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The Complexity of Fungal Vision

REINHARD FISCHER,[1] JESUS AGUIRRE,[2] ALFREDO HERRERA-ESTRELLA,[3] and LUIS M. CORROCHANO[4]

[1]Karlsruhe Institute of Technology (KIT), Institute of Applied Biosciences, Department of Microbiology, D-76131 Karlsruhe, Germany; [2]Departamento de Biología Celular y del Desarrollo, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Mexico City, Mexico; [3]Laboratorio Nacional de Genómica para la Biodiversidad, CINVESTAV-Irapuato, Irapuato, Guanajuato 36821, Mexico; [4]Department of Genetics, University of Seville, 41012 Seville, Spain

ABSTRACT Life, as we know it, would not be possible without light. Light is not only a primary source of energy, but also an important source of information for many organisms. To sense light, only a few photoreceptor systems have developed during evolution. They are all based on an organic molecule with conjugated double bonds that allows energy transfer from visible (or UV) light to its cognate protein to translate the primary physical photoresponse to cell-biological actions. The three main classes of receptors are flavin-based blue-light, retinal-based green-light (such as rhodopsin), and linear tetrapyrrole-based red-light sensors. Light not only controls the behavior of motile organisms, but is also important for many sessile microorganisms including fungi. In fungi, light controls developmental decisions and physiological adaptations as well as the circadian clock. Although all major classes of photoreceptors are found in fungi, a good level of understanding of the signaling processes at the molecular level is limited to some model fungi. However, current knowledge suggests a complex interplay between light perception systems, which goes far beyond the simple sensing of light and dark. In this article we focus on recent results in several fungi, which suggest a strong link between light-sensing and stress-activated mitogen-activated protein kinases.

INTRODUCTION

Sunlight, harvested by photosynthetic organisms (plants, algae, and some bacteria) and used to synthesize energy-rich molecules (sugars) from carbon dioxide and water, provides the energy required to sustain life on Earth. In addition, sunlight properties such as intensity, duration, polarization, and spectral composition are used as sources of information (1). Indeed, all forms of life are continuously obtaining and decoding information from their environment. In fungi sunlight, ranging from ultraviolet (UV) to infrared wavelengths, regulates a diversity of biological processes including circadian rhythms, morphogenesis, tropism, and synthesis of pigments, among others (reviewed in reference 1). UV light can be harmful, since DNA modification products of photochemical reactions may be transmitted to the next generation as a mutation. Visible light appears not only to provide early warning of the presence of impending UV radiation and further damage, but also seems to contribute to the capacity of these organisms to deal with abiotic stress in general (2–5). Thus, the ability of most fungi to perceive and respond to light has very likely contributed to their survival and fitness.

Light responses in fungi, some of which can be extremely rapid (e.g., phototropism), were observed more than 150 years ago, and light-induced alterations in fungal morphology have been described for hundreds of fungi (6, 7). Responses may be triggered by very low light and require only nanoseconds to minutes of exposure with a rate of photons that could be only 10^{-10} mol of photons m^{-2} (8–10). Long-term effects of light rely mainly on genetic reprogramming of the fungal genome and usually involve major changes in gene expression patterns. A major question is how such coor-

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Correspondence: Reinhard Fischer, reinhard.fischer@KIT.edu

dinated activation and repression of hundreds of genes is achieved. Photoreceptors are proteins that contain light-sensing chromophores that modulate their biological activity after photoreception (10). The first step of light perception is a physical reaction, the absorption of photons by an organic molecule followed by conformational protein changes and transduction into biochemical reactions such as phosphorylation events.

Few physical and many genetic, molecular biology, and biochemical analyses have provided detailed information on the mechanisms of fungal vision. Although many open questions remain, it becomes clear that light sensing is a rather complex and multifaceted process with a strong impact on most aspects of fungal life. Hence, although most results rely on studies of a few model organisms, foremost *Neurospora crassa* but also *Aspergillus nidulans*, *Phycomyces blakesleeanus*, and *Trichoderma atroviride*, the strong impact of light in these organisms prompted studies of other fungi with pathogenic or symbiotic lifestyles or with biotechnological potential. All these studies continuously improve our knowledge of light regulation and help to unravel common principles but also species- or lifestyle-specific impacts of light. As a consequence of the growing number of publications combined with a long history of the field, it would be impossible to give a comprehensive overview and discuss all papers related to fungal vision. Instead we will concentrate on recent findings and refer to older publications when necessary. For more information the reader is referred to references 10 through 17.

FUNGAL VISION: THE PHENOMENON

Light represents only a small fraction of the electromagnetic radiation produced by the sun that organisms use for photosynthesis, photomorphogenesis, or orientation in the environment. Human vision, for instance, detects wavelengths between roughly 400 and 700 nm. However, shorter wavelengths such as UV and X rays (which are rare in nature) are also important, due to their damaging effects. Thus, the reaction of organisms to light can be divided into reactions to damaging irradiation and reactions to visible light (as defined by the human eye). Whereas the sensing and reaction to damaging radiation seems obligated for life on Earth, the reaction to visible light could be optional. However, one important function of light sensing may be the adaptation to harmful irradiation because visible light is a reliable indicator of the presence of UV radiation during the day.

Most fungi are able to sense and respond to light, with only a few exceptions that lack any indication of genes for sensing light (Fig. 1). Those organisms include the yeasts *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae* and some dermatophytic pathogenic fungi such as *Microsporum*. An exception appears to be the fission yeast *Schizosaccharomyces japonicus*, in which a blue-light effect and the presence of blue-light photosensors have been reported. However, it has to be considered that *S. japonicus* is a dimorphic fungus, which can switch between yeast and hyphal form (18). It has been speculated that light sensing may be of special interest for multicellular fungi that constantly need to adapt to changing environments (16). Most fungi respond in one or another way to light, and it is important to mention that only in some cases have the analyses of light responses been done using defined wavelengths (i.e., light-emitting diodes or monochromatic filters) and strict control of fluence rates (19–23).

Development of Basidiomycetes fruiting bodies depends on, among other factors, light or light-dark cycles (24). Scientists noted 60 years ago that under laboratory conditions the mushroom *Cyathus stercoreus* required light to initiate fruiting body development (25). Later it was shown that *Coprinus macrorhizus* primordia formation and stalk development, as well as the timing of meiosis, were all light dependent (26, 27). Some mushrooms not only produce meiotically derived spores in their caps, but are also able to generate different asexual spores, named oidia or chlamydospores. Oidia formation occurs in monokaryons and dikaryons of *Coprinus cinereus* and is blue-light dependent in dikaryons but not in monokaryons (28). In the basidiomycetous dimorphic yeast *Cryptococcus neoformans*, blue light controls growth, development, and virulence (29, 30).

In ascomycetes, light also has a strong impact in morphological and physiological processes, including the regulation of conidial germination, hyphal branching, sexual and asexual development, and secondary metabolism. Blue light induces sporulation in many ascomycetes, such as *T. atroviride*, *Aspergillus ornatus*, and *Penicillium isariiforme* (31). In contrast, *Alternaria solani* and *Botrytis cinerea* produce conidiophores under starvation conditions and after induction with UV light, which—if kept in the dark—produce conidia. Blue light inhibits the last step, conidia formation (31, 32). Furthermore, the inhibitory effect of blue light can be reversed by red-light illumination, which again can be reversed by far-red light (33). These complicated photoconidiation experiments suggested the presence of several photoreceptors in *B. cinerea*. In *A. nidulans*, conidiation is also induced by blue and red light, which together reach the level of white-light induction (34).

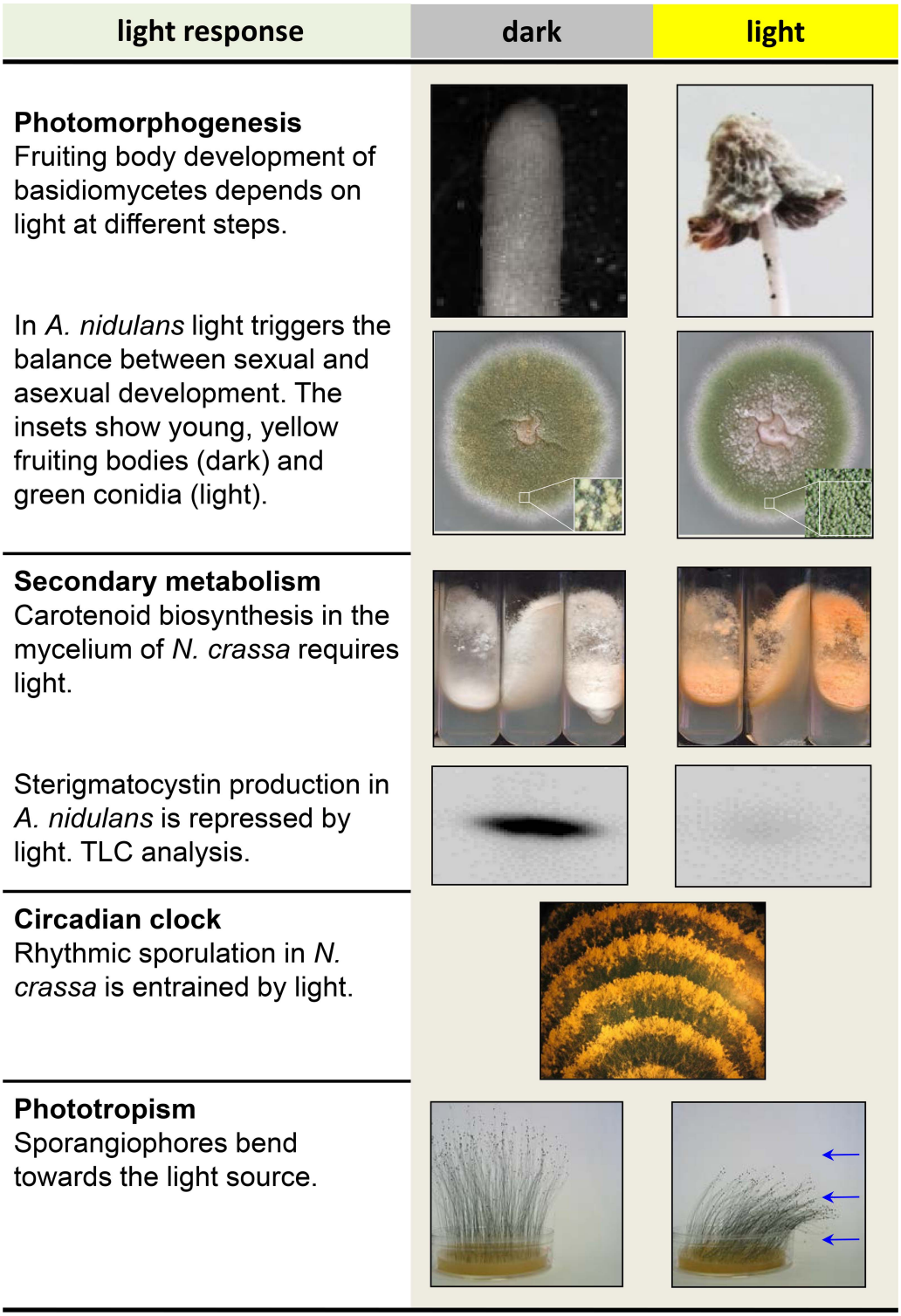


FIGURE 1 Phenomena of fungal responses to light. Light has a large impact on fungal morphology and physiology. The pictures of *Coprinus cinereus* were provided by Shanta Subba and Ursula Kües (University of Göttingen).

Hence, light controls the balance between asexual and sexual development in this fungus (35). In *Trichoderma reesei* sexual development occurs in light (36), whereas in *N. crassa* fruiting bodies can be produced in the dark, although the number of protoperithecia is greatly increased upon exposure to blue light (37). Additionally, the position of the perithecium neck is also light dependent (38), with necks oriented to the light source but randomly oriented in the dark (39). Light is also required to obtain the maximum number of conidia in *N. crassa*, with a 4-fold increase in the number of conidia obtained in the light over the number obtained in the dark (40).

Germination, growth, and secondary metabolism are also affected by light. In *A. fumigatus* and *A. nidulans* light inhibits spore germination (41, 42), whereas it promotes hyphal branching in *N. crassa*, *Tuber borchii*, *T. atroviride*, and the plant pathogen *Colletotrichum trifolii*. Therefore, colonies look more compact in the presence of light (40, 43–45). In *N. crassa* and *Fusarium fujikuroi*, light activates the biosynthesis of carotenoids in vegetative mycelia, resulting in hyphae with a deep-orange color (46, 47). In *A. nidulans* sterigmatocystin (an aflatoxin precursor) and penicillin production are regulated by light (34, 48, 49). The study of the circadian clock in *N. crassa*, a light-regulated phenomenon, led to an enormous stimulation of the entire research field (15, 50–52). Conidiation in *N. crassa* is governed by a circadian clock that can be entrained by light (53), and it turned out that a main component of the clock system is the blue-light photoreceptor WC-1 (50, 54, 55).

Within zygomycetes, light regulates many aspects of the biology of *P. blakesleeanus*, *Mucor circinelloides*, and *Pilobolus crystallinus*, including growth and growth direction of fruiting bodies (phototropism), the development of sexual and asexual reproductive structures, and the biosynthesis of the beta-carotene pigment (56). Light effects have also been described in other basal fungi, including the regulation of zoospore mobility in the chytridiomycete fungus *Allomyces reticulatus* (57) and phototaxis in *Blastocladiella emersonii* (58). All these phenomena illustrate well the broad distribution of fungal vision and support the early evolutionary appearance of this feature.

The great variety of phenomena observed in response to light suggests that illumination causes a large reprogramming of the genetic machinery in fungal cells. Indeed, many genome-wide expression studies in various fungi show that hundreds of genes representing a significant fraction of the genome (5 to 10%) are differentially regulated by light (59–66). Whereas in animals one type of photoreceptor, rhodopsin, is used to sense blue, green, and red light, microbial eukaryotes and bacteria employ different classes of photoreceptors, each perceiving a narrow spectrum of light in the blue, green, or red part of the rainbow (Fig. 2). Here, we summarize the main properties of the classes of photoreceptors present in fungi.

PHOTOSENSORY PROTEINS AND THEIR MODES OF ACTION

The Flavin-Based White Collar Photoperception System

The search for components of the light perception machinery in fungi was first approached in *P. blakesleeanus* and *Trichoderma viride* (67–70). Max Delbrück and his research group described in detail the properties of *Phycomyces* responses to light and initiated the genetic study of the signal transduction pathways (68). Eventually, it was concluded that in both fungi the most likely receptor for blue-UV light was a flavoprotein (69–71). More than 30 years later the *T. atroviride* blue-light regulator gene (*blr1*) was cloned, corroborating the original conclusions reached based on action spectra (45). Blr1 belongs to a family of fungal blue-light receptors, whose founding member is the white collar-1 (WC-1) protein of *N. crassa* (72, 73). In *A. nidulans* the WC proteins are also conserved, although their role appears to be different because red light and phytochrome play dominant roles in light sensing (34, 74). Fungal photoreceptors belonging to the WC-1 family contain three PAS domains, the first of which is a LOV (light, oxygen, voltage) domain (55). LOV domains are specialized domains belonging to the PAS (Per Arnt Sim) superfamily and are present in proteins that sense UV-blue light in plants and fungi. They are about 110 to 120 amino acids in length and adopt a conserved α/β-fold that binds flavin dinucleotide (FAD) or flavin mononucleotide. Upon absorption of blue light, LOV domains undergo a photocycle, transiently forming a covalent flavin-thiol adduct with a conserved cysteine residue present in the LOV domain (75). The other two PAS domains are involved in protein-protein interactions (76). These photoreceptors also contain GATA zinc finger DNA binding domains, nuclear localization signals, and activation domains in several cases (10). However, there are exceptions to the presence of the activation domains, suggesting the involvement of additional proteins for the control of gene expression (1). The *N. crassa* WC-1 protein dimerizes with its partner, the WC-2 protein, which contains a PAS, a GATA zinc finger do-

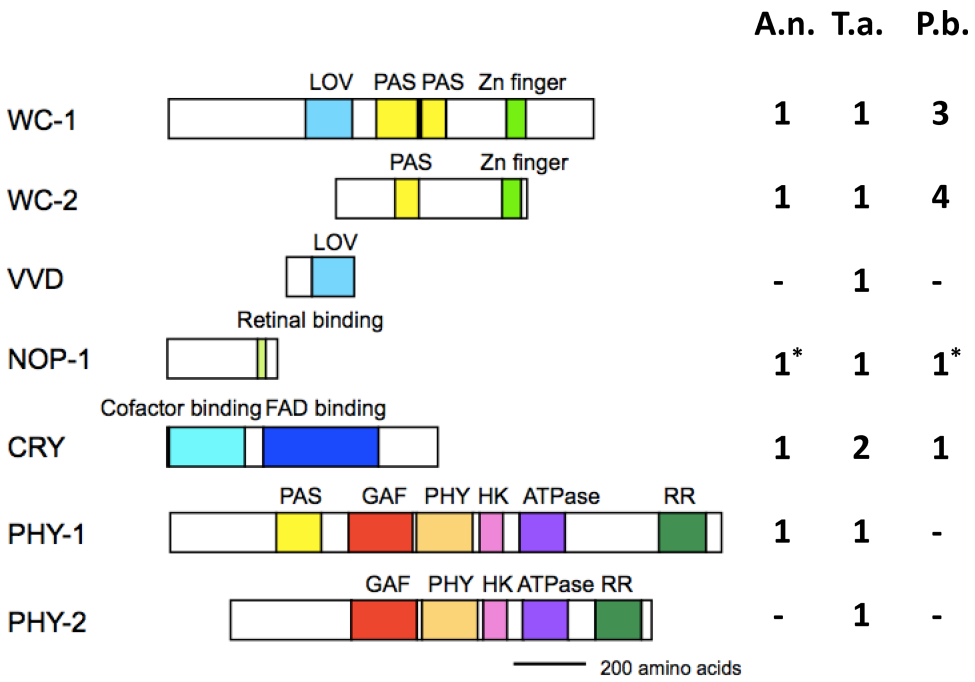


FIGURE 2 Schemes of the *Neurospora crassa* photoreceptor proteins and their presence in *Aspergillus nidulans*, *Trichoderma atroviride*, and *Phycomyces blakesleeanus*. The figure shows the set of *N. crassa* photoreceptors and a comparison of the presence of homologous genes in other model fungi, including the LOV-domain photoreceptors WC-1 and VIVID (VVD) together with WC-2, the protein that interacts with WC-1 to form the WC complex. Other photoreceptors identified in the *Neurospora* genome are a rhodopsin (NOP-1), a cryptochrome (CRY), and two phytochromes (PHY-1 and PHY-2). LOV-domain photoreceptors contain the flavin chromophore-binding domain (LOV) and may also contain the protein-interaction domains (PAS) and the Zn finger domain. Rhodopsins contain the retinal-binding domain. Cryptochromes contain the FAD chromophore-binding domain and the domain for binding the antenna cofactor. Phytochromes contain an amino-terminal sensory domain and a carboxy-terminal output domain. The sensory domain involved in binding the bilin chromophore is composed of three domains (PAS, GAF, and PHY). The output domain is composed of the histidine kinase domain (HK), the ATPase domain found in ATP binding proteins, and the response-regulator domain (RR) that is likely involved in relaying the light signal to other proteins. The number indicates the presence and number of photoreceptor protein encoding genes in the genomes of *A. nidulans* (A.n.), *T. atroviride* (T.a.), and *P. blakesleeanus* (P.b.). The * indicates that the protein is present but lacks the critical lysine residue required for retinal binding.

main, and an activation domain to form the WC complex (WCC). Through Chip-Seq experiments, WCC has been found to directly control gene expression, functioning as a transcriptional factor (77). Only WC-2 is required for binding the WCC to DNA, whereas the zinc finger of WC-1 is needed for clock-related DNA regulation and DNA binding of the WCC. This suggests different mechanisms of gene regulation for light or clock-related processes (78). Mutants in either *wc-1* or *wc-2* are affected in all known blue-light responses. Similarly, mutants in the orthologs of these genes in other fungi are clearly affected in blue-light perception (1, 17).

As a product of genome duplication events, multiple WC genes are found in the *M. circinelloides* and *P. blakesleeanus* genomes (66). In *M. circinelloides*, three *N. crassa* WC-1 orthologous genes (*mcwc-1a*, *mcwc-1b*, and *mcwc-1c*) have been identified, all encoding LOV-domain proteins. *mcwc-1a* regulates phototropism, whereas *mcwc-1c* regulates photocarotenogenesis (79). The *mcwc-1b* gene product is also involved in carotenoid synthesis and is regulated by ubiquitylation by CrgA (80). In *P. blakesleeanus* three *wc-1* genes and four *wc-2* genes have been described (81, 82). The main key players in *P. blakesleeanus* photobiology are MadA and MadB,

orthologs of WC-1 and WC-2, respectively, which form the main photoreceptor complex (81). Whole-genome transcriptome analysis carried out in *P. blakesleeanus* led to the proposal that the stage-specific transcriptional response to light relied on the expanded set of photoreceptors and other light-dependent transcriptional regulators that arose after genome duplication (66). In this regard, whole-genome duplication in vertebrates has resulted in specialization of genes for signal transduction that are part of their visual system (83). Thus, expansion of photoreceptors or downstream signal transduction genes has resulted in more elaborate photoperception systems in both vertebrates and fungi.

Some fungi contain secondary photoreceptors (Vivid and/or Envoy), consisting of a LOV domain and a few extra amino acids, and bind either FAD or flavin mononucleotide as a chromophore (84–86). These photoreceptors are important for photoadaptation under constant light and for responding to changes in light intensity. In *Neurospora*, vivid (VVD) fine-tunes light responses by interacting with the WCC through the WC-1 LOV domain by quenching these responses (87, 88).

Phytochrome: A Linear Tetrapyrrole-Containing Histidine Kinase

Phytochromes, first discovered in land plants, were later also found in algae, diatoms, bacteria, and fungi and are absent in animals (89–93). Phytochromes are composed of a multidomain protein with a linear tetrapyrrole covalently attached to the protein. The protein moiety consists of an N-terminal PGP or photosensory domain, which combines domains named PAS (found in Per, Arnt, and Sim), GAF (named for vertebrate cGMP-specific phosphodiesterases, cyanobacterial adenylate cyclases, and the transcription activator FhlA), and PHY (phytochrome-specific PAS-related). The chromophore attaches autocatalytically to a cysteine, located in most bacterial and fungal phytochromes in the PAS domain and in the GAF domain in the case of plants. The chromophore, a linear tetrapyrrole, absorbs red light and undergoes a conformational change, which in turn changes its spectroscopic properties, and the absorption maximum is shifted toward far-red light. The conformational changes are reversible, and thus the chromophore interconverts from the red-light-absorbing Pr form to the far-red-light-absorbing Pfr form. The photosensory domain has been crystallized from bacterial phytochromes and recently from *Arabidopsis thaliana* (94–96).

The PGP domain is followed by a histidine-kinase domain, which consists of an ATP-binding and a substrate domain with a critical histidine residue. In plants this histidine residue is replaced by an arginine or glutamate, and thus the enzyme is not catalytically active. In contrast, in bacteria and fungi the histidine is conserved and phosphorylation activity has been demonstrated (91, 97, 98). In some bacteria and in fungi the histidine-kinase domain is followed by a response-regulator domain. Unlike plant phytochromes, *A. nidulans* FphA possess an N-terminal extension of 172 amino acids, which was shown to stabilize the Pfr form (97). The sequence similarities suggest a bacterial two-component signaling module as the origin of phytochrome and hence phosphorylation events as part of the signaling cascade (99, 100). In *A. nidulans*, *in vitro* experiments showed that the protein can become autophosphorylated at histidine number 770 and that it is capable of intermolecular phosphotransfer to the aspartate residue number 1181 of the response-regulator domain of a second phytochrome molecule (97). While autophosphorylation was stimulated by red light and shown to be dependent on the chromophore, transphosphorylation was independent of the chromophore and also found with apo FphA as the substrate. Autophosphorylation was stimulated with red light. In addition to the autophosphorylation activity of FphA, it was shown that aspartate 1181 serves as a substrate for YpdA, a histidine-containing phosphotransfer protein, *in vitro* (101). Hence, phosphorylation events are likely to play crucial roles in signal transduction in fungi and perhaps the interconnection with other pathways.

An open question concerns the nature and production of the chromophore. Although *in vivo* data are not yet available, it was shown that *A. nidulans* phytochrome incorporates biliverdin *in vitro* and, with less efficiency, phycyanobilin (74). Linear tetrapyrroles are normally generated by heme oxygenases. This is also how active phytochrome can be expressed in *Escherichia coli*, namely the coexpression of phytochrome along with a cyanobacterial heme oxygenase (74). However, heme oxygenase candidates were not found in the genome of *A. nidulans*.

Many fungi contain phytochromes, and sometimes even two or three genes can be found in their genomes (13, 102) (Fig. 2). However, functional studies remain to be conducted for most fungi. *N. crassa* contains two phytochrome genes, and it was only very recently that a role in the timing of sexual development could be assigned to one of them. Both phytochromes, though, affected the expression of a large number of genes (103). Thus, our knowledge of fungal phytochrome functioning is largely based on the results obtained in

A. nidulans, and it is highly desirable that the light response of other fungi with pronounced red-light effects be studied at the molecular level. No phytochrome genes have been detected in the genomes of *P. blakesleeanus*, *M. circinelloides*, or other Mucoromycotina fungi, but a candidate phytochrome gene has been found in the chytrid *Spizellomyces punctatus* (Fig. 2) (17).

Cryptochrome and Photolyases

Cryptochromes are plant blue-light photoreceptors very similar to photolyases, enzymes required for blue-light-dependent DNA repair. They bind noncovalently the flavin chromophore FAD and other, probably secondary, chromophores (pterin or deazaflavin) and do not show photolyase activity (104, 105). Cryptochrome genes have been described in the genomes of several fungi, but their role in light sensing or DNA repair has been investigated only in some species (Fig. 2).

Neurospora CRY belongs to the cryptochrome-DASH subfamily, and the gene is induced by light in a WC-1-dependent manner and by the circadian clock (106). The *Neurospora* cryptochrome binds the blue light-absorbing chromophores FAD and MTHF (methenyltetrahydrofolate) when the gene is expressed in *E. coli* and shows DNA binding activity *in vitro* (106). A role has been proposed for CRY in the regulation of the activity of the WCC for the activation of some light-induced genes such as *con-10* (107). However, genome-wide activation of transcription by light is not significantly altered in the *Neurospora cry* mutant (106), suggesting a very limited role of CRY in the regulation of transcription by light. CRY also plays a marginal role in the regulation of the *Neurospora* circadian clock as a component of a secondary oscillator (108).

F. fujikuroi cryptochrome CryD is also a member of the CRY-DASH family and participates in the regulation of secondary metabolism and the development of conidia (109). In the ascomycete *Sclerotinia sclerotiorum*, deletion of the CRY-DASH gene results in minor developmental defects, suggesting that, as in *Fusarium*, this protein may have a sensory role in this fungus (110).

A. nidulans CPD photolyase CryA is phylogenetically related to cryptochromes and has dual roles as DNA repair enzyme and photoreceptor. CryA provided DNA repair activity in *E. coli*, and deletion of the *cryA* gene reduced the sensitivity in the near-UV/blue region of the spectrum for the inhibition of sexual development, supporting its role in this process (19). A similar dual role has been proposed for *T. reesei* Cry1, a member of the 6-4 photolyase family. Cry1 provides DNA repair activity in conidia of *T. reesei*, and its biochemical characterization shows that it can bind and repair DNA lesions *in vitro* or in *E. coli* cells expressing *cry1* (111). The changes in the pattern of light-dependent transcription in the *cry1* mutant suggested a sensory and regulatory role in the regulation of light-induced transcription (64).

A role in DNA repair has been proposed for a cryptochrome in *P. blakesleeanus*. This fungus shows a blue-light-dependent photoreactivation that is typical of photolyases despite the absence of a photolyase gene in the genome (112). Indeed, cryptochrome-DASH (CryA) provides DNA repair activity *in vivo* when expressed in *E. coli* and can bind and repair single-stranded and double-stranded DNA *in vitro*, suggesting that CryA acts as a photolyase for DNA repair in *P. blakesleeanus* (113). As such, CryA seems to represent an early step in the evolution of cryptochromes from DNA repair enzymes to sensory photoreceptors. It is tempting to speculate that proteins homologous to CryA in fungi related to *P. blakesleeanus* play similar roles as DNA repair enzymes despite being identified as cryptochromes by their amino acid sequences (113).

Opsins

Rhodopsins are membrane-embedded seven-transmembrane helix photoreceptors composed of a retinal chromophore bound to an opsin apoprotein (114–116). Despite their ubiquitous role as photoreceptors for animal vision, the opsin genes described in several fungi and their role in fungal photobiology are only starting to be appreciated.

Neurospora NOP-1, the first example of a fungal opsin, shows a slow photocycle and long-lived intermediates, consistent with a role as a sensory photoreceptor (117–121). However, the inactivation of *nop-1* did not result in a blind phenotype (120). *nop-1* mRNA accumulates during asexual or sexual development, with a large amount of the mRNA observed during late conidiation but not during early vegetative growth (120). A regulatory role for the NOP-1 protein has been suggested based on changes in mRNA accumulation of light and conidiation-regulated genes (122).

A rhodopsin gene has been isolated from *Leptosphaeria maculans*, the fungus responsible for blackleg disease of *Brassica* species. The *Leptosphaeria ops* gene seems to be constitutively expressed, unlike its *Neurospora* homolog (123), and is active as a light-driven proton pump when expressed in yeast membranes (124). The capacity of *Leptosphaeria* rhodopsin to act as a proton pump seems to require specific amino acids and the presence of hydrogen-bonded water molecules (119).

However, the role of a light-dependent proton pump in the biology of *L. maculans* remains to be clarified.

Two opsin genes, *carO* and *opsA*, have been identified in the genome of *Fusarium* species. The gene *carO* was identified in a cluster of genes for carotene biosynthesis, suggesting a common regulation. Indeed, *carO* was induced after light exposure and was overexpressed in carotene-overproducing strains, like other neighboring *car* genes (125). Since the synthesis of the retinal chromophore requires a regular supply of carotenes, the coregulation of the opsin apoprotein gene with the genes involved in carotenoid biosynthesis may ensure that opsin apoproteins are not wasted in the absence of retinal molecules. CarO is a light-driven proton pump that is abundant in conidia and retards germination under light, suggesting a role for CarO in the regulation of fungal germination (126). The other opsin gene, *opsA*, is not linked to the *car* cluster and is subject to a different regulation: mRNA levels are moderately induced by light, and *opsA* is not overexpressed in carotene-overproducing strains (127).

In *A. nidulans* an opsin homolog can be found in the genome as well. However, the critical lysine residue for retinal binding is absent, and thus it is not yet clear if it is a chromoprotein and plays any role in light regulation. A similar opsin-like gene has been identified in the genome of *T. atroviride*, but its role remains to be identified. Opsin genes have not been detected in the genomes of *P. blakesleeanus* or *M. circinelloides* (Fig. 2) (17).

A detailed characterization of the role of an opsin as a fungal photoreceptor has been described for *B. emersonii*. The photoreceptor for phototaxis in this fungus is a fusion protein containing an opsin domain and a guanylyl cyclase catalytic domain, suggesting a role for the cGMP signaling pathway in vision as it has been described in vertebrates (58). It is tempting to speculate that this is an ancient mechanism of vision that was lost in most fungi and is still observed in vertebrates.

The absence of obvious phenotypes in most fungal strains lacking a functional rhodopsin gene is puzzling. However, the use of action spectroscopy and chromophore replacements with retinal analogs indicated that rhodopsins are the most likely photoreceptors that guide zoospore motility in the chytridiomycete fungus *A. reticulatus* (57). It is possible that rhodopsins play a key role in zoospore motility in other members of the Chytridiomycota.

BLUE-LIGHT SENSING: THE WC SYSTEM

In *N. crassa*, which is considered the model fungus for the study of blue-light responses, it has been found that most blue-light responses are controlled by WC-1 and WC-2 (128). In the dark a WCC composed of a WC-1/2 heterodimer is formed (54) that binds to light response elements in the promoters of light-responsive genes. However, this complex appears to be unable to trigger transcription *in vivo* (77, 129, 130). It is believed that upon exposure to light, structural changes in the WC-1 LOV domain take place, resulting in changes in the quaternary structure of the WCC that make it active (54). Upon activation by light, the WCC transiently binds to the light response elements of early light-responsive genes. Subsequently, transcriptional initiation takes place, which has been associated with transient phosphorylation events of WC-1 preceding removal of WC-1 from light response elements (130–133) (Fig. 3). This mechanism is assumed to be similar in many other fungi that respond to light using WC orthologs, although in most cases this has not been proven (1).

Chromatin modifications are also involved in the photoinduction of gene expression regulated by the WCC (Fig. 3). Light-induced acetylation of promoter histone H3-K14 appears to be essential for the activation of light-induced genes (134, 135). Furthermore, a strain expressing a mutant allele of H3 (*hH3K14q*) that cannot be acetylated at K14 behaves like a *wc-1* mutant strain (135). Such histone acetylation is carried out by the acetyltransferase NGF-1, which directly interacts with WC-1 (134). Recently, H3K9me3 DNA methylation by the methyltransferase DIM-5 has been found to be involved in the repression of light-induced gene expression (136). Thus, there are at least two levels of control of WCC light-induced expression of genes at the chromatin level.

Organisms must be capable not only of perceiving the presence or absence of light but also of detecting subtle changes in its intensity to elicit adequate behavioral and developmental responses. Consequently, they have evolved mechanisms to adapt to prolonged exposure to light while retaining sensitivity to changes in its intensity. After prolonged exposure to light, gene expression undergoes photoadaptation in *Neurospora* and *Trichoderma*, returning to basal levels after 1 to 4 h of exposure to light (137, 138). To remain sensitive to an additional increase in ambient light intensity, both fungi are able to adapt to various levels of light intensity (137–139).

In *N. crassa*, VIVID (VVD) is a small LOV domain-containing blue-light photoreceptor that functions downstream of the WCC to negatively regulate the light responses initiated by the WCC. In light VVD forms a rapidly exchanging dimer in solution, suggesting the

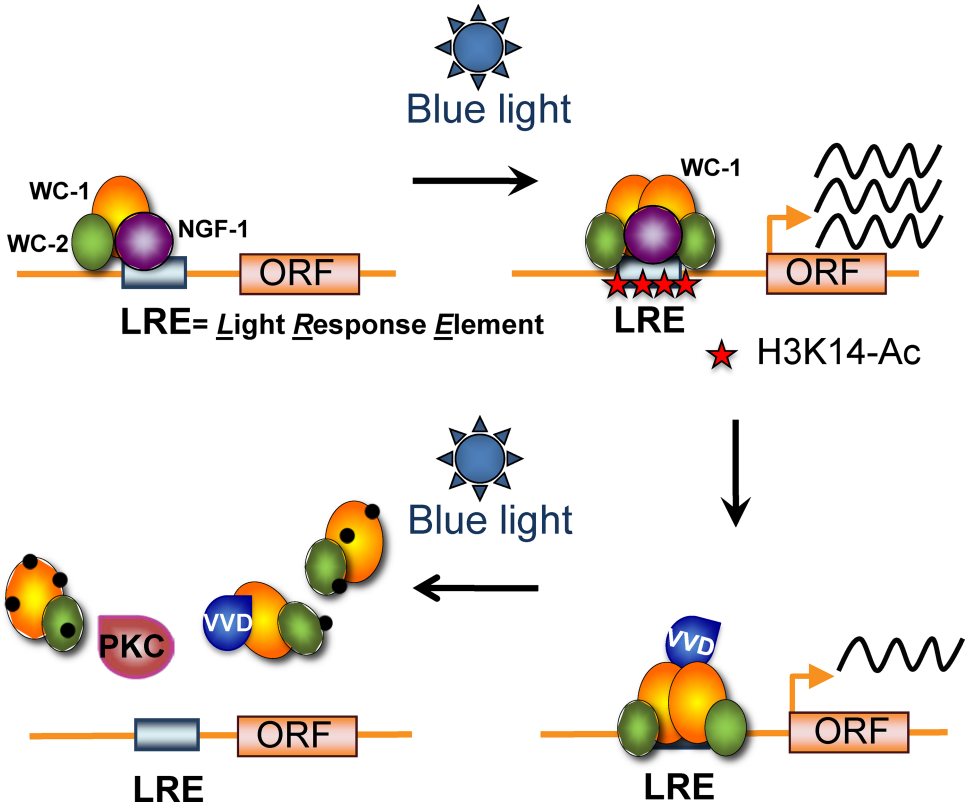


FIGURE 3 Model for WCC-dependent light signaling in *Neurospora crassa*. A simplified model for the activation of transcription by light and photoadaptation. Light reception by the FAD chromophore of WC-1 should trigger the formation of a flavin-cysteinyl adduct, causing a conformational change that leads to WCC dimerization, chromatin remodeling through the histone acetyltransferase NGF-1, and the activation of gene transcription. The modified histones are shown by stars at the site of promoter binding. Light exposure stimulates the transcription of *vvd*, *frq*, and other light-induced genes. Newly synthesized VVD competes with the light-activated WC-1 and disrupts the formation of WCC dimers, reducing WCC binding to the promoter. The WCC bound to VVD is not transcriptionally active, and it results in the attenuation of the response to light. Different fractions of the light-activated WCC are stabilized by FRQ (not shown) and transiently phosphorylated (black dots) and partially degraded, probably through an interaction with the protein kinase C (PKC) and other kinases and phosphates, some of them not yet identified (not shown).

possibility that the LOV domain of VVD could interact with other PAS domains, including those found in the WCC proteins (84). Indeed, it was shown that there is a physical interaction between VVD and the WCC that results in a reduction of the transcriptional response, which could explain photoadaptation (87, 137, 140, 141) (Fig. 3). Further, a data-driven mathematical model proposes that VVD allows *Neurospora* to detect relative changes in light intensity. In this model VVD acts as an inhibitor of WCC-driven gene expression and as a positive regulator that sustains the responsiveness of the photosystem. The authors of that model suggest that this function is carried out by a futile cycle involving the light-induced sequestration of the active form of WCC by VVD and the replenishment of the activatable WCC pool through the decay of the photoactivated state (142).

RCO-1 and RCM-1, the *Neurospora* homologs of the corepressor complex Tup1-Ssn6 in yeast, play a role in photoadaptation. RCO-1 and RCM-1 accumulate in *Neurospora* nuclei (107) and interact to form a repressor complex similar to that observed in yeast (143). When exposed to five hours of light, the *rco-1* and *rcm-1* mutants show a sustained expression of light-induced genes, suggesting that the RCO-1/RCM-1 complex is involved in photoadaptation. The absence of the RCO-

1/RCM-1 repressor complex leads to a reduction in the amount of VVD that is available for the regulation of the WCC. The reduction in the amount of VVD results in increased WCC binding to the promoters of light-regulated genes in the dark and after long exposures to light, leading to the modification of photoadaptation that has been observed in *rco-1* and *rcm-1* mutants. These results indicate that the photoadaptation phenotype of mutants in the RCO-1/RCM-1 repressor complex is, at least in part, an indirect consequence of the reduction of *vvd* transcription and the resulting modification in the regulation of transcription by the WCC (144).

Photoadaptation has been observed in other fungi too. In *P. blakesleeanus* the activation of *hspA* gene expression by light was transient, which suggested the presence of a photoadaptation mechanism similar to that described for *Neurospora* and *Trichoderma*. However, photoadaptation of *hspA* was not prevented by changes in light intensities or dark incubations, unlike photoadaptation in *Neurospora* (145). Photoadaptation has been observed for the light-dependent transcription of the developmental regulator *brlA* in *A. nidulans* (59). The differences in the sensitivity to changes in light intensities, and the absence of a *vvd* homolog in the genomes of *P. blakesleeanus* or *A. nidulans* (Fig. 2), suggests the operation of a molecular mechanisms for adaptation in these fungi that is different from that described for *N. crassa*.

In addition to the central blue-light perception system constituted by the WCC, biochemical and molecular data suggest the participation of at least two light perception systems that regulate photoconidiation in *T. atroviride* (64, 146, 147). One of the proposed signal transduction pathways participating in this alternative light perception system involves cAMP, given that protein kinase A activity increases and induction of gene expression have been observed after a pulse of blue light in Δ*blr1* mutant strains (147). Additionally, as mentioned above, members of the cryptochrome/photolyase family have functions as regulators of gene expression in several fungi (1, 19, 111, 148, 149).

RED-LIGHT SENSING AND THE INTERPLAY WITH BLUE-LIGHT AND STRESS-SENSING SYSTEMS

In *A. nidulans* light can have activating and repressing functions. Whereas asexual sporulation occurs in light, sexual development is repressed and occurs in the dark. Interestingly, both red and blue light stimulated asexual sporulation, and for full induction, both light qualities were required (34, 150). This suggested the involvement of both FphA and the blue-light-sensing WC system (LreA and LreB). However, whereas deletion of *fphA* caused a reduction of conidia production, deletion of *lreA* and *lreB* caused a slight increase in conidia formation, suggesting a positive function for FphA and a negative function for LreA (34). Red light inhibits cleistothecia formation more effectively than blue light, but the combination of the two wavelengths increases the inhibition to the level of white light. Deletion of the phytochrome gene caused a slight increase, and deletion of *lreA* caused a decrease in the number of cleistothecia. The latter effect suggests a function of LreA independent of light. To analyze the effects of the light regulators at the molecular level, light-regulated genes were identified in genome-wide analyses (59). Two of those genes, *ccgA* and *conJ*, were chosen for further analysis, because the orthologs were known to be light regulated in *N. crassa*. In contrast to the effect of light on sporulation, both genes were highly upregulated by red but not by blue light (34, 150). Because *ccgA* and *conJ* do not play any obvious role in asexual development, it is possible that the regulation of the two genes is distinct from the regulation of genes involved in conidiation. In addition, it has to be considered that sporulation or cleistothecia formation involves hundreds of differentially expressed genes. Some of these genes may be regulated like *ccgA* or *conJ*, but others may be regulated differently. Therefore, *ccgA* and *conJ* will be discussed as models to understand the effects of light at the molecular level.

Because FphA, LreA, and LreB were found within the nuclei, direct interactions of those proteins with the two promoters were feasible. Indeed, LreA was detected bound to the *ccgA* and *conJ* promoters in the dark and was released after illumination (150). Phytochrome, however, could not be detected at the promoters of these genes (Fig. 4). Thus, LreA/B could have a repressing effect and FphA an activating function without interacting directly at the promoter level, raising the question of how the information from FphA could be transmitted to the promoters. One key protein could be VeA (velvet A), another well-known fungal regulator involved in the light response (151–153). VeA contains a domain with structural similarity to NF-κB, a well-known transcription factor (154). It localizes to nuclei, and we found a physical interaction between VeA and FphA within nuclei (34). It was demonstrated that it is a multiphosphorylated protein, and a phosphorylation code has been postulated to explain the involvement of the protein in many different pathways (155, 156). The

localization and accumulation of VeA in nuclei appears to be dependent on the phosphorylation of certain amino acids, where it binds to the *ccgA* and *conJ* promoters. However, this was independent of the illumination conditions, and therefore the exact role of VeA is still unclear. Apparently, VeA is required for LreA binding to the promoters (150). In summary, it appears that only FphA has an essential function in gene induction and that other proteins studied so far serve minor functions, probably allowing the integration of different regulatory cues. A breakthrough for the understanding of signal transduction from FphA to the gene expression level was achieved using a classical mutant-screening approach, where SakA, the stress-activated kinase, was identified (4). This indicates a link between light and stress signaling and a role for the transcription factor AtfA as a central component of light-dependent gene induction (157) (discussed below). In agreement with these recent findings connecting phytochrome signaling stress, mitogen-activated protein kinase (MAPK) signaling has been studied in *Beauveria bassiana*, in which phytochrome was shown to be involved in multistress tolerance (158). However, a mechanistic link between light sensing and other stresses has not yet been established in *B. bassiana*.

Besides a role of phytochrome in triggering the activity of transcription factors, a role in chromatin remodeling in *A. nidulans* is also likely (Fig. 4A). The acetylation level of the *ccgA* and *conJ* promoters changed upon illumination, and this change depended on LreA and FphA (150). It was also found that LreA interacts with the acetyltransferase GcnE and the histone deacetylase HdaA. Since FphA interacts with the WCC, it could be that FphA indirectly modulates the activity of these enzymes, but there is also some evidence that FphA directly interacts with the two enzymes (150). Hence, phytochrome-dependent gene regulation appears to occur at transcriptional and chromatin-structural levels. Unfortunately, the interplay between LreA, LreB, and phytochrome in this process is not yet well understood.

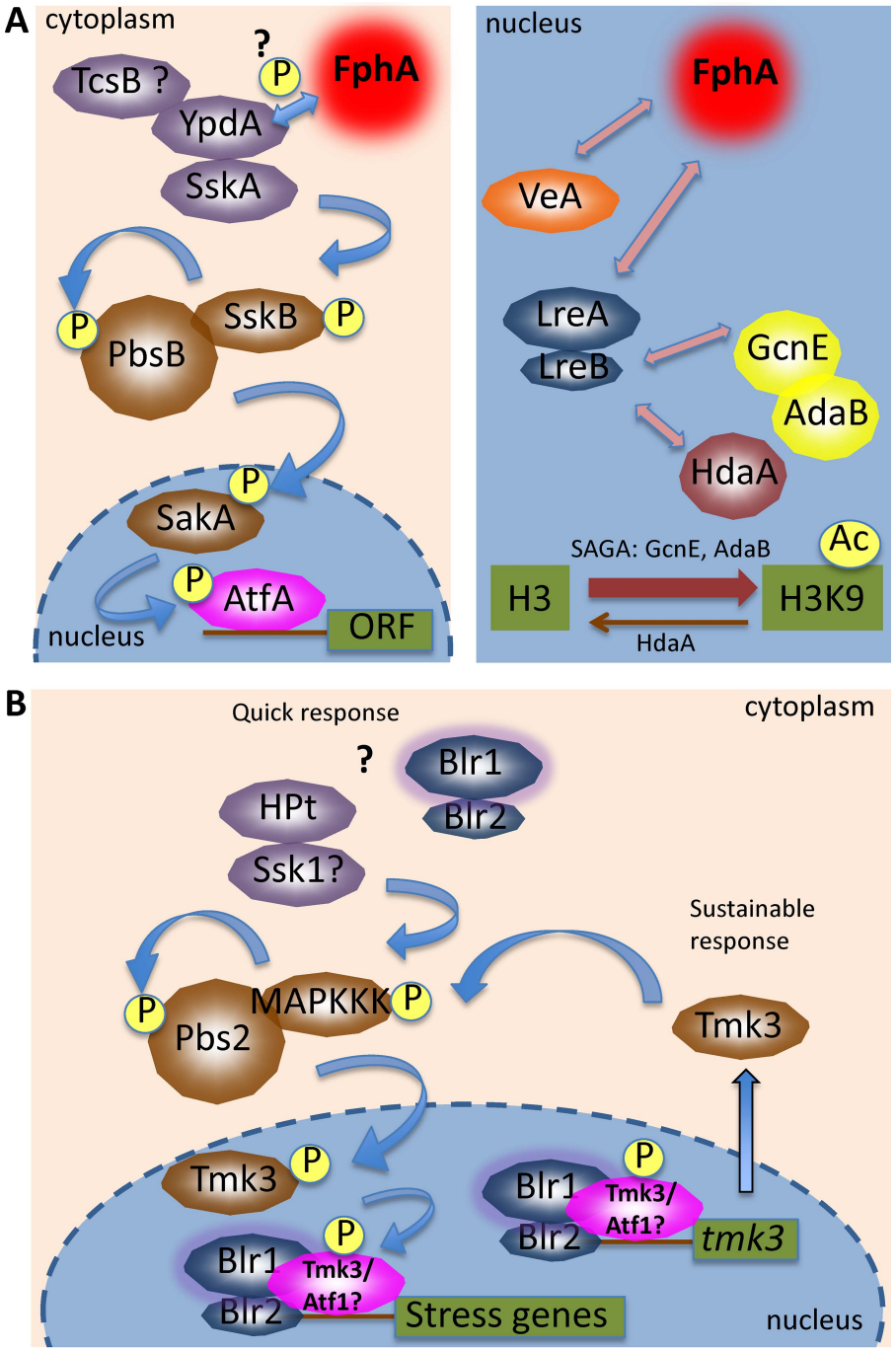
Phytochrome interacts with several other proteins, and these interactions could be indicative of its function as well. It is possible that some of the interaction partners modulate or control the phosphorylation activity of FphA. Indeed, it was shown that the autophosphorylation activity increased if inactive phytochrome was added (97). New insights and hypotheses into red-light signaling in fungi may also come from the comparison with red-light signaling in plants (159).

The current model for phytochrome-dependent gene regulation in fungi mostly relies on findings in *A. nidulans*, and it will be interesting to compare the system with other fungi in which phytochrome is likely to play a role. For example, conidiophore production in *B. cinerea* is induced by UV light, but conidia formation then occurs in the dark. Blue- but also red-light illumination inhibits spore production (33, 160). The molecular basis for red-light sensing in this fungus has not been investigated in detail yet, although three phytochrome-encoding genes were identified in the genome (102). In *Trichoderma*, red light provokes a reduction in mycelial growth and also has an impact on the transcriptional regulation of some genes, indicating the participation of a phytochrome in these responses (45, 161). However, expression of the set of genes that respond to red light is also controlled by blue light (64). These observations suggest that blue and red light photoreceptors act together to regulate expression of these genes. In this regard, it has been suggested that in *N. crassa* the photoreceptors CRY-1, NOP-1, and PHY-2 modulate the activity of the WCC, presumably through the light-dependent activation of a putative repressor of the WCC (162). Furthermore, expression analysis of a small set of genes in the Δ*blr1*, Δ*phr1*, and Δ*cry1* mutants of *T. atroviride* showed that the three potential blue-light photoreceptors are involved in the control of gene expression in both blue and red light (64).

LIGHT SIGNALING TO STRESS MAPKS

Most of recent research in fungal photobiology has focused on the identification and characterization of the WC photoreceptor complex and other photoreceptors, but little attention has been paid to the components of the signal transduction pathway that relies on the light input into the cell. The key role of the transcription factor and blue-light WC photoreceptor complex in *N. crassa* and other fungi suggests a prominent role for light-dependent gene regulation in fungal photobiology. However, it is possible that the WCC and other photoreceptors regulate other aspects of fungal biology at the posttranscriptional level through the action of a signal transduction pathway that starts with the reception of light by the photoreceptor. As mentioned earlier, a connection between light sensing and MAPK signaling has been established in some fungi, which could constitute a more general aspect of fungal photobiology.

Indeed, many environmental signals are transmitted through conserved three-tiered phosphorylation cascades composed by a MAPK, a MAPK kinase (MAPKK), and



a MAPKK kinase (MAPKKK). Active MAPKs phosphorylate multiple targets including other enzymes and usually translocate from the cytoplasm to the nucleus to phosphorylate nuclear targets such as transcription factors. Stress-activated protein kinases (SAPKs) are MAPKs that are specialized in transducing stress signals. In fungi, SAPK input involves the participation of phosphorelay signal transduction systems composed by different sensor histidine kinases (HK), a phosphotransfer protein (HPt) Ypd1, and a response regulator (163) (RR) (Fig. 4).

The first report connecting light to MAPK signaling in fungi showed a circadian rhythmic activation of the SAPK OS-2 in *N. crassa*, which was dependent on WC-1, the clock component FRQ-1, and the RR RRG-1 (164). Notably, OS-2 phosphorylation induced by osmotic stress required RRG-1 but not the WC-1/FRQ-1 oscillator, indicating that OS-2 regulation by osmotic shock and circadian clock occurs through different pathways, upstream of RRG-1. Later it was shown that WC-1 mediates SAPK light input by binding to the promoter of the *os-4* gene, encoding MAPKKK OS-4, both in response to light and in a rhythmic fashion under constant darkness. Deletion of *os-4* WC-1 binding sites disrupts *os-4* mRNA and OS-2 phosphorylation rhythmic oscillations. Since WC-1 is also indirectly required for antiphase rhythmic expression of the HPt gene *hpt-1*, it was proposed that such WC-1-mediated antiphase expression of positive (OS-4) and negative (HPT-1) SAPK regulators is coordinated to enhance the rhythmic activation of the OS-2 pathway (5). The negative relationship between phosphotransfer HPt proteins and SAPKs has been indicated by the fact that the elimination of HPt proteins is lethal in wild-type backgrounds in *A. nidulans* (165) and *N. crassa* but is viable in an *os-2* null background (166). Furthermore, the transcription factor ALS-1, also reported as ATF-1 and proposed to act downstream of OS-2 (167), is required for the circadian rhythmic oscillation of OS-2 responsive genes *bli-3*, *ccg-1*, *cat-1*, *gcy-1*, and *gcy-3*, in the absence of osmotic stress (168).

More recently, it has been shown that transcript levels of the *T. atroviride tmk3* gene, which encodes SAPK Tmk3, are increased after blue-light exposure, and this depends on the WC homolog Blr1. Likewise, light-induced conidiation and the induction of the blue-light-regulated genes *blu1* and *grg2* is drastically reduced in mutants lacking Tmk3 or the upstream MAPKK Pbs2 (3). Although it is not known if transcription factor Atf1 is required for light induction of these genes, these data show that through Blr1, light regulates SAPK signaling at the transcription or mRNA stability levels. Because the *tmk3* promoter contains putative Blr2-binding sites, the authors propose a model in which the Blr1/Blr2

FIGURE 4 Phytochrome functions in light regulation in *Aspergillus nidulans* and the link of light and stress sensing in *A. nidulans* (A) and *Trichoderma atroviride* (B). **(A, left panel)** There is good evidence that the light signal is perceived by FphA in the cytoplasm and transmitted into the nucleus by activating the SakA stress signal pathway. SakA becomes phosphorylated, shuttles into the nucleus, and activates the transcription factor AtfA. (modified after 177) **(A, right panel)** Light signaling also involves chromatin remodeling of the promoters of light-regulated genes such as *ccgA* or *conJ*. It was shown that the acetylation level of lysine 9 of histone H3 increases upon illumination, that LreA interacts with the acetyltransferease GcnE and the histone deacetylase HdaA, that deletion of the SAGA/Ada complex component AdaB causes reduction, whereas deletion of *hdaA* causes induction of the photoinduction, and that changes of lysine 9 in histone H3 phenocopy the phenotypes of *adaB*- or *hdaA*-deletion strains. VeA is always bound to the *ccgA* or *conJ* promoter, whereas LreA leaves the promoter upon illumination. Hence, LreA could keep GcnE inactive and stimulate HdaA in the dark. The situation would be reversed after illumination, and the acetylation level of the lysine residue 9 of histone H3 would increase. There is evidence that GcnE is further activated through FphA. Lysine 9 acetylation was dependent on FphA, but an interaction between the two proteins was only shown by split YFP and could not be verified by Co-IP. The arrows indicate protein interactions verified by different methods. It should be noted that the current models rely solely on the results obtained with two light-regulated genes, *ccgA* and *conJ*. **(B)** The link between light and stress regulation in *T. atroviride*. In a quick response light causes phosphorylation of the MAPK Tmk3, which requires the MAPKK Pbs2. Nevertheless, it is still unclear where the WCC is linked to the Tmk3 MAPK pathway. At the promoter of a set of light-regulated genes the WCC could interact either with Tmk3 or with a not-yet-identified AtfA ortholog. Light also stimulates the transcription of the *tmk3* gene, giving rise to higher levels of Tmk3, which may aid in keeping a sustained response.

photoreceptor complex could regulate *tmk3* expression and also mediate light input to the SAPK pathway upstream from Pbs2 and/or interact with Tmk3 in the nucleus to promote the transcription of stress and light-responsive genes (Fig. 4, B). It seems possible that Blr1/Blr2 could also regulate the expression of MAPKKK and Hpt1 proteins, as in *N. crassa* (5). In addition, Blr1 is required for Tmk3 transient phosphorylation after mycelia exposure to a light pulse or constant illumination. One possibility is that *T. atroviride* Blr1/Blr2 forms a complex with the HK equivalent to phytochrome FphA, as it occurs in *A. nidulans* (34, 155), and transduces direct phosphorylation signals to the SAPK pathway (4). Alternatively, Blr1/Blr2 could feed the pathway downstream of Tmk3. As in *S. pombe* (169) and *A. nidulans* (170), Tmk3 is required for resistance to different types of stress (3), and SAPK activation by heat shock (171) and nutrient limitation (172) in *S. pombe* occurs downstream of Spc1/Sty1 through inhibition of specific tyrosine phosphatases.

As mentioned before, red-light sensing has recently been connected to MAPK signaling in *A. nidulans* through the phytochrome FphA (4), which is a hybrid HK (34, 155). This fungus contains 15 HKs, and the function of most of them is unknown. Genetic evidence indicates that the HK NikA transmits osmostress and fungicide signals to the phosphotransfer protein YpdA and to the response regulator SrkA, which is coupled to the SAPK SakA (170), as well as to the SAPK-independent RR called SrrA (165). SakA was also identified as HogA and shown to be involved in gene regulation in response to osmotic stress (173). Upstream, MAPKK PbsB and MAPKKK SskB regulate SakA (174), which is phosphorylated in response to multiple types of stress, including osmotic, oxidative (170), nutrient starvation (157), and hypoxia (Sánchez and Aguirre, unpublished). Stress-activated SakA translocates to the nucleus, where it interacts with transcription factor AtfA, which is required for induction of several genes, including catalase genes *catA* and *catB*, and both *ΔsakA* and *ΔatfA* mutants are sensitive to oxidative stress (157). Both SakA and AtfA are also required for osmotic-induced gene expression (175). It is worth mentioning that SakA also interacts with MAPK-activated protein kinase SrkA and that both show H_2O_2-induced interaction with other proteins involved in SAPK signaling, cell-cycle regulation, DNA damage response, and mitochondrial function (176), because such interactions might become relevant to the light-sensing process. In addition, SakA and AtfA play important roles during development, repressing sexual development and being activated during asexual development (170). *ΔsakA* intact conidia progressively lose their viability, and this is consistent with the fact that SakA accumulates in asexual spores (conidia) in an AtfA-dependent manner. SakA becomes phosphorylated during conidia development and needs to be dephosphorylated for germination to take place, indicating that this SAPK plays essential roles in the transition between growth and differentiation (157).

Yu et al. isolated "blind" mutants by using a light-responsive promoter fused to a nutritional marker (4). By genomic sequencing, these authors found that different mutants carried inactivating mutations at the MAPKKK (SskB), MAPKK (PbsB), or MAPK (SakA) components of the SAPK pathway. Indeed, several lines of evidence support the involvement of this pathway in red-light and, to a minor extent, blue-light sensing. First, blind and *ΔsakA* mutants show the same phenotypes in terms of asexual/sexual development. Second, deletion of FphA upstream (SskA, SskB, PbsB) or downstream (AtfA) SAPK components results in failure to induce *ccgA* and *conJ* genes in response to light. Third, FphA physically interacts with the HPt protein YpdA, as shown by BiFC and coimmunoprecipitation. Fourth, light induces increased SakA phosphorylation and its nuclear localization in a way that depends on FphA but is independent of blue-light receptors LreA and LreB. Somewhat unexpectedly, blue light partially induces SakA nuclear localization, not as strongly as red light, and this response depends only on FphA. Notably, FphA-mediated regulation of SakA is not required for osmotic stress-induced activation of SakA.

Under certain conditions, FphA histidine kinase is able to autophosphorylate and transfer the phosphoryl group to the response regulator of a second interacting FphA molecule *in vitro* (97). Both phosphorylation sites in FphA, the histidine in the histidine-kinase domain and the aspartate in the response regulator domain, are essential for function (150). *In vitro* experiments showed that FphA autophosphorylation activity was higher in light than in dark (97), and the phosphotransfer from YpdA to FphA has been shown *in vitro*, using a truncated version of FphA lacking the first 677 amino acids (101). Taken together, these results clearly support the role of FphA as a light-sensitive histidine kinase connected to the SakA-AtfA pathway at the YpdA level. However, they tell little about the actual phosphotransfer dynamics *in vivo*. Nevertheless, it is clear that *in vivo* red-light illumination results in the activation of the MAPK SakA and the regulation of red-light-responsive genes through the AtfA transcription factor.

Discussing these results, Yu et al. considered that FphA had a higher kinase activity in the dark, when actually it shows red-light-induced autophosphorylation *in vitro* (97). This led to a proposed model in which under dark conditions the HK FphA phosphorylates and associates with the HPt protein YpdA, and this leads to phosphorylation of the response regulator SskA and inactivation of SakA. Light would cause YpdA dephosphorylation and activation of the SakA pathway (4, 177). Such a model is consistent with the fact that light inhibits the germination of conidia in an FphA-dependent way (42), because it is known that high levels of phosphorylated SakA prevent spore germination (157). However, the exact mechanism by which red light activates SakA remains to be demonstrated.

LIGHT: A STRESS, A SIGNAL, OR BOTH?

The presence and functioning of different photoreceptors in fungal cells and the low threshold for some responses to light suggests that light is used as a source of environmental information, because it clearly occurs during the phototrophic reaction of Phycomyces. The connection between light, photoreceptors, and the stress MAPK can be interpreted as a mechanism that uses the light cue to activate the SAPK pathway to anticipate and prepare the cell for later stress (164). In this scenario, light is a reliable signal about incoming changes in temperature, osmotic stress, oxidative stress, and damaging UV radiation. Such alarm signaling can occur many times during the day as hyphae grow in and out of their substrate or in circadian rhythms as an alarm system that every morning prepares fungi for the stress of the day. However, recent evidence suggests that excessive light can also directly cause cell stress (i.e., the production of H_2O_2 and other reactive oxygen species [ROS]), which in turn might activate photoreceptors and SAPKs. The fact that the replacement of key cysteine 196 by threonine in *T. reesei* ENV1 (138), a homolog of *N. crassa* VVD, abolishes adaptive responses to both light and oxidative stress *in vivo* (85) suggests that light and ROS signals perceived by a single protein could be transmitted to SAPK or other signal transduction pathways.

Additional, less direct evidence connecting light irradiation and ROS production has been reported in other fungi. In *B. cinerea*, constant light impairs growth of a wild-type strain, and this is more drastic in mutants lacking the WC homolog BcWCL1. Notably, this can be enhanced and reversed by adding H_2O_2 and antioxidants, respectively (102). In *N. crassa*, deletion of the superoxide dismutase *sod-1* gene results in circadian rhythmic conidiation (178). Microarray analyses of the light response of *A. nidulans* and *N. crassa* revealed that stress-related genes are activated by light (59, 137). Similarly, transcriptome analyses of this response in *T. atroviride* showed that a significant proportion of the light-induced genes are related to oxidative and other types of stress responses (64). Furthermore, a recent proteome analysis of the *Penicillium verrucosum* response to light indicated that many of the induced proteins are involved in responses to stress (179). In *A. fumigatus* exposure to light results in enhanced resistance to acute UV and oxidative stresses and an increased susceptibility to cell wall perturbation (41), and in *B. bassiana* the putative phytochrome (*Bbphy*) is not only a photoreceptor essential for asexual development, but it also acts as a regulator of the fungal responses to a variety of stresses, including oxidative stress (158).

Evidence linking light and ROS production has also been reported in animal systems. In zebra fish light induces H_2O_2 production, while external H_2O_2 induces cryptochrome *zCry1a* and period *zPer2* gene expression and the subsequent circadian oscillation of *zPer1*. Notably, the expression of the catalase gene *zCat* shows antiphasic oscillation to *zCry1a* and *zPer2*, and consistent with this, *zCat* overexpression causes reduced induction of *zCry1a* and *zPer2* by light (180).

All these results clearly show a connection between light, circadian rhythms, and redox metabolism, which is consistent with the idea that monitoring ROS levels is essential in triggering cell differentiation (181). Such interesting relationships can now be studied from the perspective of the established connections between light, stress, and SAPK signaling.

WHY SO MANY PHOTORECEPTORS?

Although the effect of light on fungal development and physiology was recognized long ago, the molecular analysis reveals a complex picture of light sensing. It appears that light is an important environmental cue mainly to adapt fungal biology to stressful or harmful conditions. One of the open questions, however, is why several photoreceptor and light-sensing systems were established during evolution if their role was only to detect light or darkness. Although normally one photoreceptor system appears to dominate the light response in a given species, such as the blue-light-sensing system in *N. crassa* or the red-light response in *A. nidulans*, there is very good evidence that the additional systems also play certain roles. It could be that the different photosensing systems evolved for the sake of robustness

in light sensing. However, one system does not seem to substitute for the lack of the other, suggesting that sensing different light qualities provides an advantage. Although monochromatic light is rare in nature, the composition of daylight may vary significantly. For instance, blue light penetrates deeper into water than red light, red light is more present in the evening, plants absorb the blue and red range of the spectrum, and fungi living in the shade of plants are exposed to more green light. Fungi are able to sense these spectral differences as additional environmental cues to adapt to their lifestyles accordingly. The existence of several photoreceptors and their relative conservation during evolution also suggests that the light stimulus needs to be transduced to different biological processes, which might be more difficult with a single photoreceptor. In *B. bassiana* phytochrome appears to be also involved in sensing the length of the illumination period. Whereas a wild-type strain grown for 7 days produced the maximum amount of conidiospores with 3 h of white light illumination (21 h darkness), the phytochrome mutant required 16 h of light (8 h darkness) (158). Although such adaptive changes may be rather subtle in other fungi and hard to detect under laboratory conditions, they might be important for fitness and survival in nature.

In addition to our improved understanding of photoreceptors in light responses, it appears that some of these proteins also serve functions in the dark. One prominent example is the WCC in *N. crassa*. This is the positive element in the circadian clock system, and it enables its entrainment by light. However, one of the conspicuous features of the clock is its free running in the absence of external stimuli (53). As germination is delayed in the dark in the absence of phytochrome in *A. nidulans* (42), phytochrome also appears to have functions in the dark. A still open question is, Which was the ancestral function of photoreceptor proteins? We think that initially, fungal vision originated as a mechanism to anticipate the stress and damage caused by light. Alternatively, it is possible that the fungal ancestor, being a motile cell living in the ocean, could use low and different colored light as a guide, explaining the large number of different photoreceptors in all fungi. Once fungal ancestors changed their living habitat to soil and plant surfaces, the primordial light detection system was adapted as a protective system to predict excess light.

CONCLUDING REMARKS

Fungal genome projects have allowed the identification and characterization of several photoreceptor genes, many of them unexpected. The identification of the WCC in *N. crassa* has served as a model for other fungi, and in most cases mutants in the homologs of the WCC result in blind phenotypes. On the other hand, *A. nidulans* displays a pronounced red-light response, and phytochrome has been characterized in some detail. Recently, also in *N. crassa*, a role for phytochrome was assigned. In addition, opsin may be a new player in photosensing. When all this is taken together, it becomes evident that fungi employ several photoreceptors, and we are just at the beginning of unraveling their functions and interlinked signaling cascades. Given the broad impact of light on fungal growth, development, and physiology, the understanding of the roles of and interactions among fungal photoreceptors will be a major avenue of fungal research in the near future.

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