ANNUAL REVIEWS

Annual Review of Genetics

Light in the Fungal World: From Photoreception to Gene Transcription and Beyond

Luis M. Corrochano

Departamento de Genética, Facultad de Biología, Universidad de Sevilla, 41012 Sevilla, Spain; email: corrochano@us.es

Annu. Rev. Genet. 2019. 53:149–70

First published as a Review in Advance on August 26, 2019

The *Annual Review of Genetics* is online at genet.annualreviews.org

https://doi.org/10.1146/annurev-genet-120417-031415

Keywords

photobiology, photoreceptor, white collar, phytochrome, opsin, cryptochrome

Abstract

Fungi see light of different colors by using photoreceptors such as the White Collar proteins and cryptochromes for blue light, opsins for green light, and phytochromes for red light. Light regulates fungal development, promotes the accumulation of protective pigments and proteins, and regulates tropic growth. The White Collar complex (WCC) is a photoreceptor and a transcription factor that is responsible for regulating transcription after exposure to blue light. In *Neurospora crassa*, light promotes the interaction of WCCs and their binding to the promoters to activate transcription. In *Aspergillus nidulans*, the WCC and the phytochrome interact to coordinate gene transcription and other responses, but the contribution of these photoreceptors to fungal photobiology varies across fungal species. Ultimately, the effect of light on fungal biology is the result of the coordinated transcriptional regulation and activation of signal transduction pathways.

1. INTRODUCTION

Fungi perceive and react to light, and they use light as a source of information about the environment to regulate many aspects of their biology. Like humans, the fungus *Neurospora crassa* uses light to set its circadian clock so that reproduction and other aspects of its biology occur at specific times of the day (46). Different fungal species use light as a signal to regulate developmental transitions such as the germination of spores or conidia, the growth of vegetative hyphae, and the development of sexual or vegetative reproductive structures. In addition, light regulates fungal metabolism and enzyme biosynthesis and, in some fungi, directs the growth of reproductive structures (phototropism)—similar to the tropic growth of plants seeking light to optimize photosynthesis (38, 40, 78, 140). An excess of light can be harmful owing to the damaging effect of UV radiation on DNA and the production of reactive oxygen species, and fungi use light as a signal to activate defensive mechanisms such as antioxidant enzymes and DNA repair enzymes and to accumulate protective pigments such as carotenes and melanin (4, 57). Some of the responses to light can be fast. For example, phototropism of the fruiting body of *Phycomyces blakesleeanus* is detected after a few minutes of unilateral illumination (40). Other photoresponses may take hours or days to visualize, as is the case for accumulating carotenoid pigments in *N. crassa* (43) and for developing reproductive structures in many fungi (38, 78, 140). Most fungi see blue light, but some fungi can see red light, green light, and even UV light (40, 78, 140).

Fungal photobiology is a good example of sensory perception in eukaryotes, and its study offers basic knowledge about how cells respond and react to environmental stimuli. An advantage to studying photobiology is that the stimulus, light, reaches the cell at light speed: It is easily applied and quickly removed, and this facilitates the quantification of stimulus–response relationships. Light can be applied briefly, for a few seconds, or for longer periods, lasting hours or days, to evoke molecular or cellular responses for quantification. The role of light as an environmental signal has driven the design of light-regulated promoters for the regulation of gene expression in yeasts and filamentous fungi (74, 108). Fungal photobiology has an applied aspect as well, since many pigments that accumulate after exposure to light (e.g., carotenes) are used by the cosmetic and food industries (63). The accumulation of fungal metabolites by light may have useful applications. For example, in the pearl oyster mushroom, *Pleurotus ostreatus*, blue light promotes the accumulation of shikimic acid, a precursor to the biosynthesis of an antiviral compound (82). In addition, optimum illumination is needed in industrial settings for improved production of edible fruiting bodies such as *P. ostreatus* (2) and fungal enzymes such as cellulases in *Trichoderma reesei* (117). Light is now recognized as one of several environmental stimuli that fungal pathogens use for host invasion and pathogenesis, which suggests that identifying chemicals that block light reception may help fight them (75).

What are the mechanisms of fungal vision? Which fungal proteins allow light perception and signal transduction? How did vision evolve in the fungal kingdom? What is the purpose, if any, of light perception in the fungal world? These questions have puzzled fungal photobiologists for many decades. Initial characterization of fungal photoresponses led to the determination of thresholds and stimulus–response relationships and to the characterization of active colors by action spectroscopy in select model fungi (15, 39, 44, 61, 72). These experimental approaches helped define the activity of complex photoreceptor systems and propose candidates for photoreceptor pigments. Ultimately, however, these candidates were not confirmed by biochemical purification and assays (60). Instead, it was genetics—specifically, the hunt for blind mutants, the characterization of these mutants, and, eventually, the identification of altered genes—that led to major breakthroughs in the identification of the blue-light photoreceptor first in *N. crassa* and later in other model fungi across the kingdom. Photobiologists were amazed by the number of different photoreceptor genes encoded in the *N. crassa* genome and in the genomes of other fungal species

after their sequencing; the biological roles of most of these genes were unknown (78). These examples remind us of our ignorance about the origin and evolution of light perception in fungi, and they reflect the magnitude of the task that lies ahead in our effort to understand the role of light in fungal biology.

In this article I review the most relevant aspects of fungal photobiology. Interested readers can complement this text with a selection of recent reviews (38, 51, 57, 78, 140).

2. LIGHT IN THE FUNGAL WORLD: FUNGAL RESPONSES TO LIGHT

Light regulates many aspects of the life cycle of fungi. An excess of light reduces germination in conidia of *Aspergillus fumigatus*, *Aspergillus nidulans* (43), and *Fusarium fujikuroi* (62). In some fungi, light produces compact colonies. In *N. crassa* this occurs by regulation of hyphal branching (43), whereas in *Trichoderma atroviride* it occurs by the inhibition of hyphal growth (27). In many fungi, light regulates the transition from vegetative growth to sexual or asexual reproduction and often has a key role in the decision to reproduce sexually or asexually. For example, light activates conidiation and represses sexual development in *N. crassa* (43), *A. nidulans* (11), and *Botrytis cinerea* (119). In other fungi, light has a key role in promoting conidiation, for example, in species of *Trichoderma* (26, 117) and *Fusarium* (3) and fruiting body formation in *Coprinopsis cinerea* (80) and *P. blakesleeanus* (40).

Fungal growth is controlled by light, for example, phototropic growth of the fruiting bodies of *P. blakesleeanus*, *Mucor circinelloides*, and *Pilobolus crystallinus*, presumably to optimize spore dispersal (40) (**Figure 1**). Other types of phototropic responses include phototropism of the perithecial beak in *N. crassa* (43) and the direction of the germination tubes in *B. cinerea* (119).

Conidiation: the development and formation of conidia, a type of vegetative spore that allows dispersal and the colonization of new substrates

Perithecial beak: the tip of the *N. crassa* female sexual body, the perithecium, that allows the discharge of the ascospores, the cellular products of the sexual cycle

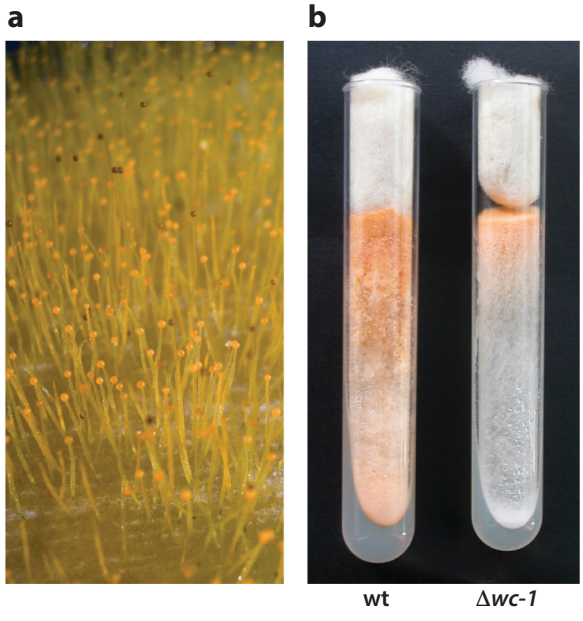

Figure 1

Fungal responses to light. (*a*) Blue light regulates the initiation and direction of growth (phototropism) of the fruiting bodies of *Phycomyces blakesleeanus*. Each fruiting body, or sporangiophore, has one sporangium (a small sphere) with vegetative spores at the top. (*b*) Light activates biosynthesis of the orange pigment neurosporaxanthin in vegetative mycelia of wild-type *Neurospora crassa* (wt) but not in the *white collar-1* mutant (Δ*wc-1*). The upper part of each tube is full of conidia that accumulate large amounts of the pigment.

A conspicuous effect of light on fungi is the activation of pigment biosynthesis. Carotenoids, for example, turn white fungal mycelia yellow or deep orange after exposure to light. This phenomenon has been the subject of detailed investigation in *P. blakesleeanus*, *M. circinelloides*, *N. crassa*, and *F. fujikuroi* (3, 40, 43) (**Figure 1**). The biosynthesis of additional pigments, such as melanins, is also induced by light in several fungi (57).

Why does light regulate such a wide variety of biological responses? In some cases, the ability to perceive light is a key component of the mechanisms that help fungi cope with the consequences of an excess of light, including UV radiation damage and the generation of reactive oxygen species. Good examples of coping mechanisms are the light activation of genes encoding DNA repair enzymes in several fungi (57). The ability to activate the biosynthesis of protective pigments and enzymes for DNA repair is probably at the origin of fungal photoreception. The phototropic use of light as a signal to guide the growth of reproductive structures should help optimize spore dispersal: Fungi growing under heavy cover need to bring their reproductive structures up from the soil and into the air to facilitate the dispersion of spores and conidia by wind currents and passing animals. It is more difficult to explain light regulation of fungal development, however, and the uncharacterized links between light, circadian clock regulation, development, and pathogenicity. The pathogenicity of *B. cinerea*, for example, changes with the timing of the infection (70), and photoreceptors are thought to have a role in the pathogenicity of *Fusarium oxysporum* (106) and *Cryptococcus neoformans* (76). Additional observations that wild-type isolates of *A. fumigatus* (56), *B. cinerea* (120), and *N. crassa* (86) show differences in their capacity to respond to light indicate that we also need to learn more about the natural habitats in which fungi thrive.

3. FUNGAL PHOTORECEPTORS

Fungal photoreceptors receive light signals through light-absorbing molecules, termed chromophores, that lead to structural changes or active output modules. The activation of photoreceptors starts the signal transduction pathway that leads to the cellular response to light (78, 140). How should we identify the fungal photoreceptor of a given response? Most fungi respond to blue light, but responses to other colors have been reported as well. For example, reproduction in *A. nidulans* is regulated by blue light and red light (99), and *B. cinerea* reacts to a wide variety of colors (119). Initial action spectra for blue-light responses suggested flavins or carotenes as chromophores (15, 39, 44, 61). The photoresponses in *albino* mutants ruled out a photosensory role for carotenoids in *N. crassa* (107), and experiments with flavin analogs supported the proposal that a flavin should act as a chromophore for phototropism in *P. blakesleeanus* (95). The search for blind mutants helped identify the components of light-transducing pathways for phototropism in *P. blakesleeanus* (16), photoconidiation in *Trichoderma harzianum* (71), and photocarotenogenesis in *N. crassa* (45), including candidates for the sensory components. For example, *white collar* (*wc*) mutants in *N. crassa* accumulated carotenoids in conidia under all culture conditions but not in vegetative mycelia after exposure to light, hence the *wc* phenotype (**Figure 1**). This behavior suggested that the *wc* mutants had an altered photosensory system but that the biochemical pathway for carotenoid biosynthesis was not altered. Identification of *wc-1* and *wc-2* in *N. crassa* (7, 85) and biochemical characterization of WC-1 have shown that this protein is a blue-light photoreceptor (54, 66). WC-1 and homologous proteins have been identified in many fungi, and they act as blue-light photoreceptors, but fungal genomes contain additional photoreceptor genes. They include genes for cryptochromes and phytochromes that sense blue light and red light, respectively, and genes for opsins, the photoreceptors for animal vision.

Most of our current knowledge on fungal photoreceptors comes from studies of *N. crassa*. I describe the photosensory system in *N. crassa* in Sections 3.1 and 3.2, and I discuss similarities and differences of this system with the photoreceptors in other fungi in Section 3.3.

WCC: White Collar complex

Light-oxygen-voltage-sensing (LOV) domain: a flavin-binding domain

VIVID (VVD): a small protein with a flavin-binding domain that regulates the White Collar complex

3.1. The White Collar Complex in *Neurospora crassa*: Sensing Light to Regulate Transcription

The White Collar complex (WCC) is composed of WC-1 and WC-2 and is essential for light sensing in *N. crassa* (7, 85). Each protein has a zinc finger that allows binding to specific sequences in DNA, and WC-1 has, in addition, a light-oxygen-voltage-sensing (LOV) domain. LOV domains bind flavins, which are chromophores, and they have been characterized in plant phototropin photoreceptors. During photoreception, blue light promotes a structural change in the protein: A link between the flavin and a nearby cysteine (a flavin-cysteinyl adduct) leads to further changes in protein structure and photoreceptor activation (50). It is assumed that a similar mechanism activates WC-1 and other LOV domain photoreceptors after exposure to light. The combination of a LOV domain and a zinc finger in WC-1 allows the WCC to operate as a transcription factor with an activity regulated by light (54, 66). The main regulator of the WCC is VIVID (VVD), a small photoreceptor protein with a LOV domain and a few additional amino acids at either end (69).

The regulation of the WCC by light and the role of light in regulating transcription have been investigated in detail, and the results of these investigations can be summarized as follows (**Figure 2**). The WCC binds to DNA in cultures kept in the dark, and the WCC-binding sites, most of which are in the promoters of light-regulated genes, have been characterized (109, 130, 138). After light exposure, two WC-1 proteins interact through their LOV domains to form dimers of WCCs (88). In addition, the histone acetyltransferase NGF-1 (*Neurospora* GCN five-1) binds to WC-1 and acetylates histone H3 (H314ac) in promoters (23, 64). WCC binding to promoters also causes the displacement of nucleosomes, a process supported by the transcription factor SUB-1 (109). Modification of histones and the resulting eviction of nucleosomes should increase the accessibility of the RNA polymerase, the initiation of transcription, and the accumulation of light-regulated messenger RNAs (mRNAs). Light activates *wc-1* (7, 79) and leads to phosphorylation of both WC-1 (67, 123, 124, 133) and WC-2 (123). Phosphorylation of WC-1 after exposure to light promotes its partial degradation while reducing its DNA-binding capabilities (67, 116). Protein kinase C (PKC) interacts with WC-1 in the dark and after long light exposures and phosphorylates a fragment of WC-1 in vitro. A mutant version of PKC that is always active has a reduced accumulation of WC-1 and reduced activation of *albino-2* (*al-2*) by light (52). We do not know how light promotes the interactions between PKC and WC-1 or how light regulates PKC activity. In addition, other kinases and phosphatases and the protein FREQUENCY (FRQ), the key regulator of the circadian clock, regulate the activity and stability of the WCC (46).

An interesting feature of light-activated transcription is that this regulation is transient. After extended illumination, the increase in light-regulated mRNAs is reduced and, eventually, mRNA accumulation returns to dark levels in a process known as photoadaptation (84, 124, 125). During photoadaptation, the WCC binds transiently to promoters, suggesting that the regulation of this transient binding to DNA is a key aspect of photoadaptation (67, 93).

How is WCC binding to DNA regulated by light? The photoreceptor VVD regulates the interactions of the WCC. Light activates the transcription of *vvd* so that VVD is detected only in cultures exposed to light. *vvd* mutants have a defect in photoadaptation that results in increased accumulation of light-regulated mRNAs, including the mRNAs for the enzymes needed for carotenoid biosynthesis, that leads to the deep orange color of the mutant mycelia (69, 88, 124, 125, 127). Light promotes the accumulation of VVD and its activation by the formation of

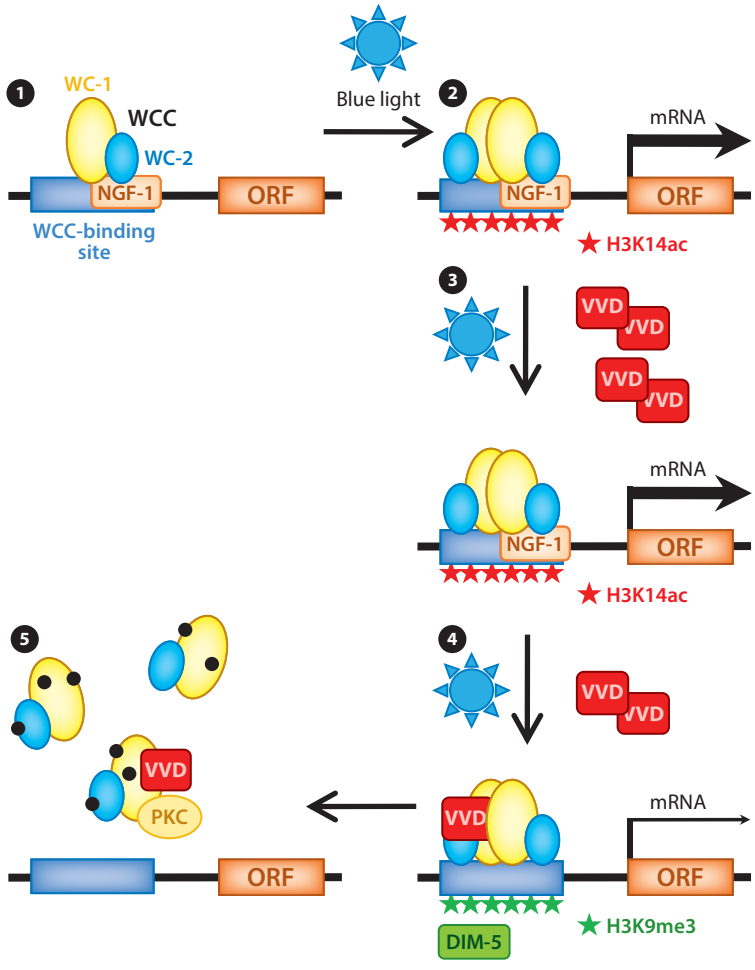

Figure 2

A model for light-regulated transcription. (❶) The WCC binds to the promoters in the dark. (❷) Light reception by WC-1 leads to the formation of WCC dimers, chromatin modification (H3K14ac) by the histone acetyltransferase NGF-1, and activation of transcription. (❸) The activation of *vvd* results in accumulation of the photoreceptor VVD in the nucleus. (❹) Further light promotes the formation of VVD dimers and the interaction between VVD and WC-1. This interaction leads to a disruption of WCC dimers and less WCC binding to the promoter. Modification of histones (H3K9me3) by DIM-5 further contributes to WCC eviction from the promoters. (❺) The transient phosphorylation of WCCs (*black dots*) and the partial degradation of WC-1 probably occur through the activity of PKC and other kinases and phosphatases (not shown). Abbreviations: DIM-5, defective in DNA methylation-5; H3K14ac, histone H3 acetylated lysine 14; H3K9me3, histone H3 trimethylated lysine 9; NGF-1, *Neurospora* GCN five-1; ORF, open reading frame; PKC, protein kinase C; VVD, VIVID; WCC, White Collar complex. Figure adapted with permission from Reference 51; copyright 2016 American Society for Microbiology. No further reproduction or distribution is permitted without the prior written permission of the American Society for Microbiology.

a flavin-cysteinyl adduct (125, 142). One of the structural consequences of the activation of the LOV domain is its dimerization: VVD dimerizes after light exposure, and light promotes the formation of WCC dimers by interactions between two WC-1 proteins (88, 135, 141). In addition, interaction between LOV domains of VVD and WC-1 disrupts WCC dimers and reduces the

transcriptional response, thus resulting in photoadaptation (32, 73, 88). The interactions between VVD and WC-1 prevent WC-1 from degrading but render the WCC inactive. In support of this proposal, an excess of VVD in a strain that overexpresses the gene leads to WCC desensitization (88). Any reduction in the transcription of *vvd* should alter photoadaptation. For example, RCO-1 and RCM-1 form a repressor complex that regulates *vvd*, and the corresponding mutants show reduced transcription of *vvd*, reduced accumulation of VVD, and altered photoadaptation. As expected, the *rco-1* mutant shows changes in the kinetics of WCC binding to the promoters, presumably due to the reduction in VVD and the altered regulation of WCC binding to DNA (92, 104). Mutations in the LOV domain of VVD result in changes to the photocycle length and a reduced capacity to interact with the WCC or to modify the capacity of VVD to form dimers, thus impairing photoadaptation (42, 135).

The interactions between VVD and WC-1 provide a mechanism for dampening the transcriptional response to light and preventing the accumulation of light-regulated mRNAs in constant light. A key aspect of light regulation in *N. crassa* seems to be the capacity to react to the transition from darkness to light as it occurs during dawn in nature.

Histone modification occurs during photoadaptation, and it may help evict the WCC from promoters. DIM-5 (defective in DNA methylation-5) is responsible for increasing the degree to which lysine 9 in histone H3 is trimethylated (H3K9me3) in the *frq* promoter, which is detected after long exposures to light. In the absence of DIM-5, the accumulation of *frq* mRNA increases after light exposure and more WC-2 proteins bind to the promoter, supporting the role of H3K9me3 in WCC eviction (103).

Photoadaptation is a complex process that may be regulated by additional proteins. A novel genetic screen found three additional mutants in genes that have yet to be identified, with alterations in photoadaptation of the conidiation-specific genes *con-10* and *con-6*, but not in *vvd* or *wc-1*, an indication that photoadaptation is gene specific (90).

The mechanism of gene photoactivation is not completely understood but the main features allow the proposal of a model (**Figure 2**). Light promotes dimerization of the WCC and its binding to DNA, initiation of chromatin remodeling, nucleosome eviction, and activation of transcription. Light activates *vvd* and VVD competes with WC-1 in WCC dimers. The disruption of WCC dimers reduces the WCC's capacity to bind to promoters. During light exposure the WCC is transiently phosphorylated, a process regulated by PKC and other kinases and phosphatases. The modification of histones after long light exposures helps release the WCC from promoters, after which it is partially degraded. The result of this process is a transient transcriptional response to light (photoadaptation).

3.2. Other Photoreceptors in *Neurospora crassa*

Additional photoreceptor genes in *N. crassa* have been described: a cryptochrome, two phytochromes, and an opsin (59). The presence of photoreceptor genes in addition to *wc-1* was unexpected, as *N. crassa* reacts only to blue light and its photoresponses require only the activity of the WCC. Thus, the additional photoreceptors were hypothesized to have a secondary role, at least when the fungus was grown in laboratory conditions.

Cryptochromes, phytochromes, and rhodopsins have been observed in many organisms. Cryptochromes are blue-light photoreceptors that are evolutionarily related to the photolyases that repair DNA. They act as photoreceptors for photomorphogenesis in plants and regulate the circadian clock in animals, but their role in other organisms is mostly unknown (31). Phytochromes regulate many responses to red light in plant biology, and they have been described for other organisms as well (34). Rhodopsins are photoreceptors in animals, including humans, and work as

light-regulated proton pumps and sensory photoreceptors in many bacteria. Unlike other photoreceptors, rhodopsins are located in the plasma membrane (47).

Genes for these photoreceptors in many other fungal genomes have been described (78), but their role in fungal photobiology remains elusive, with a few notable exceptions. The genes for these photoreceptors in *N. crassa* have been deleted, and the photoreceptor proteins have been expressed and characterized in vitro (17, 53, 55). The summary of these experiments is that these photoreceptor proteins act in vitro as expected for a photoreceptor: They bind the expected chromophores and demonstrate the expected photoreactions. The phenotypes of the photoreceptor mutants, however, are mild. One could assume that a useless photoreceptor gene would be mutated and eventually deleted by evolutionary pressures to streamline the genome. It is possible, however, that these photoreceptors play key roles in the biology of *N. crassa* in nature. The presence of many unexpected photoreceptor genes highlights our ignorance of the biology of *N. crassa* in nature.

What are the roles of these secondary photoreceptors in *N. crassa*? They have been proposed to play a minor role repressing the WCC (94), and none of the mutants show major changes in the transcriptome after light exposure (33, 53). In addition, the cryptochrome (CRY) partially regulates the circadian clock (91). Some of these photoreceptors may play a role in light-regulated sexual development in coordination with the WCC, as mutants in the phytochrome (Δ*phy-2*) or the opsin (Δ*nop-1*) show alterations at the onset of and in the environmental regulation of sexual development (136, 137).

3.3. Photoreceptors in Other Fungi

Photoreceptor genes in many fungal genomes have been described, but the few cases in which the *wc* genes have been mutated have shown that the WCC is the most important photoreceptor in fungal biology (78). The similarities in sequence and domains suggest that all fungal WCCs regulate transcription, as in *N. crassa*. However, the characterization of photoreceptors and the phenotypes of photoreceptor mutants in select fungi has revealed major differences from *N. crassa*, despite a similar repertoire of photoreceptors.

3.3.1. Photoreception in *Aspergillus nidulans*: sensing red light and blue light. Unlike in *N. crassa*, blue light and red light regulate the development and accumulation of secondary metabolites in *A. nidulans* (11, 43). The reception of red light relies on the phytochrome FphA (18, 21). FphA resembles bacterial phytochromes and has a histidine kinase domain in addition to a chromophore-binding domain. The histidine kinase activity of FphA should be functional, as the protein can be autophosphorylated. Most of FphA is present in the cytoplasm, but a small fraction of the protein is located in the nucleus, where it interacts with other photoreceptors. FphA expressed in vitro binds a chromophore, biliverdin, and shows all the photochemical properties of phytochromes. FphA molecules interact, but the role of these interactions in photoreceptor activity has not been investigated (18, 21).

A photoreceptor complex in *A. nidulans* has been described, but unlike in *N. crassa*, it contains the photoreceptors for blue light and red light, among other proteins. LreA and LreB are the *A. nidulans* homologs of WC-1 and WC-2, respectively, and they interact presumably as in *N. crassa*. In addition, LreB interacts with FphA in the nucleus. Since the majority of FphA is observed in the cytoplasm, a small fraction of FphA is likely transported to the nucleus to participate in the regulation of the photoreceptor complex (98, 99). Another protein that interacts with FphA is the velvet-domain protein VeA, a putative transcription factor that represses conidiation and regulates secondary metabolism (99). VeA is detected in the nucleus in vegetative hyphae kept in the dark, and light promotes a change in its subcellular localization in a process mediated by the

importin alpha. This allows VeA to be detected in the cytoplasm, with a small fraction still present in the nucleus. The presence of VeA in the cytoplasm after light exposure suggests that VeA acts as a repressor in the dark and that light, by promoting a change in the subcellular localization of VeA, helps release this repression, perhaps by changing the interactions between VeA and the photoreceptors (131).

A. nidulans has another blue-light receptor, the photolyase CryA. This enzyme has DNA repair activity and is a repressor of the sexual cycle (9). Most of these findings for *A. nidulans* can be extended to other species of *Aspergillus*. For example, the pathogen *A. fumigatus* reacts to blue light and red light using homologs of LreA and LreB and a homolog of FphA together with other photoreceptors still to be characterized (58).

How are the activities of the blue and red photoreceptors coordinated? In *A. nidulans*, blue light and red light promote the development of vegetative conidia and repress the sexual cycle, but blue light inhibits sterigmatocystin biosynthesis, whereas red light stimulates the accumulation of this secondary metabolite (99). *A. nidulans* may coordinate the activities of the different photoreceptors in a multisensory complex regulated by interactions with VeA—entering or leaving the nucleus—to activate or repress development and metabolism.

The transcriptional activities of LreA and LreB have not been characterized in detail, and it would be tempting to assume that these proteins would operate similarly to the WCC in *N. crassa*. In *A. nidulans*, *ccgA* is induced by red light but not blue light, but FphA is not detected at the promoter, although it is required for the red-light activation of *ccgA*. However, VeA and LreA bind to the promoter of *ccgA*, but the binding of LreA is transient: It is detected in the dark, and after illuminations of 15 or 30 min but not longer (68). The transient binding of LreA, a blue-light photoreceptor, to the promoter of a red-light-induced gene is puzzling but resembles the transient binding of the WCC in *N. crassa*. LreA interacts with the histone acetyltransferase GcnE, the homolog of NGF-1 in *N. crassa*, in the nucleus. In addition, light promotes the acetylation of lysine 9 in the promoter of *ccgA*, suggesting that the initial effect of light is to promote changes in the histones at promoters to facilitate gene expression, as in *N. crassa* (68). Future experiments should explore the role of LreA, FphA, and VeA in histone modifications and the interactions of these proteins with GcnE and other histone-modifying enzymes during exposure to red or blue light.

3.3.2. Photoreception in other fungi: new roles for old photoreceptors. Fungal photobiology has been explored in several ascomycetes and basidiomycetes. Detailed characterizations of photoresponses and the phenotypes of photoreceptor mutants have uncovered an unexpected variety in the role of each fungal species' photoreceptor. Additional variation in the role of fungal photoreceptors will likely be uncovered as photoreception is explored in additional fungi. Relevant examples are the photoresponses in species of the ascomycetes *Fusarium* and *Botrytis* and in the basidiomycete *C. cinerea*.

B. cinerea is a plant pathogen with a rich photobiology. This fungus reacts to a wide variety of wavelengths that range from near UV to red light, and it possesses an impressive array of photoreceptor genes. The effects of light on *B. cinerea* include the regulation of different stages of development, the accumulation of pigments, the regulation of tropic growth, and the regulation of its circadian clock (119). WC proteins and the cryptochrome are needed to repress conidiation and to regulate transcription, but the identity of the photoreceptors that participate in other light responses remains elusive (25, 36).

Like in *N. crassa*, light regulates the biosynthesis of carotenoid pigments in *Fusarium* species (3). However, unlike in *N. crassa*, the *wc-1* mutants, named *wcoA* in *F. fujikuroi*, *F. oxysporum*, and *Fusarium graminearum*, show a reduced accumulation of carotenoids, but light regulation is not completely disrupted. These observations suggest that other uncharacterized blue-light

photoreceptors should cooperate with WcoA in the activation of photocarotenogenesis (49, 81, 106). Other blue-light photoreceptors in *Fusarium* are the homolog of VVD, VvdA, and the cryptochrome CryD. VvdA regulates the development of vegetative mycelia and participates in the regulation of carotenoids by light (28). CryD participates in the regulation of secondary metabolism and conidial development (29). It is possible that only a combination of mutations in some or all blue-light photoreceptors in *Fusarium* will block the accumulation of carotenoids by light. In addition, *Fusarium* species have two opsin genes. The opsin CarO accumulates in conidia and operates as a proton pump to delay conidial germination in light (62). Understanding CarO function in *Fusarium* may help us understand the regulatory role of CarO homologs in other fungi, including *N. crassa*.

A new photoreceptor may regulate fruiting body development in *C. cinerea*. As expected, the WC-1 homolog, Dst1, mediates the regulation by blue light of this photoresponse as the corresponding mutant has a blind phenotype (80). However, another blind mutant had a mutation in a gene, *dst2*, encoding a protein with a segment of the binding site for a flavin. Dst2 may be the first representative of a novel type of WC-1 regulator (83).

3.3.3. Multiple *white collar* genes in early-diverging fungi. The presence of many types of photoreceptors is a characteristic of ascomycetes and basidiomycetes, but a group of early-diverging fungi, the Mucoromycotina, have duplicated and specialized genes for WC proteins. Major genomics changes have occurred in the evolution of Mucoromycotina fungi, and the role of genome duplications in photoreceptor evolution has been proposed. The analysis of the genomes of *P. blakesleeanus*, *M. circinelloides*, and *Rhizopus delemar* led to the discovery of two whole-genome duplications that had occurred during their evolution and that had allowed for the expansion of many gene families, including genes for signal transduction proteins (41, 87). *P. blakesleeanus* and *M. circinelloides* have many responses to light, some of them conspicuous, such as the induction of the pigment beta-carotene or the phototropism of asexual fruiting bodies (40) (**Figure 1**). One of the consequences of the whole-genome duplications was the duplication of *wc* genes, resulting in three *wc-1* genes and four to five *wc-2* genes in these fungi (41, 77, 87, 111, 129). During their evolution, however, phytochromes and opsin genes were lost (41, 87). We can expect a similar distribution of photoreceptor genes—multiple *wc* genes and the absence of phytochromes and opsin genes—in other Mucoromycotina genomes. However, only the sequence and characterization of genomes in additional early-diverging fungi related to the Mucoromycotina will help uncover when and how these evolutionary events, gene duplications, and gene deletions took place.

What is the role of the duplicated *wc* genes in Mucoromycotina fungi? Unfortunately, molecular technologies for gene manipulation are available only for *M. circinelloides*, but many blind or partially blind mutants of *P. blakesleeanus* have been identified and characterized. The role of the WC proteins in these two fungi show how each fungus can use the same photoreceptor repertoire differently, a cautionary tale against generalizing observations from model organisms.

In *M. circinelloides*, WC-1 proteins act as photoreceptors for specific responses: Mcwc-1a for phototropism and Mcwc-1c for photocarotenogenesis (129). The role of Mcwc-1b is less clear, but it is ubiquitylated and, as a transcription factor, regulates the genes for the enzymes that participate in the biosynthesis of beta-carotene (89, 128). Mcwc-1b and Mcwc-1c should act in a coordinated way to regulate the biosynthesis of beta-carotene, perhaps by interactions in a multicomponent WCC. We need additional molecular characterization of the interacting partners of these proteins, and information about how and where they bind DNA, in order to understand how they regulate transcription in *M. circinelloides*.

It is not possible to delete genes in *P. blakesleeanus*. However, clever mutant selection procedures and an efficient sexual cycle have provided a wealth of phototropic mutants, *mad* mutants (named after Max Delbrück), many of them altered in other responses to light (16). Genome sequencing

of a combination of wild type and *mad* mutants helped identify the nature of some of the *mad* genes. The results have shown that two genes, *madA* and *madB*, encode homologs of WC-1 and WC-2 to regulate all the responses of *P. blakesleeanus* to light, unlike in *M. circinelloides*.

In the absence of clean gene deletion, the phenotypes and the nature of mutant alleles may help researchers understand the role of MadA and MadB in the photobiology of *P. blakesleeanus*. The reduced sensitivity to light of *madA* or *madB* mutants showed their key role in regulating photobiology (40). Mutant alleles of *madA* produce proteins with mutations in the LOV domain or without the zinc finger, while the only *madB* allele available produces a protein without the zinc finger (77, 111). These mutations highlight the relevance of the LOV domain and the zinc finger in the activities of MadA and MadB and suggest that these proteins exert their regulatory roles by controlling transcription (77, 101, 111). MadA and MadB interact and form a photoresponsive transcription factor complex, the Mad complex, similar to the WCC in *N. crassa*. Interactions between WC proteins in fungal species across the kingdom are the basic feature of the activity of WC proteins as transcriptional regulators. However, MadA and MadB do not interact with the other *P. blakesleeanus* WC proteins, at least not in yeast two-hybrid assays, despite having similar domains that, presumably, could have allowed interactions (111).

What role do the other WC proteins have in *P. blakesleeanus*? The presence of LOV domains and zinc fingers suggests that the WC proteins should work as components of additional blue-light-dependent transcription factor complexes. However, the absence of interactions between WC proteins in yeast two-hybrid assays suggests that their capacity to interact and form protein complexes similar to the Mad complex is limited or that the interactions are brief and require additional proteins. The secondary *wc* genes are induced by light, unlike *madA* and *madB*, and their induction requires the Mad complex (77, 101, 111). These secondary *wc* genes may provide additional photosensory components for fine-tuning the responses to light. Only the detection of the secondary WC proteins in vivo and the characterization of their DNA-binding activities will help us understand their role in the photobiology of *P. blakesleeanus*.

An additional blue-light photoreceptor in *P. blakesleeanus* is the cryptochrome CryA, which repairs DNA after sensing blue light. CryA belongs to the cryptochrome DASH family, but unlike other members of this family, it shows DNA repair activity in vivo and can bind to and repair cyclobutane pyrimidine dimer lesions in single- and double-stranded DNA in vitro. These data suggest that CryA should act as a photolyase despite having a sequence similar to that of cryptochromes (132). Cryptochromes have been hypothesized to have originated from ancestral photolyases, and this origin would place *P. blakesleeanus* CryA early in the evolution of cryptochromes, from photolyase DNA repair enzymes to sensory photoreceptors. It is tempting to speculate that CryA homologs in related fungi may have roles similar to those of DNA repair enzymes (132).

3.3.4. Could the last common ancestor of fungi see a rainbow of colors? What type of photoreceptor was present in the last common ancestor of fungi? How ancient is fungal vision? The sequencing of fungal genomes has allowed researchers to identify photoreceptor genes in select members of each fungal lineage (78). Genes for all the photoreceptors in fungi—WC proteins, cryptochromes, phytochromes, and opsins—have been detected in all major fungal lineages (**Figure 3**). Opsin genes have not been detected in early-diverging fungi, but opsins regulate phototaxis in two members of the Blastocladiomycota: *Allomyces reticulatus* and *Blastocladiella emersonii* (5, 112). Some fungi do not have photoreceptor genes, which may be explained by evolutionary pressures to adapt to an endoparasitic lifestyle with a small genome, such as for *Rozella allomycis* (Cryptomycota). The absence of photoreceptor genes in the ascomycete yeasts such as *Saccharomyces cerevisiae* is puzzling. However, *S. cerevisiae* uses light to regulate the transport of a transcription factor to the nucleus. The light signaling pathway initiates with the synthesis of hydrogen

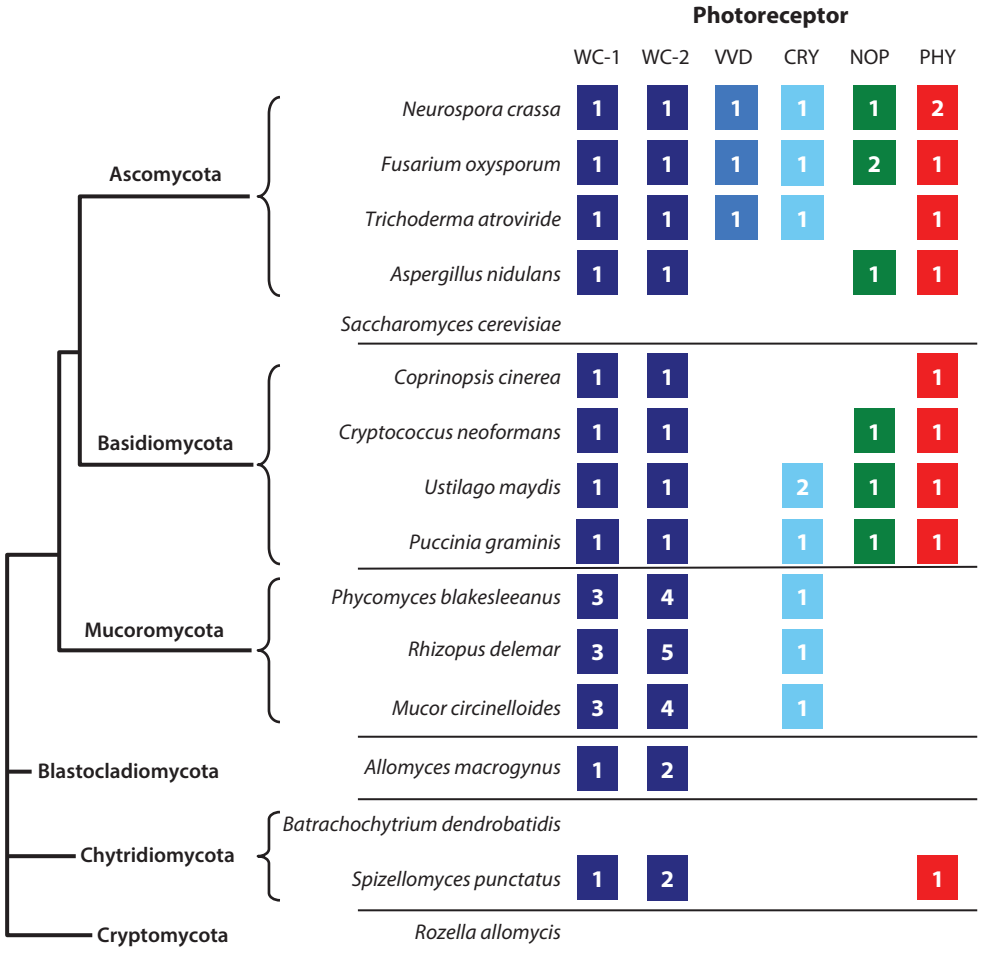

Figure 3

Photoreceptors in the kingdom Fungi. Distribution of homologs of the *Neurospora crassa* photoreceptors for blue light (WC-1 and its partner WC-2, VVD, and the cryptochrome CRY), green light (the opsin NOP-1), and red light (the phytochromes PHY-1 and PHY-2) in a selection of representatives of the kingdom Fungi. The numbers in each box indicate the number of homologous genes in each genome. The evolutionary relationship among early-diverging fungi is still uncertain. The genes were identified using BLAST and the public database of the Joint Genome Institute (**https://genome.jgi.doe.gov/programs/fungi/index.jsf**). Figure adapted with permission from Reference 78.

peroxide, which is sensed by a peroxiredoxin (19). We can speculate that *S. cerevisiae* developed this novel signal transduction pathway after losing all the photoreceptor genes.

The presence of different types of photoreceptors in most fungal groups suggests that the last common ancestor could detect and react to many colors, from near UV to red light. Different evolutionary strategies were then followed by different fungal lineages; for example, the Mucoromycotina lost genes for red light and green light but expanded their repertoire of *wc* genes (40). In this scenario, the presence of genes homologous to *vvd* in a select group of the Ascomycota suggests a specific adaptation for the regulation of the WCC. Specific deletion or expansion of photoreceptor genes probably reflects local adaptation to certain environmental conditions.

3.4. A General Mechanism for Photoadaptation?

The presence of WC proteins for the regulation of blue-light responses and light-dependent transcription is widespread in fungi, but the mechanism of photoadaptation by interactions between the WCC and VVD homologs is not. Photoadaptation in *P. blakesleeanus* (101, 111) and *A. nidulans* (105) has been described. Unlike in *N. crassa*, changing the light intensity or incubating the fungus for long periods in the dark does not change the photoadaptation response in *P. blakesleeanus* (101). Photoadaptation in *N. crassa* is mediated by the competitive interactions between the LOV domains of WC-1 and VVD, but the genomes of *A. nidulans* or *P. blakesleeanus* do not contain *vvd* homologs (78), and other mechanisms of photoadaptation may be operating in these fungi. In *P. blakesleeanus*, a reduction in the amount of the Mad photoreceptor complex with long light exposures has been proposed as an alternative mechanism for photoadaptation (101), but the roles for other proteins that may negatively regulate the activity of WCC homologs are plausible as well. However, a *vvd* gene in the genome does not imply that a fungus has a VVD-related photoadaptation mechanism. For example, the Δ*vvdA* mutant in *F. fujikuroi* has a pale orange color, unlike that of *N. crassa*, owing to a reduction in the photoactivation of genes for carotenoid biosynthesis (28).

4. LIGHT REGULATES THE FUNGAL TRANSCRIPTOME

The relevance of the WCC and its homologs to fungal photobiology suggests that the most immediate consequences of photoreception are the modification of the transcriptome and the differential accumulation of light-regulated mRNAs and proteins. In fact, reductions in the cost of transcriptome characterization suggest that this is the easiest way to demonstrate fungal photoreception in new fungal species.

In *N. crassa*, differential hybridization to genomic microarrays indicates that 5.6% of genes are light regulated. Light regulation occurs in waves, and early light-regulated genes show maximum accumulation after 15–30 min, while late light-regulated genes accumulate after 60–90 min of light exposure (33). Early-transcribed genes included genes for transcription factors, such as the GATA transcription factor SUB-1 (submerged protoperithecia-1). SUB-1 participates in the activation of late light-responsive genes after the activation of *sub-1* by the WCC. The characterization of WCC binding to the *sub-1* promoter supports a hierarchical response to light, with the WCC activating *sub-1* transcription, which then activates transcription of late light-responsive genes (33). However, further characterization of the roles of the WCC and SUB-1 on light-dependent transcription showed that SUB-1 is required for full nucleosome eviction by the WCC and that the photoactivation of the late-light-induced genes *rds1* and *hyr1* required both the WCC and SUB-1, supporting the proposal that the two transcription factors cooperate during the transcriptional response to light (109).

Homologs of SUB-1 have been identified in other fungi. In *B. cinerea*, the SUB-1 homolog is required for pathogenesis and light-regulated transcription and development (121). In *T. reesei*, the SUB-1 homolog regulates sexual development and secondary metabolism by controlling transcription (14). Both genes are induced by light, as in *N. crassa*, and their relevance to light-regulated differentiation confirms the proposal that initial light activation of the WCC is followed by a cascade of light-regulated gene transcription. The light regulation of genes for many other transcription factors in other fungi, such as *B. cinerea* and *P. blakesleeanus*, has been described (20, 37, 41). This suggests that the activity, which is perhaps coordinated, of different transcription factors is involved in the transcriptomic response to light after initial activation by the WCC homologs.

A light-regulated gene in *N. crassa*, *fl*, encodes a transcription factor required to activate conidiation (6). The WCC binds the promoter of *fl* to quickly activate transcription after illumination,

presumably increasing the amount of FL and subsequently activating conidiation (93). Similarly, light activates the transcription of *brlA*, which encodes the main regulator of conidiation in *A. nidulans* (105). Thus, light may regulate conidiation in these and perhaps other fungi by activating genes that encode key transcription factors.

Light-regulated transcription in *N. crassa* has been further characterized by identifying WCC-binding sites in the genome. The results indicate that several important transcription factors are controlled by light or by the WCC, and they confirm the key role of transcriptional regulation by light in *N. crassa* (109, 130, 138). An interesting observation of these studies was the high number (approximately 30%) of light-regulated genes in *N. crassa*. These include genes needed for pigment biosynthesis and for the defense against oxygen stress (138). Other fungi have a similar transcriptional response to light; these percentages range from 3% to 5% in other ascomycetes and up to 12% in *P. blakesleeanus*, a member of the Mucoromycota (41, 58, 105, 121). However, in *T. atroviride* only 72 proteins changed their abundance after light exposure, with 461 genes (4.8% of the genes) showing light regulation (30, 110). It is possible that changes in the amount of proteins, particularly low-abundance proteins, were more difficult to detect than changes for mRNA, but these observations raised questions about the biological relevance of the effect of light on transcription, at least in *T. atroviride*. Patterns of light-dependent mRNA accumulation differ noticeably between vegetative mycelia and the fruiting body in *P. blakesleeanus*, suggesting that the way that the Mad complex regulates transcription changes during development, perhaps with the aid of the additional WC proteins (41).

5. TRANSDUCING THE LIGHT SIGNAL INTO A CELLULAR RESPONSE

Many photoreceptors combine a sensory module and an output module within the same protein to facilitate the coupling between photoreception and the first event in signal transduction (78, 140). The discovery in *N. crassa* that WC-1 combines a sensory LOV domain and a zinc finger that allows binding to DNA suggested a simple transduction pathway with few, if any, additional elements. This discovery also led to the assumption that cellular responses to light were the consequence of differential transcription and the corresponding changes in the accumulation of proteins. However, further exploration of the fungal photoresponses, the characterization of blind mutants, and the phenotypes of mutants in genes for potential sensory transducers have enabled the discovery of new components in the transduction pathways for photoreception. The overall picture is that light promotes changes in the transcriptome and activates signal transduction chains, at least in the fungi that have been characterized.

In *A. nidulans*, VeA interacts with photoreceptors for blue light and red light, but this protein participates in other regulatory complexes (10, 115). VeA forms the *velvet* complex with the velvet-domain protein VelB and LaeA, a methyltransferase, and this complex is required for the regulation by light of the sexual cycle and the accumulation of secondary metabolites (12). Another complex is composed of VelB and the velvet-domain protein VosA, and both complexes require the activity of LaeA (114). The presence of VeA in the nucleus, where it participates in these regulatory complexes, depends on light (131) and on the interaction of VeA with other methyltransferases (96, 113). VeA is phosphorylated at several sites to regulate its nuclear localization and interaction with other protein partners (100). The MAP kinase MpkB phosphorylates VeA to regulate how it interacts with other proteins (8). Another kinase, ImeB, participates in the light responses of *A. nidulans* (13), and it is tempting to speculate that it does so also by VeA phosphorylation.

Velvet proteins have a velvet domain that binds DNA at specific sequences, and they may participate in the direct regulation of gene transcription as transcription factors (1). In addition, VeA may regulate transcription by chromatin modification through interactions with methyltransferases

(113). This proposal is supported by the observations that VeA binds to the promoter of *ccgA*, a gene that is transcribed after red light, and that LreA and FphA mediate the light-dependent modification of histones during the light response (68). The interaction of VeA with VipA, a protein that may bind to DNA and that interacts with LreA and FphA, suggests either an alternative mechanism or an additional mechanism for direct light-regulated transcription (102). In any case, light modifies the nuclear localization and the interactions of VeA and other velvet proteins, resulting in changes in transcriptional regulation and the subsequent regulation of development (105). Details of the mechanism that regulates the differential localization of VeA by light to initiate this signaling cascade remain to be elucidated. There are VeA proteins in other fungi (24). In many cases—for example, in *Mycosphaerella graminicola* (35), and *B. cinerea* (120)—they participate in light regulation, perhaps like in *A. nidulans*.

cGMP: cyclic guanosine monophosphate

Posttranslational modification of proteins during the responses to light has been observed in several fungi, and these modifications could be part of the corresponding light signaling transduction pathways. We have already discussed the transient phosphorylation of the WC proteins in *N. crassa* and the ubiquitylation of the photoreceptor Mcwc-1b in *M. circinelloides*. In *A. nidulans*, ubiquitylation of proteins is part of the mechanism by which light regulates the sexual cycle. This is mediated by either the COP9 signalosome or sumoylation (22, 65), presumably for the degradation or modification of regulatory proteins.

Interaction between the stress-sensing pathway and light perception has been uncovered in *A. nidulans* and *T. atroviride* and provides additional elements for a complex signal transduction pathway. A genetic screen for blind mutants revealed a key role in the processing of the light signal for the MAP kinase SakA, a component in the transduction pathway that senses stress and changes in the osmotic balance in *A. nidulans* and other fungi. The relevance of the stress-sensing pathway in light perception was confirmed by the blind phenotype of other mutants in the pathway. In addition, the phytochrome FphA promotes the phosphorylation of SakA by light and its transfer to the nuclei, presumably to continue its regulatory cascade (139). The relationship between the stress-sensing pathway and light perception may be more general than anticipated: Similar blind phenotypes were observed in Pbs2 and Tmk3 kinase mutants in *T. atroviride* (48).

Other fungi display interactions between light and other sensory transduction pathways, suggesting additional relationships between signal transduction components in the fungal cell. For example, in *T. reesei*, heterotrimeric G proteins mediate the interaction between light sensing and nutrient sensing. Transcription of the cellulase gene is controlled by light and requires the coordinated activities of the WC homologs BLR-1 and BRL-2 and the VVD homolog ENVOY with components of the heterotrimeric G protein signaling pathway (118, 126, 134). Mutants in the downstream components of this pathway, protein kinase A and adenylate cyclase, altered the regulation of cellulase transcription by light, further supporting the interaction between both pathways (122). cGMP has a key role in phototaxis in *Blastocladiella emersonii*. The rhodopsin photoreceptor of this early-diverging fungus contains a guanylyl cyclase catalytic domain that is presumably activated after light exposure. This complex photoreceptor connects the cGMP signaling pathway with vision, as occurs in vertebrates (5). We can speculate that the *B. emersonii* photoreceptor represents an ancient precursor to vision mechanisms that are still used in vertebrates. Ras signaling has been proposed to mediate the phototropic growth of *P. blakesleeanus* fruiting bodies. One of the phototropic *mad* mutants, *madC*, encodes a protein that regulates Ras activity, a GTPase-activating protein. The connection between light perception and Ras signaling is not yet clear, since MadC does not interact with the photoresponsive Mad complex, at least in yeast two-hybrid assays. However, these results show that signaling through Ras is part of the pathway that starts with light perception by the Mad photoreceptor and leads to the modification of cell wall growth during the phototropic response (97).

6. CONCLUSIONS

Fungi have a variety of photoreceptors at their disposal. The WCC and its homologs are the main receptors for most fungi, but the contribution of each photoreceptor to the photobiology of each species cannot be predicted by its photoreceptor gene repertoire. Unfortunately, there is not a model fungus for fungal photobiology, and only the characterization of photoreception in select fungi across the kingdom will allow us to identify common and specific mechanisms and to understand the variety of fungal responses to light.

Future research should aim to understand how photoreceptors interact and coordinate during light responses. We have a good working model of the mechanism by which the WCC and VVD regulate transcription in *N. crassa*, but the details of WCC binding to the promoters and interactions of the WCC with different regulatory proteins (VVD, kinases, and others) still need to be clarified. In addition, the absence of VVD in many fungi suggests other regulatory mechanisms should be further explored.

A major effect of photoreception is a global change in the transcriptome, but the effect of differential transcription on the accumulation of proteins remains to be investigated in detail. Long-term effects of light can be explained by light-dependent transcription as well as subsequent changes in the amount of proteins needed for biological responses, such as conidiation after the accumulation of conidiation-specific transcription factors and carotenoid biosynthesis after the accumulation of biosynthetic enzymes. However, the role of differential transcription in short-term responses such as phototropism is less clear. Phototropism requires asymmetric growth of the cell wall, and it is difficult to envision how differential transcription and translation and asymmetric protein localization could lead to tropic growth in less than five minutes.

Beyond transcription, other roles for WC proteins in fungal photobiology should be explored, as these proteins may regulate and coordinate the activity of signal transduction components. The characterization of the effect of light on transcription has been the focus of recent research in the field, but I anticipate that understanding the role of signal transduction elements such as kinases, G proteins, and Ras and the interactions of these proteins with photoreceptors will further elucidate fungal photobiology.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Research in fungal photobiology in my laboratory is supported by the European Regional Development Fund (ERDF) and the Spanish Ministerio de Ciencia, Innovación y Universidades (BIO2015-67148-R and RTI2018-098636-B-I00). I thank Gabriel Gutiérrez for help in the identification of photoreceptor genes in fungal genomes.

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