* contains two phototropins, phot1 and phot2, that exhibit overlapping functions in addition to having unique physiological roles. Phototropins are light-activated serine/threonine protein kinases. Light sensing by the phototropins is mediated by a repeated motif at the N-terminal region of the protein known as the LOV domain. Photoexcitation of the LOV domain results in receptor autophosphorylation and an initiation of phototropin signaling. Here we summarize the photochemical and biochemical events underlying phototropin activation in addition to the current knowledge of the molecular mechanisms associated with photoreceptor signaling.

Contents

INTRODUCTION

Environmental cues have an extensive regulatory influence on the growth and development of plants. Among the most important environmental factors is light. Light is not only an energy source for photosynthesis but also a stimulus that regulates numerous developmental processes, from seed germination to the onset of flowering. Collectively, these light-dependent responses are known as photomorphogenesis.

Several classes of photoreceptors that absorb light in two spectral regions act to control photomorphogenesis. Phytochromes (phy) predominantly absorb red and far-red light (600–800 nm) and mediate a wide range of photomorphogenic responses (19, 44). Two distinct classes of photoreceptors mediate the effects of UV-A/blue light (320–500 nm): the cryptochromes and the phototropins (7). Cryptochromes (cry), like the phytochromes, play a major role in plant photomorphogenesis (8, 100). Phototropins (phot), on the other hand, are involved in regulating light-dependent processes that serve to optimize the photosynthetic efficiency of plants and promote growth (14, 18). More recently, a third class of putative blue-light receptors related to the phototropins was identified in plants. This novel family of photoreceptors includes proteins that mediate targeted proteolysis of components associated with circadian clock function and flowering (7).

It has been just under a decade since the first phototropin gene was identified in plants, yet our knowledge of these and related blue-light receptors has increased dramatically during this time. In this article, we summarize the major advances in phototropin research with respect to their physiological roles, their mode of action, and the mechanisms underlying phototropin receptor signaling. For additional information, readers are directed to a number of recently published reviews (7, 18, 87, 107) and book chapters on phototropins (16, 20, 25, 146, 147). Historical overviews describing the discovery of plant blue-light receptors, including the phototropins (12, 157), will also provide a valuable resource for the interested reader.

PHOTOTROPISM AND THE DISCOVERY OF PHOTOTROPIN

The effects of blue light on plant development have been studied for almost two

centuries (12, 65). Phototropism, for example, is specifically induced by UV-A/blue light and has provided researchers with an excellent experimental system to study blue-light perception and signaling in plants (65, 66, 157). Generally, shoots show positive phototropism, i.e., movement toward the light, whereas roots exhibit negative phototropic movement. Photobiological studies using shoots of dark-grown seedlings from a variety of plant species have uncovered a surprising degree of complexity in the bending response to blue light. Phototropism can be divided into two phases depending on the fluence and time requirements (66). First-positive curvature is generally described as the bending of shoots toward unilateral blue light delivered in brief pulses at very low fluences. These curvature responses obey the Bunsen-Roscoe reciprocity law in that they are the same for a given fluence over a wide range of time-fluence rate combinations (17). Second-positive curvature occurs with prolonged irradiation in a time-dependent manner. Although fluence-response measurements have provided important photobiological information about the photosensors mediating phototropism (65), a greater understanding of the photodetection mechanisms involved has come from biochemical and molecular genetic approaches.

Insights into the biochemical properties of the photoreceptors responsible for phototropism were obtained prior to the isolation of the first phototropin gene back in 1997 (60). Briggs and colleagues were the first to identify a plasma membrane-associated protein from the growing regions of dark-grown pea epicotyls that became phosphorylated upon blue-light irradiation (47). Extensive photochemical and biochemical characterization of the light-induced phosphorylation reaction (15) and its correlation with phototropism (51, 52, 119, 136) indicated that the phosphoprotein in question was a candidate photoreceptor for phototropism that undergoes autophosphorylation in response to blue-light treatment.

The molecular identity of the aforementioned phosphoprotein was later uncovered through the use of the plant genetic model *Arabidopsis thaliana*. The nonphototropic hypocotyl (*nph*) mutants of *Arabidopsis* show impaired hypocotyl phototropism to low fluence rates of unilateral blue light (101). A particular class of *nph* mutant, *nph1*, was found to lack the activity of the plasma membrane-associated protein that becomes heavily phosphorylated upon irradiation with blue light. The encoded protein, originally designated NPH1, was therefore hypothesized to represent a phototropic receptor that undergoes autophosphorylation in response to blue light (101). Subsequent biochemical experiments confirmed this hypothesis and the NPH1 protein was renamed phototropin 1 (phot1) after its functional role in phototropism (13, 22).

PHYSIOLOGICAL ROLES OF THE PHOTOTROPINS

Biological Functions in Higher Plants

Phototropins are ubiquitous in higher plants and have been identified in several plant species (35, 78, 88, 121). Genetic analysis using *Arabidopsis* has been instrumental in identifying the molecular nature of the phototropins and establishing their roles as blue-light receptors. *Arabidopsis* contains two phototropins designated phot1 and phot2 (14, 18). Analysis of phot-deficient mutants has shown that phot1 and phot2 exhibit partially overlapping roles in regulating phototropism. Both phot1 and phot2 act to regulate hypocotyl phototropism in *Arabidopsis* in response to high intensities of unilateral blue light (123). By contrast, hypocotyl phototropism under low light conditions is solely mediated by phot1 (101, 123, 124).

Besides phototropism, phot1 and phot2 mediate other light responses in *Arabidopsis* that serve to regulate and fine-tune the photosynthetic status of plants. Blue light induces the opening of stomatal pores in

the leaf and stem epidermis, a response that allows plants to regulate CO_2 uptake for photosynthesis and water loss through transpiration. This response is controlled redundantly by phot1 and phot2, which unlike the situation for phototropism contribute equally to stomatal opening by acting across the same light intensity range (88). Phototropins also control the movement of chloroplasts in response to different light intensities (156). Under low light conditions, phot1 and phot2 induce chloroplast accumulation movement to the upper cell surface to promote light capture for photosynthesis (123). Phot1 is more sensitive than phot2 in activating chloroplast accumulation movement, as phot2 activity requires a higher light threshold (77, 123). In high light conditions, chloroplasts move away from the site of irradiation (156) to prevent photodamage of the photosynthetic apparatus in excess light (79). The avoidance movement of chloroplasts is mediated only by phot2 (74, 76), demonstrating that a given phototropin can play a unique role. Likewise, the rapid inhibition of hypocotyl elongation of dark-grown seedlings by blue light is controlled exclusively by phot1 (43). This process represents the earliest light response initiating the transition from growth dependent on seed reserves to photoautotrophy. Phototropins also promote cotyledon expansion (116) and leaf expansion in *Arabidopsis* (125). In addition, a possible role for phototropins in controlling light-stimulated leaf movement in kidney bean was recently reported (70).

Together, the abovementioned responses serve to enhance photosynthetic performance and promote plant growth under weak light conditions (150). Gene expression analysis indicates that phototropins have only a minor role in transcriptional regulation in light-grown *Arabidopsis* seedlings (116). Nevertheless, phot1 is required for the destabilization of specific nuclear and chloroplast transcripts in response to high-intensity blue light (41). A summary of the known phototropin-mediated responses found in higher plants is illustrated in **Figure 1*a***.

Biological Functions in Lower Plants

Owing to their simplified cell architecture, blue-light responses have been studied extensively in ferns, mosses, and green algae (146). The fern *Adiantum capillus-veneris* has two phototropins (75, 115). Phot2, like its higher plant counterpart, is solely responsible for mediating chloroplast avoidance movement in *Adiantum* (75). *Adiantum* also contains a novel photoreceptor neochrome, formerly known as phy3 (115, 145). *Adiantum* neochrome (neo) is a chimeric protein containing a phytochrome photosensory domain fused to the N terminus of an entire phototropin receptor (115, 145). Neo is required for phototropism and chloroplast relocation in *Adiantum* (82), both of which are regulated by red and blue light in this organism. Fern species such as *Adiantum* appear to lack stomatal responses to blue light despite having functional phototropins (32).

Four phototropins have been identified in the moss *Physcomitrella patens* that mediate chloroplast movements in this organism (80). The function of phototropins in higher and lower plants is therefore likely to be conserved. The filamentous green alga *Mougoetia scalaris* contains two phototropins in addition to two neochromes (145). A comparison of algal and fern *NEO* genes suggests that they have arisen independently, providing an intriguing example of convergent evolution (145). Only one phototropin exists in the biflagellate unicellular green alga *Chlamydomonas reinhardtii* (62, 81) where it is necessary for completion of the sexual life cycle (61). Unlike higher plant phototropins, light activation of *Chlamydomonas* phot causes major changes in the transcription of specific gene targets (61). However, whereas the function of *Chlamydomonas* phot is distinct from its higher plant counterparts, the gene encoding *Chlamydomonas* phot can restore phototropin-mediated responses in the *phot1 phot2* double mutant of *Arabidopsis* (118), indicating that the mechanism of action of higher and lower plant phototropins is highly conserved.

PHOTOTROPIN STRUCTURE AND ACTIVITY

Protein Structure and Receptor Autophosphorylation

Protein structures of plant phototropins can be separated into two segments: a photosensory domain at the N terminus and a serine/threonine kinase domain at the C terminus (**Figure 1*b***). Phototropins belong to the AGC family of kinases (cAMP-dependent protein kinase, cGMP-dependent protein kinase G and phospholipid-dependent protein kinase C) and are members of the AGC-VIIIb subfamily (11). The N-terminal photosensory domain of the phototropins contains two very similar domains of ~110 amino acids designated LOV1 and LOV2. LOV domains are members of the large and diverse superfamily of PAS (Per, ARNT, Sim) domains associated with cofactor binding and mediating protein interactions (152). LOV domains, however, are more closely related to a subset of proteins within the PAS domain superfamily that are regulated by external signals such as light, oxygen, or voltage, hence the acronym LOV (60). LOV domains bind the cofactor flavin mononucleotide (FMN) and function as blue-light sensors for the protein (22, 126). *Adiantum* neo is unique in that it contains a phytochrome chromophore-binding domain in addition to a phototropin protein sequence (**Figure 1*b***), consistent with its function as a dual red-/blue-light photoreceptor (82).

Photoexcitation of the LOV domains by blue light leads to phototropin receptor autophosphorylation (21, 123). Phototropin autophosphorylation can be monitored in vivo (15) and in vitro (21, 23, 123). Whether autophosphorylation occurs intra- or intermolecularly is not known although biochemical evidence suggests that phot1 autophosphorylation involves intermolecular communication between separate phototropin molecules (121). Autophosphorylation, at least for phot1, occurs on multiple serine residues (120, 127, 130, 137). Indeed, phot1 from several plant species exhibits reduced electrophoretic mobility after blue-light irradiation, consistent with autophosphorylation on multiple sites (94, 101, 138). Interestingly, autophosphorylation of oat phot1 is accompanied by a loss in immunoreactivity with an antibody raised against the N-terminal region of *Arabidopsis* phot1 (127). Irradiation with UV-C (280 nm) induces an electrophoretic mobility shift for oat phot1 without any change in immunoreactivity (94), implying that distinct serine residues may be phosphorylated in response to different light qualities.

LOV-Domain Structure and Function

Purification of milligram quantities of bacterially expressed LOV domains has greatly facilitated the spectral and structural analysis of these blue-light-sensing motifs. Indeed, enormous progress has been made in elucidating the primary processes associated with LOV-domain photochemistry and readers are directed to several recent excellent reviews for a more extensive description of the reaction mechanisms involved (28, 97, 107).

Owing to their FMN-binding capacity, LOV domains expressed and purified from *Escherichia coli* are yellow in color and emit a strong green fluorescence when irradiated with UV/blue light. Upon illumination, LOV domains undergo a photocycle that can be monitored by absorbance or fluorescence spectroscopy (81, 126). In darkness, LOV domains bind FMN noncovalently forming a spectral species, designated LOV_{447}, which absorbs maximally near 447 nm (22, 126, 148). Irradiation of the domain induces a unique mode of photochemistry that involves the formation of a covalent adduct between the C(4a) carbon of the flavin chromophore and a conserved cysteine residue within the LOV domain (**Figure 2*a***). Mutation of the cysteine to either alanine or serine results in a loss of photochemical reactivity (126). Light-driven FMN-cysteinyl adduct formation occurs in the order of microseconds producing

cGMP: cyclic guanosine monophosphate

cAMP: cyclic adenosine monophosphate

LOV: light, oxygen, or voltage

PAS: domain acronym derived from a class of sensory proteins named after Drosophila Period (Per), vertebrate Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT), and Drosophila Single-minded (Sim)

FMN: flavin mononucleotide

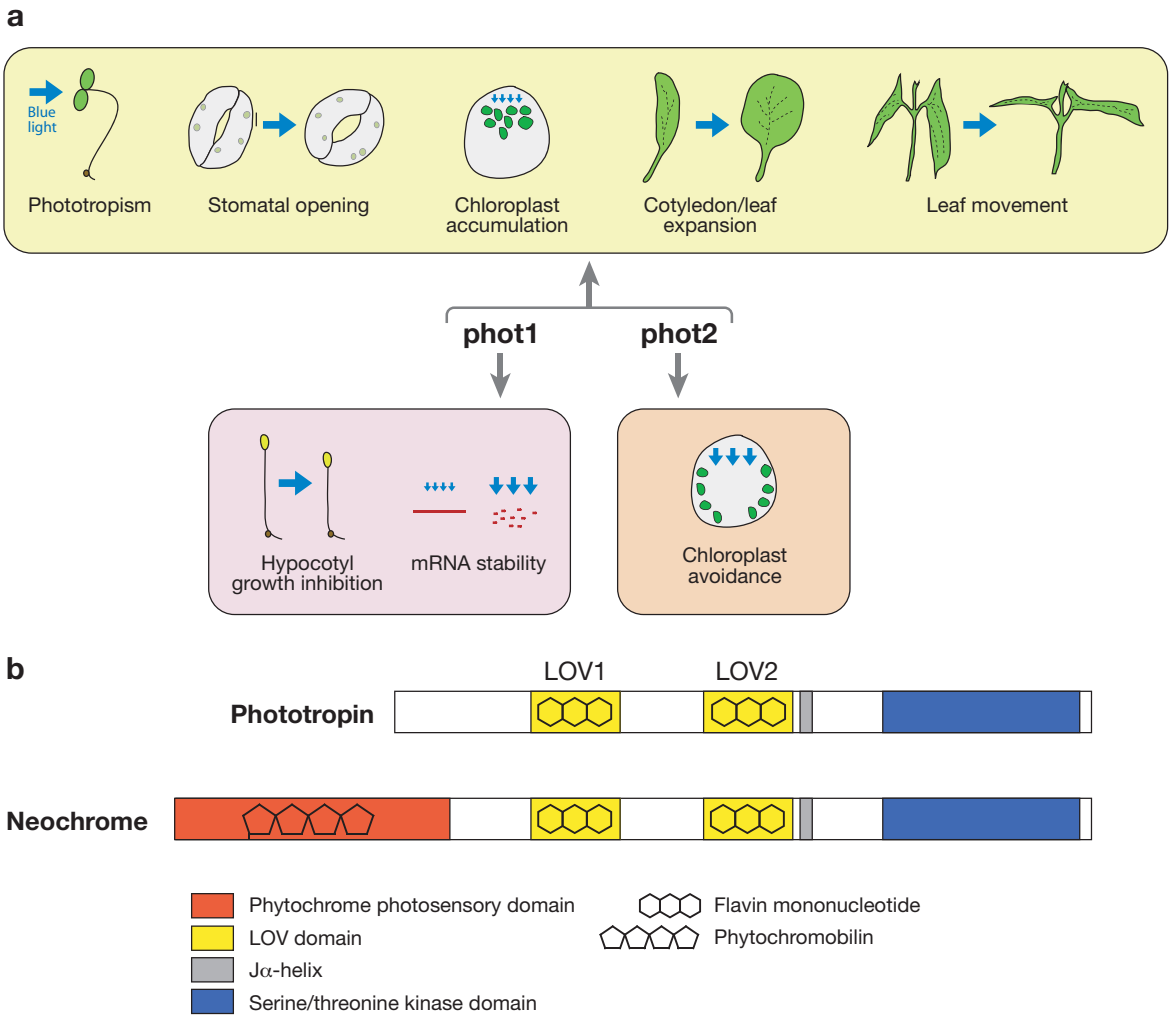

Figure 1

Phototropin structure and function. (*a*) Diagram illustrating the range of phototropin-induced responses in higher plants. Phot1 and phot2 are activated by blue light and overlap in function to mediate several responses. These are enclosed in the yellow rectangle and include phototropism, stomatal opening, chloroplast accumulation movement, and cotyledon and leaf expansion. Phototropins have also been implicated in controlling blue-light-induced leaf movements. Chloroplast avoidance movement is only mediated by phot2. Likewise, phot1 alone plays a role in mediating the rapid inhibition of hypocotyl growth and promoting the destabilization of specific transcripts under high light intensities. (*b*) Protein structures of phototropin and neochrome photoreceptors. Domain structures of these proteins along with their respective chromophores are indicated.

a spectral species (LOV_{390}) that absorbs maximally at 390 nm (81, 126, 148). For phototropin LOV domains, formation of LOV_{390} is fully reversible in darkness, returning the LOV domain back to its initial ground state (LOV_{447}) within the order of tens to hundreds of seconds (81, 126). LOV domains therefore cycle between active (LOV_{390}) and inactive (LOV_{447}) states depending on the light conditions (**Figure 2*b***). Illumination with near

UV-light can revert LOV_{390} to its initial dark state (84). However, the biological significance of this UV-mediated reversibility with respect to receptor function is not known.

Intermediates of the LOV-domain photocycle have been defined spectrally. Initial absorption of blue light by the FMN chromophore results in the formation of an excited singlet state, which subsequently decays into a flavin triplet state (LOV_{660}) that absorbs maximally in the red region of the spectrum (83, 96, 148). The triplet state in turn decays to form the FMN-cysteinyl adduct. Although there is still some debate as to the reaction mechanism for LOV_{390} formation from LOV_{660} (107), it is generally accepted that LOV_{390} represents the active signaling state that leads to photoreceptor activation. Crystal structures of LOV1 and LOV2 from *Chlamydomonas* phot and *Adiantum* neo, respectively, have been solved and show a close resemblance in overall structure to other PAS domains (26, 39). Importantly, structures for dark and illuminated states of LOV1 and LOV2 have been obtained and confirm the reaction mechanism of light-driven adduct formation (26, 27, 39). The structures of LOV1 and LOV2 are almost identical and comprise five antiparallel β–strands interconnected by two α-helices (**Figure 3**). The FMN chromophore is held tightly within a central cavity by hydrogen bonding and van der Waals forces via 11 conserved amino acids (26, 39). The constraints imposed by the protein environment surrounding the flavin chromophore account for the vibronic fine structure observed in the absorption spectrum of the LOV domain, which is not observed for free flavins in solution (126, 148). The ribityl phosphate side chain of FMN is not essential for LOV-domain photochemistry, since flavin exchange analysis has shown that riboflavin can function efficiently as chromophore (33).

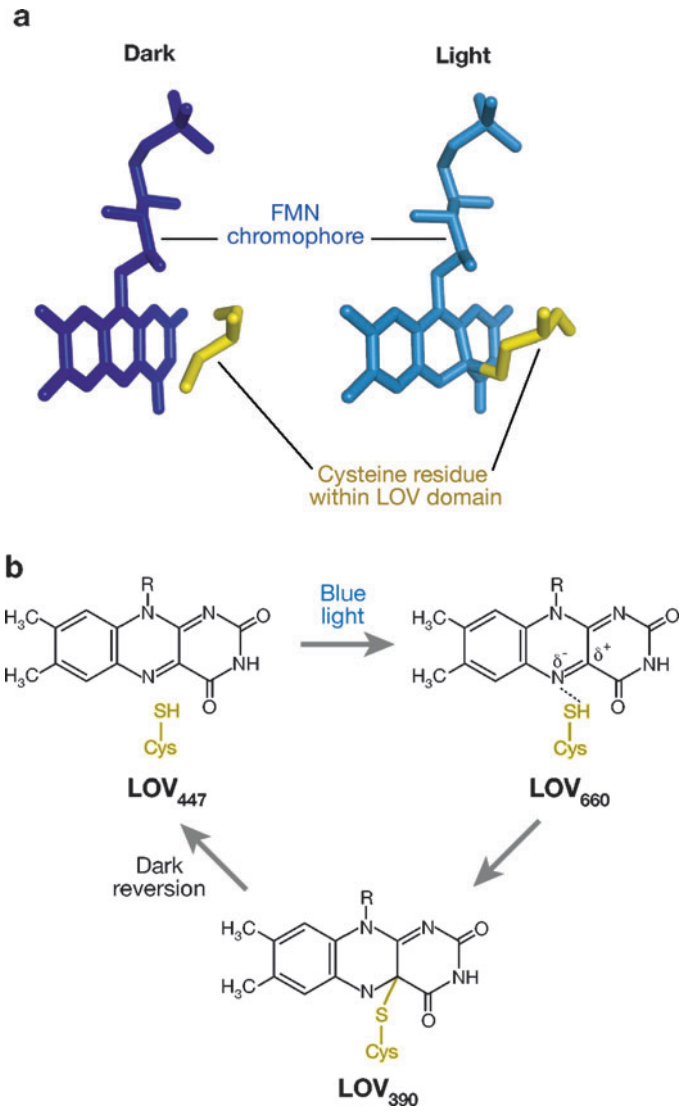

Figure 2

LOV-domain structure and photochemistry. (*a*) Close-ups of the vicinity of the FMN chromophore within the LOV domain under dark and light conditions. Light drives the formation of a covalent adduct between the FMN chromophore and a conserved cysteine residue within the LOV domain. Coordinates were obtained from Protein Data Bank ID codes 1G28 and 1JNU. (*b*) Schematic representation of LOV-domain photochemistry. In darkness, the FMN chromophore is noncovalently bound within the LOV domain, forming a species that absorbs maximally at 447 nm (LOV_{447}). Light drives the production of a highly reactive triplet-state flavin (LOV_{660}) that leads to formation of a covalent bond between the C(4a) carbon of the FMN chromophore and a conserved cysteine residue within the LOV domain (LOV_{390}). The photoreaction process is fully reversible in darkness.

Functional Roles of LOV1 and LOV2

LOV1 and LOV2 exhibit different quantum efficiencies and photochemical reaction

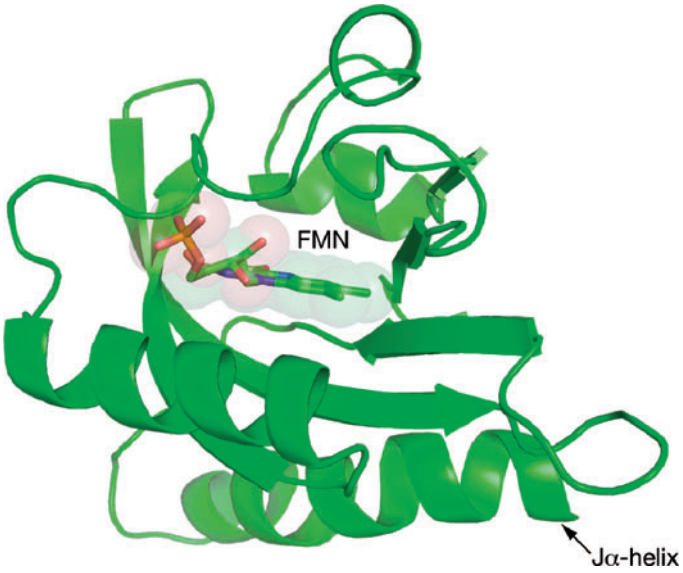

Figure 3

Structural model of the LOV2 domain from oat phot1 in the dark state as determined by nuclear magnetic resonance analysis and homology modeling (57). Positions of the FMN chromophore and the Jα-helix are indicated.

kinetics (81, 126), implying that these domains have different light-sensing roles in regulating phototropin activity. LOV2 has a higher quantum efficiency for light-induced cysteinyl adduct formation than that of LOV1 for both phot1 and phot2 (81). Mutagenesis studies have shown that LOV2 photoreactivity is required for phot1 autophosphorylation and to elicit phot1-mediated hypocotyl phototropism in *Arabidopsis* (23). LOV1 photoreactivity, however, is not sufficient to elicit phot1 autophosphorylation and phot1-induced phototropic curvature. Thus, at least for phototropism, LOV2 is essential for phot1 function in *Arabidopsis*. Similarly, the LOV2 domain of phot2 is sufficient to mediate chloroplast avoidance movement in *Adiantum* (75).

Whereas LOV2 plays an important role in regulating phototropin activity, the exact role of LOV1 remains unknown. Size exclusion chromatography (128) in addition to small-angle X-ray scattering (SAXS) analysis (110) of purified LOV1 suggests that this domain may play a role in receptor dimerization. The function of LOV1 has also been proposed to prolong the lifetime of phototropin receptor activation (75). This hypothesis certainly warrants further investigation given that the LOV1 domain of phot2 has been shown to modulate the activity of a bacterially expressed phot2 kinase (108).

Bacterially expressed fusion proteins containing both LOV domains exhibit photochemical properties that more closely resemble those of the full-length photoreceptor proteins (81) than those of individual LOV1 and LOV2 domains. Although tandem LOV-fusion proteins for phot1 and phot2 exhibit similar relative quantum efficiencies, the dark recovery for phot2 is about 10-times faster than that for phot1 (23, 75, 81). The faster dark recovery might account for why phot2 requires higher light intensities for activity in vivo (77, 123, 150). However, at least for phototropism, the functional activity of phot2 observed under high light conditions results from differential gene expression as *PHOT2* transcripts are induced by light in dark-grown seedlings (74, 76) through the photoactivation of phyA (154). Conversely, long-term exposure of dark-grown seedlings to light results in a decrease in *PHOT1* transcript levels (78, 125), which also depends on phytochrome photoactivation (35).

MODE OF RECEPTOR PHOTOACTIVATION

LOV2-Induced Structural Changes

Light-induced phototropin kinase activity requires LOV2 photoreactivity (23, 108). Therefore, LOV2 can be viewed as a molecular light switch that controls the activity of the C-terminal kinase domain. The photoexcited crystal structure of *Adiantum* neo LOV2 shows only minor, light-induced protein changes within the vicinity of the FMN chromophore (27). Yet, Fourier transform infrared spectroscopy (FTIR) and circular dichroism (CD) studies (24) demonstrate that photoactivation of purified LOV2

Quantum efficiency: the ratio of photoreceptor molecules that carry out photochemistry to the number of photons absorbed

SAXS: small-angle X-ray scattering

FTIR: Fourier transform infrared spectroscopy

in solution is accompanied by changes in the LOV-domain apoprotein (71, 149). In particular, the βE sheet region of *Adiantum* neo LOV2 exhibits a significant conformational change upon cysteinyl adduct formation (114). The βE sheet region contains a conserved glutamine residue (Gln^{1029}) that when mutated to leucine results in a loss of these light-driven protein changes (72, 114). Gln^{1029} forms hydrogen bonds with the FMN chromophore and undergoes side chain rotation upon cysteinyl adduct formation (26, 27). This residue therefore appears to be important for signal transmission from inside the chromophore-binding pocket to protein changes at the LOV2 surface. Only minimal light-induced protein changes are reported for LOV1 despite the presence of the conserved glutamine residue (3, 72, 104).

Nuclear magnetic resonance (NMR) studies involving extended LOV2 fragments derived from oat phot1 have identified a conserved α–helix (designated Jα) that associates with the surface of LOV2 in the dark state (57). The Jα-helix is located at the C terminus of LOV2 and is amphipathic in nature, consisting of polar and apolar sides, the latter of which docks onto the β–sheet strands of the LOV2-core (**Figure 3**). The interaction between Jα and LOV2 is disrupted upon cysteinyl adduct formation. The Jα-helix becomes disordered and more susceptible to proteolysis (57). Independent approaches provide further support for light-induced helical movements associated with extended LOV2 fragments (24, 34, 72). Moreover, artificial disruption of the LOV2-Jα interaction through site-directed mutagenesis results in phot1 autophosphorylation in the absence of light (56), indicating that unfolding of the Jα-helix results in activation of the C-terminal kinase domain.

Kinase Regulation

An important question to address now is whether LOV2 acts as a dark-state repressor of phototropin kinase activity or a light-state activator. In vitro studies involving protein fragments derived from *Arabidopsis* phot2 are in accordance with LOV2 functioning as a dark-state inhibitor of phototropin kinase activity (107, 108). The bacterially expressed kinase domain of *Arabidopsis* phot2 can phosphorylate the artificial substrate casein in vitro. Substrate phosphorylation by phot2 kinase occurs constitutively but becomes light dependent upon the addition of purified LOV2. A similar PAS-kinase interaction mechanism has been proposed for regulating the activities of the bacterial oxygen sensor, FixL (49), and the eukaryotic protein kinase, PAS kinase (2, 122), a regulator of mammalian glycogen synthesis (158). A schematic representation of phototropin receptor activation is illustrated in **Figure 4*a***. Curiously, the transinteraction observed between purified LOV2 and the kinase domain of *Arabidopsis* phot2 occurs in the absence of the Jα-helix (108). Whether the dispensability of the Jα-helix reflects a difference between the mechanisms of substrate phosphorylation and receptor autophosphorylation remains to be clarified. In addition, the LOV1 domain of *Arabidopsis* phot2 has been shown to mediate a small degree of light-activated receptor autophosphorylation (23). Although this is not apparent for phot1 (23), it does raise the question as to how LOV1 can mediate autophosphorylation for phot2. A further challenge will be to uncover the mode of action of *Adiantum* neo and whether red-light-induced photoactivation of its N-terminal phytochrome chromophore-binding domain leads to receptor autophosphorylation.

The kinase domain of plant phototropins is closely related to the catalytic subunit of cAMP-dependent protein kinase A (PKA). Indeed, PKA has been shown to exhibit the same phosphorylation-site specificity as the kinase domain of oat phot1 for autophosphorylation (127). In its inactive state, PKA comprises two regulatory and two catalytic subunits (153). Each regulatory subunit inhibits kinase activity, which is achieved through the presence of a pseudosubstrate sequence within the

NMR: nuclear magnetic resonance

PKA: protein kinase A

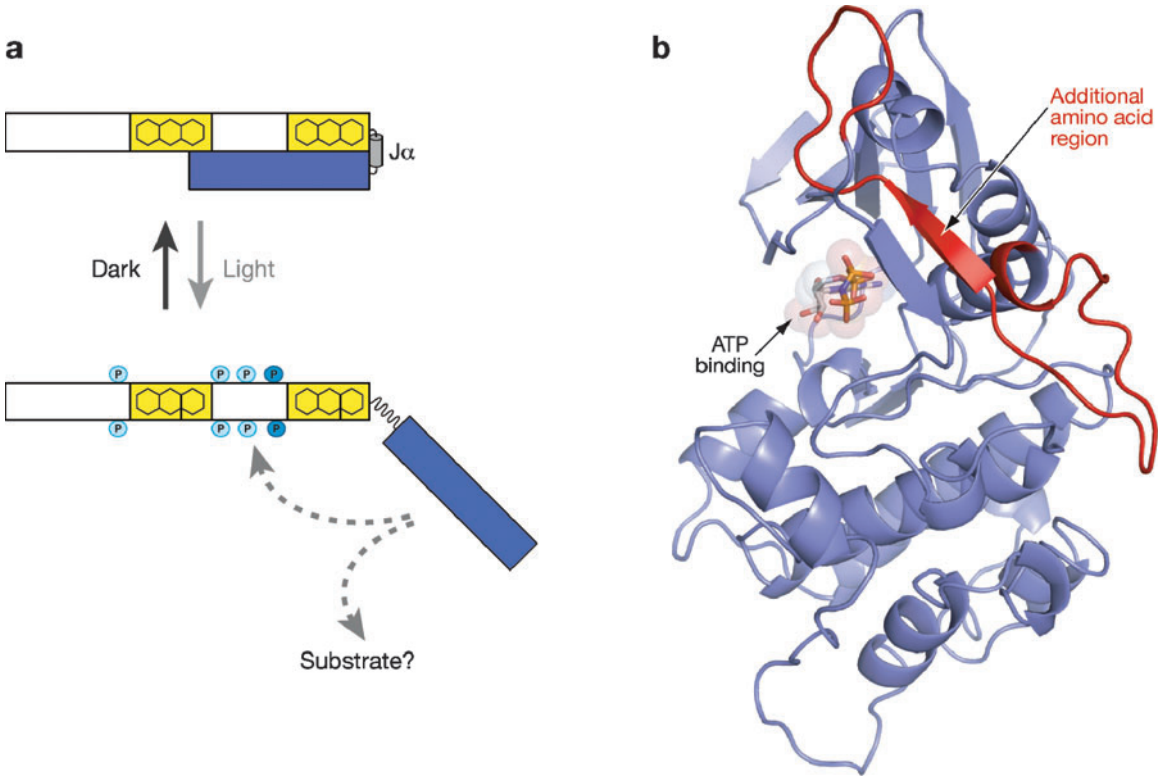

Figure 4

Phototropin kinase regulation. (*a*) Schematic overview of phototropin receptor activation by light. In the dark or ground state, the phototropin receptor is unphosphorylated and inactive. Absorption of light by the predominant light sensor LOV2 results in a disordering of the Jα-helix and activation of the C-terminal kinase domain, which consequently leads to autophosphorylation of the photoreceptor and possibly phosphorylation of an as-yet-unidentified protein substrate(s). Relative positions of known phosphorylation sites are indicated and color-coded based on their hierarchical pattern of occurrence (127): pale blue, low/intermediate fluence phosphorylation sites; dark blue, high fluence phosphorylation sites. (*b*) Structure of the kinase domain of *Arabidopsis* phot1 as determined by homology modeling based on Protein Data Bank ID codes 1O6KA, 1O6LA, and 1ZRZA. The position of the ATP-binding site is indicated. The additional amino acid region present in the phot1 kinase domain is shown in red.

regulatory subunit that specifically occupies the catalytic site of PKA (86). Binding of cAMP to the regulatory subunits leads to a release of the enzymatically active catalytic subunits (153). It is possible that LOV2 may regulate the kinase activity of plant phototropins through a similar mechanism. However, no pseudosubstrate sequence associated with the LOV2 apoprotein has been identified.

The catalytic subunit of PKA adopts a two-lobed structure connected by a deep cleft that functions as the catalytic site (159). Comparative modeling indicates that the kinase domain of *Arabidopsis* phot1 adopts a similar structure to the catalytic subunit of PKA (**Figure 4*b***). One noticeable difference in structure observed for the kinase domains of plant phototropins is the presence of an additional amino acid region within subdomain VIII. This region is rich in polar residues, but its functional significance is unknown. Interestingly, subdomain VIII plays a role in substrate recognition (53). Furthermore, subdomain VIII of many protein kinases, including

PKA, contains a conserved threonine residue that when phosphorylated results in maximal kinase activity (1). This residue is conserved in *Arabidopsis* phot1 and phot2 as a serine (107), raising the possibility that this mode of activation may also occur for plant phototropins. A peptide region C-terminal to the kinase domain in *Adiantum* phot2 is essential for mediating chloroplast avoidance movement (75). The functional significance of this region is currently not known but is likely to serve an important function given that it is conserved among higher and lower plant phototropins (75).

Sites and Function of Receptor Autophosphorylation

Phosphorylation of the N-terminal photosensory region of oat phot1 by PKA exhibits the same phosphorylation-site specificity as that observed for phot1 autophosphorylation in protein extracts from dark-grown oat coleoptiles (127). Mapping of these phosphorylation sites indicates that there are eight serine residues within the N-terminal region of oat phot1 that become phosphorylated (127). Two of these sites (Ser^{27}, Ser^{30}) are located before LOV1, near the N terminus of the protein (**Figure 4*a***). The remaining sites (Ser^{274}, Ser^{300}, Ser^{317}, Ser^{325}, Ser^{332}, and Ser^{349}) are located in the peptide region between LOV1 and LOV2. Light-dependent autophosphorylation of oat phot1 in vivo occurs in a fluence-dependent manner (127). Sites close to LOV1 (Ser^{27}, Ser^{30}, Ser^{274} and Ser^{300}) are phosphorylated at low fluences of blue light. The remaining four sites, on the other hand, are phosphorylated in response to intermediate or high fluences of blue light. Photoactivated phot1 in vivo has been shown to return to its nonphosphorylated state upon incubation in darkness (52, 89, 129, 136). The mechanism underlying this recovery process is not known, but likely involves the activity of an as-yet-unidentified protein phosphatase.

Despite these findings, the biochemical consequences of receptor autophosphorylation are still poorly understood. Autophosphorylation requires more light than is needed for a number of phototropin-mediated responses (15), indicating that it is not the primary signaling event. However, the hierarchical pattern of autophosphorylation observed for oat phot1 (127) is proposed to result in different biochemical consequences. The low/intermediate fluence phosphorylation sites may play a role in receptor signaling, whereas the high fluence phosphorylation sites may be involved in receptor desensitization (127). *Chlamydomonas* phot lacks the N-terminal extension preceding LOV1 found in higher plant phototropins but is still able to restore phot1- and phot2-mediated responses when introduced into the *phot1 phot2* double mutant of *Arabidopsis* (118). Hence, the two-phosphorylation events upstream from LOV1 in higher plant phototropins are not essential for phototropin function. One consequence of autophosphorylation may be to promote receptor dissociation from the plasma membrane. *Arabidopsis* phot1 and phot2 are hydrophilic proteins but are localized to the plasma membrane (95, 125). The nature of membrane association remains unknown but it is thought to involve posttranslational modification or binding of a membrane protein anchor. Studies involving GFP fusions show that a fraction of phot1 is rapidly internalized (within minutes) from the plasma membrane in *Arabidopsis* upon blue-light irradiation (125). Similarly, a fraction of phot2 moves to the Golgi apparatus upon blue-light irradiation (95). Although the functional significance of this partial redistribution is currently unknown, the kinase domain of phot2 appears to be essential for Golgi localization (95).

So far, there is no direct evidence to indicate that phototropins initiate signaling through the activation of a phosphorylation cascade. A truncated version of phot2 comprising only the LOV2 domain and the C-terminal kinase domain is able to complement chloroplast avoidance movement in a *phot2* mutant of *Adiantum* (75). Given that the sites of phototropin autophosphorylation are

GFP: green fluorescent protein

located before LOV2 (127), it is tempting to speculate that phot2 uses some means other than autophosphorylation to bring about this response. However, until now the only substrate identified for phot2 kinase activity is the artificial substrate casein (108).

PHOTOTROPIN RECEPTOR SIGNALING

Phototropism

Phototropic curvature is mediated by an increase in growth on the shaded side of the stem resulting from an accumulation of the plant growth hormone auxin (65). At present, little is known about how phototropin activation by blue light leads to an accumulation of auxin on the shaded side of the stem. Unilateral irradiation has been shown to induce a gradient of phot1 autophosphorylation across oat coleoptiles, with the highest level of phosphorylation occurring on the irradiated side (131, 132). A phosphorylation gradient model has therefore been proposed to account for the complex fluence response curve for phototropism (131), but the question still remains as to how a gradient in phototropin phosphorylation across the stem can bring about a lateral gradient in auxin.

Insights into the signaling mechanisms involved in phototropism have again come from *Arabidopsis* mutants. The nonphototropic hypocotyl mutant *nph3* (101, 102) led to the identification of a phot1-interacting protein that is essential for lateral auxin redistribution (50) and phototropism (50, 109). NPH3 is a novel protein containing several protein interaction motifs and has been shown to interact with phot1 in vitro (109) and in vivo (98). Like the phototropins, NPH3 is hydrophilic in nature but is associated with the plasma membrane (109). Although its biochemical function is unknown, NPH3 most likely serves as a scaffold to assemble components of a phototropin receptor complex. NPH3 is a member of a large plant-specific gene family consisting of 31 members in *Arabidopsis* (18) and at least 24 in rice (87). A protein closely related to NPH3, designated Root Phototropism 2 (RPT2), has also been shown to bind phot1 and is required for both phototropism and stomatal opening by blue light (69, 123, 124). Although the interaction between phot1 and RPT2 is unaffected by light (69), blue-light irradiation is reported to alter the phosphorylation status of NPH3. NPH3 appears to be phosphorylated in the dark and becomes dephosphorylated upon exposure to blue light (109). More recently, studies demonstrated that Phytochrome Kinase Substrate (PKS) proteins are required for hypocotyl phototropism in *Arabidopsis* (98). PKS1 binds both phot1 and NPH3 in vivo (98). Because phytochromes influence phototropic curvature in *Arabidopsis* (66), PKS proteins may provide a link between these two photoreceptor families.

Genetic analysis has also shown that auxin responsiveness is necessary for phototropism. Auxin-regulated transcription factors such as Nonphototropic Hypocotyl 4 (NPH4) and Massugu 2 (MSG2) are required for normal phototropism and gravitropism (55, 143, 151), highlighting the need for auxin-regulated gene expression. Activities of NPH4 and MSG2 are likely to be regulated by the recently identified auxin receptor Transport Inhibitor Response 1 (TIR1), a subunit of the Skp1-Cullin-F-box $(SCF)^{TIR1}$ complex, which targets proteins for degradation in the presence of auxin (30, 85). The identities of auxin-regulated gene targets involved in phototropism were recently uncovered using a transcriptomic approach (38). Gene targets of NPH4 action whose expression levels increase on the elongating side of phototropically stimulated *Brassica oleracea* hypocotyls include two members of the α–expansin family, *EXPA1* and *EXPA8*. Because members of the α–expansin family mediate cell wall extension, EXPA1 and EXPA8 may have important roles in the establishment of phototropic curvatures.

Further genetic studies have demonstrated that auxin transport is required

for phototropism. Mutants impaired in the localization of the putative auxin efflux carrier Pinformed 1 (PIN1) exhibit altered hypocotyl phototropism (10, 113). PIN3, a second member of the *Arabidopsis* PIN family, also appears to play a role in establishing the lateral auxin gradient required for phototropism (45). Given that phot1 photoactivation results in a change in PIN1 localization in *Arabidopsis* hypocotyls cells (10), a regulation of auxin transporter localization may represent a major point of control in the development of phototropic curvatures. Furthermore, phot1 is more strongly localized to the plasma membrane adjacent to the apical and basal walls rather than the sidewalls in the cells associated with auxin transport (125). This would place phot1 in an ideal location to influence the activity or distribution of auxin influx and efflux carriers. However, such a mechanism is likely to be complex since PIN proteins appear to act in conjunction with members of a second transporter family of p-glycoproteins to bring about active auxin transport in *Arabidopsis* (48).

Stomatal Opening

Stomatal guard cells of the *phot1 phot2* double mutant fail to extrude protons in response to blue-light treatment (88). Proton extrusion is essential for stomatal opening and involves activation of the plasma membrane H^+-ATPase (31). Activation of the guard cell H^+-ATPase involves phosphorylation of the H^+-ATPase and 14-3-3 binding (90, 92). Similarly, phot1 from *Vicia faba* (broad bean) guard cells binds a 14–3-3 protein upon autophosphorylation (89). Specifically, 14–3-3 binding to *Vicia* phot1 requires phosphorylation of Ser^{358} situated between LOV1 and LOV2, which is equivalent to Ser^{325} of oat phot1 that is phosphorylated in response to intermediate fluences of blue light (127). Thus, one consequence of phototropin autophosphorylation is to mediate 14–3-3 binding. 14–3-3 proteins belong to a highly conserved protein family that typically bind to phosphorylated target proteins and regulate signaling in eukaryotic cells (40). One might speculate that the binding of 14–3-3 proteins may facilitate a direct interaction between phototropins and the guard cell H^+-ATPase. Yet, the fungal toxin fusicoccin has been shown to induce phosphorylation of the H^+-ATPase and subsequent 14–3-3 binding in the absence of phot1 and phot2, implying that some other protein kinase is responsible for phosphorylation of the H^+-ATPase (91, 155). Indeed, the signaling pathway between the phototropins and the H^+-ATPase was recently reported to involve the activity of type 1 protein phosphatase in broad bean guard cells (150a). Further work is now needed to clarify the functional significance of 14–3-3 binding, especially since 14–3-3 binding to the phototropins has also been observed in etiolated seedlings (89).

A novel phot1-interacting protein from *Vicia* guard cells was isolated using a yeast two-hybrid approach (37). This protein, designated VfPIP1 (*Vicia faba* Phot1a-interacting Protein 1), shows homology to dyneins, proteins associated with microtubule function in animal cells. VfPIP is localized to cortical microtubules in *Vicia* guard cells (37), and may function in organizing the guard cell cytoskeleton to promote stomatal opening.

Chloroplast Movement

Arabidopsis mutants impaired in blue-light-induced chloroplast movements have also provided insights into the signaling events acting downstream of phototropin receptor activation. The isolation of mutants lacking chloroplast avoidance movement has led to the identification of CHUP1 (79, 117). CHUP1 (Chloroplast Unusual Positioning 1) is a novel F-actin-binding protein (117), consistent with the known requirement for cytoskeletal changes during chloroplast movement (156). CHUP1 confers the ability to target GFP into the chloroplast envelope (117), suggesting that CHUP1 may function at the periphery of the chloroplast outer membrane. In addition to lacking chloroplast

BAPTA: 1,2-bis(2-aminophenoxy)-ethane-N,N,N,M-tetraacetic acid

avoidance movement, *chup1* mutants exhibit aberrant chloroplast positioning in which chloroplasts are constantly gathered at the bottom of palisade cells, in contrast to wild type (117). Thus, CHUP1 most likely represents an essential component of the machinery required for chloroplast positioning and movement. Similarly, the plastid movement–impaired mutant *pmi1* exhibits severely attenuated chloroplast movements under low and high light intensities (29), indicating that PMI1 is necessary for both chloroplast accumulation and avoidance movements. By contrast, lesions in *PMI2* and *PMI5* lead only to impaired chloroplast avoidance movement (105). PMI2 and PMI5, like PMI1, represent novel plant-specific proteins whose modes of action have yet to be elucidated.

A genetic screen designed to isolate mutants altered in chloroplast accumulation movement has identified the protein JAC1 (144). JAC1 (J-domain Protein Required for Chloroplast Accumulation Response 1) is a cytosolic protein specifically required for chloroplast accumulation movement. Although its biochemical function is unknown, the C terminus of JAC1 exhibits homology to auxilin, a protein that plays a role in clathrin-mediated endocytosis in animal cells. The functional significance of this domain in regulating chloroplast accumulation movement now awaits further characterization of the JAC1 protein.

Calcium and the Rapid Inhibition of Hypocotyl Growth

Phototropin activation leads to an increase in cytosolic Ca^{2+} concentrations (9). Pharmacological experiments indicate that changes in cytosolic Ca^{2+} are required for the phot1-mediated inhibition of hypocotyl growth (42). The calcium-specific chelator BAPTA inhibits the phot1-mediated increase in intracellular Ca^{2+} levels observed in *Arabidopsis* seedlings (42). An equivalent BAPTA treatment prevents the rapid inhibition of hypocotyl elongation by blue light but has no effect on phototropism (42). However, phot2 as well as phot1 is reported to stimulate increases in cytosolic Ca^{2+} in *Arabidopsis* leaves (54, 142). Both phot1 and phot2 can mediate an influx of Ca^{2+} from the apoplast, whereas only phot2 can induce a release of Ca^{2+} from intracellular stores (5, 54). It is therefore likely that Ca^{2+} serves as signal messenger in processes other than hypocotyl growth inhibition. Indeed, changes in intracellular calcium levels are important for light-induced stomatal opening (31) and chloroplast movements (156). Likewise, electrophysiological studies indicate that phototropic bending involves changes in ion fluxes, including calcium (4). Intriguingly, as found for chloroplast accumulation movement (123) and the promotion of growth under low light conditions (150), phot2 is less sensitive than phot1 in mediating blue-light-induced calcium fluxes (54), again indicating that phot1 and phot2 exhibit different photosensitivities in vivo. Readers are directed to the following excellent review (54a) for further details regarding phototropin-induced Ca^{2+} changes.

OTHER LOV SENSOR PROTEINS

Light-sensitive LOV domains have also been identified in plant proteins other than the phototropins. These proteins constitute a new class of putative blue-light receptors known as the ZTL/ADO family (7) and comprise three members: Zeitlupe (ZTL, also referred to as Adagio, ADO); Flavin-binding, Kelch Repeat, F-box 1 (FKF1); and LOV Kelch, Protein 2 (LKP2). A detailed account of these proteins is beyond the scope of this article and the reader is directed to the following recent publication for further details (133). Gain- and loss-of-function analyses have shown that these proteins are required for circadian clock function and photoperiodic-dependent flowering in *Arabidopsis* (73, 93, 112, 134, 141).

ZTL, FKF1, and LKP2 share three characteristic domains: a phototropin-like LOV domain at the N terminus followed by an

F-box motif and six kelch repeats at the C terminus (7). The F-box motif is typically found in E3 ubiquitin ligases, which target proteins for degradation via the ubiquitin-proteosome system (140). In fact, evidence now indicates that members of the ZTL/ADO family mediate their effects by targeting key regulatory components for proteolysis (67, 106). Kelch-domain repeats form a β-propeller structure (99) thought to be involved in mediating protein-protein interactions. The LOV domains of ZTL, FKF1, and LKP2 contain the 11 conserved residues necessary for flavin binding, including the cysteine required for photochemical reactivity (28). Indeed, bacterially expressed LOV domains derived from each of these proteins exhibit photochemical properties analogous to those of the phototropin LOV domains (68, 111). Yet, unlike the phototropin LOV domains, the LOV domains of ZTL, FKF1, and LKP2 fail to revert back to their dark state (68, 111). Whether this inability to recover to the dark state is related to their physiological functions remains unknown. Nonetheless, the demonstration of light-driven cysteinyl adduct formation provides strong evidence that these proteins function as blue-light receptors.

Of these three proteins, only FKF1 has been demonstrated to function as a photoreceptor (68). Expression of FKF1 peaks late in the day and on long days is activated by light to mediate the degradation of CDF1 (Cycling Dof Factor 1), a transcriptional repressor of CONSTANS (CO) (67), a key factor required for the photoperiodic control of flowering. FKF1 thus plays a role in detecting long days and activating the photoperiodic flowering pathway in *Arabidopsis*. To date, no specific photoreceptor role has been ascribed to either ZTL or LKP2.

A search of the *Arabidopsis* genome has uncovered a unique LOV-domain-containing protein that is unrelated to the phototropins or the ZTL/ADO family. This protein, referred to as PAS/LOV (28), contains a conventional PAS domain followed by a phototropin-like LOV domain. To date, the function of this protein remains unknown. It will now be important to establish whether PAS/LOV binds a flavin cofactor and represents an as-yet-uncharacterized blue-light receptor in *Arabidopsis*.

LOV-domain-containing proteins are not only restricted to plants. White Collar-1 (WC-1) is a fungal blue-light receptor that contains a single LOV domain and has been shown to function as a photoreceptor for phototropism and other light responses in *Neurospora crassa* and other fungi (6, 46, 58, 63, 64). A second *Neurospora* protein VIVID (VVD) consists mostly of a LOV domain and plays an important role in mediating photoadaptive responses (59, 135, 139) and facilitating circadian clock entrainment (36). In addition, a large number of otherwise very different bacterial proteins contain LOV domains (28, 103). Those bacterial proteins investigated to date show typical LOV-domain photochemistry (28, 103). No biological function has yet been linked to these putative blue-light receptors.

FUTURE PROSPECTS

In the past decade, the progress made in understanding the photochemical and biochemical properties of the phototropins in addition to their physiological roles has been enormous. Identification of the LOV domain as a blue-light-sensing motif and deciphering its structure and photochemical reactivity represent a major advance. Furthermore, the presence of LOV-domain-containing proteins throughout various kingdoms of life clearly demonstrates that this functional light sensor is not only restricted to plants but has been conserved throughout evolution. Yet, we are still far from understanding the complete mechanistic picture with regard to receptor photoactivation. For instance, what is the function of LOV1? And what is the exact role(s) of receptor autophosphorylation? Further biochemical and structure-function analyses are now needed to address such

questions. To date, biophysical and structural studies have been directed to regions of the phototropin molecule lacking the C-terminal kinase domain. Extending these studies to LOV2-kinase fragments and ultimately the full-length receptor protein will provide a greater understanding of the photosensory transduction pathway underlying phototropin activation. A major challenge for the future will be to unravel the processes associated with phototropin signaling and how these relate to components that have already been identified, including increases in cytosolic Ca^{2+}, 14–3-3 proteins and members of the NPH3/RPT2 family. The identification of the LOV-sensing motif in proteins other than the phototropins greatly expands the possible directions for future research. Evidently, much work remains to be done and the coming decade will undoubtedly yield exciting advances in our knowledge of phototropin receptor function and signaling.

SUMMARY POINTS

1. Phototropins act to control a number of plant processes that serve to optimize photosynthetic performance, including phototropism after which they were named.
2. Phototropins are plasma membrane-associated serine/threonine photoreceptor kinases that undergo autophosphorylation in response to blue-light excitation.
3. Light sensing by the phototropins is mediated by a conserved motif called the LOV domain that binds the light-absorbing cofactor FMN.
4. Phototropins possess two FMN-binding LOV domains that exhibit distinct functional roles in regulating photoreceptor activation.
5. Induction of phototropin kinase activity by LOV2 occurs through light-driven structural changes involving a conserved α-helix designated Jα.
6. Phototropin autophosphorylation occurs on multiple serine residues in a fluence-dependent manner, the consequences of which may play a role in receptor signaling, receptor desensitization or receptor relocalization.
7. Genetic and biochemical analyses have uncovered novel plant-specific components associated with phototropin receptor signaling, in addition to 14–3-3 proteins and intracellular calcium.
8. LOV-domain-containing proteins besides the phototropins have been identified in plants, fungi, and bacteria and represent further blue-light receptors.

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Annual Review of Plant Biology
Volume 58, 2007

Contents

Indexes

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