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Seeing the rainbow: light sensing in fungi

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Light is essential for photosynthetic organisms, but also serves as an important environmental cue for non-photosynthetic species; thus, light sensing is evolutionarily conserved throughout the kingdoms, from archaea and fungi to humans. Light sensors are chromoproteins, the low-molecular weight compound of which absorbs specific wavelengths and induces a reaction from the protein. In fungi, three light-sensing systems have been described at the molecular level. Blue-light sensing is achieved by a flavin-based photoreceptor, which itself acts as a transcription factor, and red-light sensing is achieved by a phytochrome, a molecule until recently thought to be confined to plants. A retinal-based opsin-system was discovered recently, although a biological function remains to be determined. The challenge for future research will be the identification of further components of signalling cascades, the identification of light-regulated genes and the unravelling of possible functional interplays between the different light control systems.

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Introduction

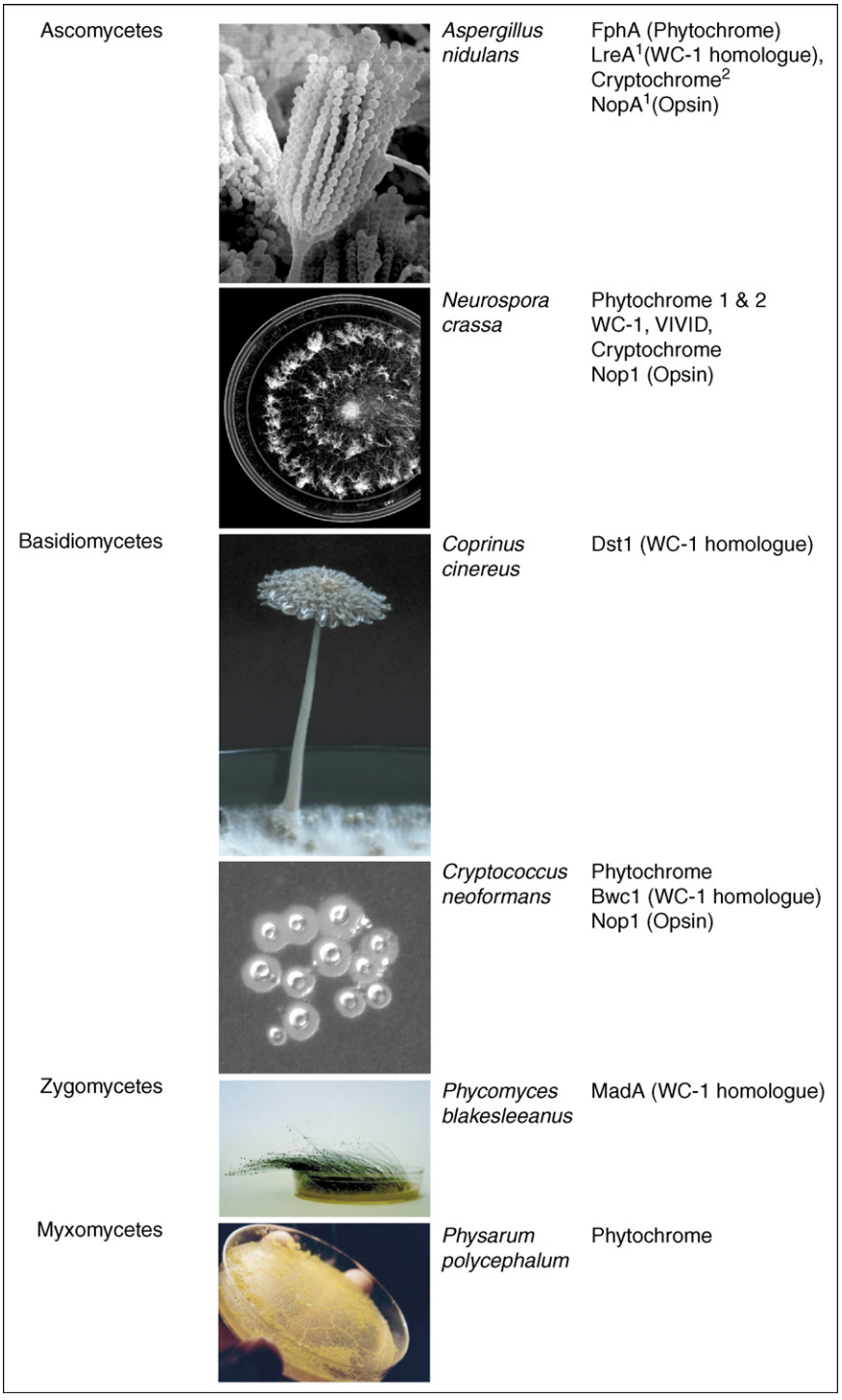
As fungi are saprophytic organisms, one of the intriguing questions is, why do they 'see' light? The most obvious answer is provided for asexual spore production in filamentous fungi. Because the fungi are sessile and spores serve as their distribution units in the environment, the spores should only be produced when the fungus grows at a water–air interface, for example on the soil surface, and light is a reliable signal to indicate if this is the case. Given that light influences many different physiological responses such as asexual conidiation, the circadian clock, secondary metabolism, pigmentation and sexual development, it is not surprising that fungi are capable of sensing light over a broad spectrum range, from ultraviolet to far-red light. The range of perceptible light intensities covers more than ten orders of magnitude, from gloomy starlight to full sunshine. Hence, a variety of photoreceptors is conserved in fungi, some of which have been analyzed in the past few years (Figure 1).

The blue-light response

The first blue-light response was reported in 1881 by Darwin when he described a blue light induced phototropic response in plants [1], and have been identified in all three domains (eukaryotes, bacteria and archaea) since. Blue-light receptors can be divided into two general classes: the phototropins and the cryptochromes. With phototropins, the photosensory N–terminal part consists of several characteristic domains, one of which is a LOV domain (light, oxygen or voltage). The C–terminus harbours a kinase domain and, in some cases, additional motifs. Cryptochromes show high similarity to photolyases — which are thought to be very ancient molecules — because they share an important role as a photo-defence system. Through gene duplication and functional changes, cryptochromes might have evolved from ancestral photolyases. The cryptochrome Cry1 from *Neurospora crassa* shows strong sequence homologies to cryptochromes from other organisms, but its role in photobiology has not yet been elucidated [2].

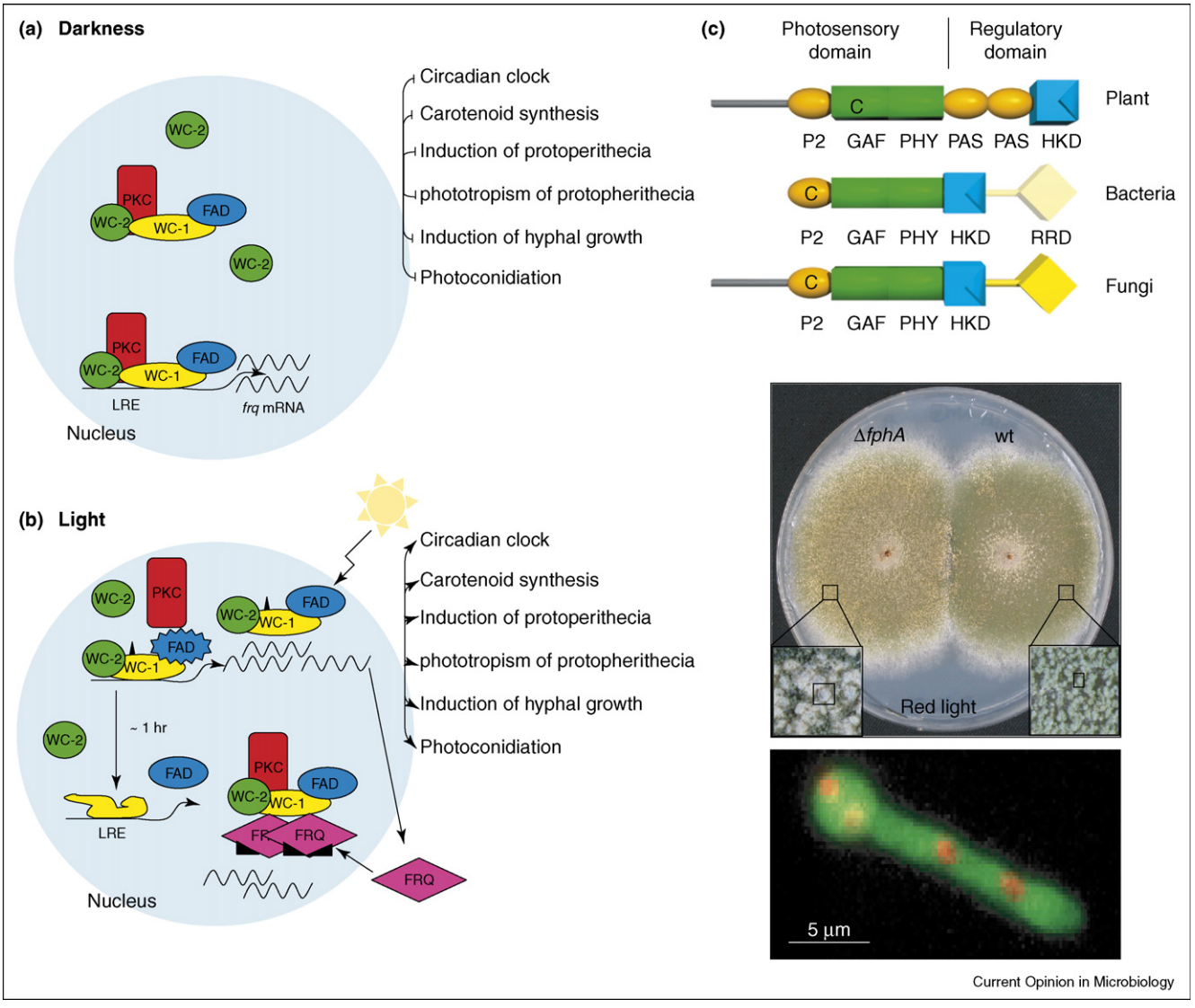
The best-described blue-light receptor in the fungal kingdom is the phototropin-like protein White Collar 1 (WC–1) from the ascomycete *N. crassa*. In this fungus, all known light responses, such as carotenoid biosynthesis, induction of protoperithecia and their phototropism, induction of hyphal growth, asexual spore formation and the entrainment of the circadian clock, are sensitive to UV or blue light (Figure 2) [3]. The WC–1 protein was discovered through the analysis of a *wc–1* mutant. The name 'white collar' derives from the observation that carotenoid biosynthesis in the mycelium of this mutant is impaired, whereas conidia are still pigmented: this leads to the appearance of colonies with a non-pigmented border or (or white collar). A second mutant with the same phenotype led to the discovery of White Collar 2 (WC–2). Sequence analyses revealed that WC–1 and WC–2 are GATA-type zinc-finger domains containing transcription factors [4,5]. Both proteins share another motif, the Per-Arnt-Sim (PAS) domain [6]. WC–1 has three PAS domains, of which the first is a LOV domain. It shares high similarity to the LOV domain containing proteins from plants, such as FKF1 (flavin-binding, Kelch repeat, F–Box 1) from *Arabidopsis* [7]. In this domain of WC–1, 11 conserved residues were identified that are necessary for chromophore-binding in plants. Using the third PAS

Figure 1



Light sensing in the fungal kingdom. Different examples of light-regulated processes and the photosensory systems characterized are displayed. Descriptions are from top to bottom. *A. nidulans,* asexual conidiophores with thousands of conidiospores (3 μm in diameter) are produced under light conditions. In the dark and under far-red-light conditions, meiotic spores are favoured. *N. crassa*: circadian rhythm of sporulation. Inoculation on one side of a Petri dish and incubation for several days in darkness. The half rings indicate rhythmic spore formation. *C. cinereus*: the heterothallic basidiomycete produces fruiting bodies with a height of 5–10 cm. Several steps of fruiting-body formation are light-dependent. *Cryptococcus neoformans*: The yeast-like pathogen *C. neoformans* forms an outer capsule of carbohydrates that is essential for infection and cause of cryptococcal meningitis. *P. blakesleeanus*: phototropic bending of sporangiophores toward white light (illumination from the left; image reproduced from [25••]) *P. polycephalum*: plasmodium of the true slime mould *P. polycephalum*. The plasmodium is a large multinuclear cell (syncytium), which is the main vegetative phase of the life cycle. It can grow to an area of up to 1 m^2. Image acknowledgements: *N. crassa*, picture kindly provided by J Dunlap (Hanover, NH, USA); *C. cinereus*, picture kindly provided by M Navarro-Gonzalez and U Kuees (Göttingen, Germany); *C. neoformans,* picture kindly provided by A Idnurm (Durham, NC, USA); *P. blakesleeanus*, reprinted from [25••], with permission; *P. polycephalum*, picture kindly provided by M Etzrodt and M von der Helm (Germering, Germany).[1]J Purschwitz, unpublished data. [2]G Braus, personal communication.

Figure 2



Molecular basis for blue-light and red-light sensing. **(a,b)** The *white collar* system in *N. crassa* (adapted from [40]). In darkness, the WCC associates with PKC and binds to LREs in the promoter of *frq*. The *frq* transcript level is very low. Upon light exposure the *frq* mRNA level increases immediately and *wc–1* expression is also induced. By contrast, the *WC–2* level is high under all conditions. PKC dissociates from WCC, leaving a phosphorylated WCC behind at the LRE site. Transcription of *frq* reaches its peak and FRQ is synthesized. One hour after light exposure, WCC experiences hypophosphorylation and is subsequently degraded. FRQ binds newly synthesized WCC and prevents its own transcriptional activation. As a result *frq* expression is again reduced to a basal level and the photo-cycle can start again. It has not yet been analyzed in such a detail if all other light-regulated processes, indicated on the right, have a similar regulation mechanism. **(c)** The phytochrome system in *A. nidulans*. (Top) Domain organization of phytochromes in plants, bacteria and fungi. (Middle) Phenotype of a phytochrome deletion strain. (Bottom) Localization of GFP-tagged phytochrome. Nuclei were stained with DsRed (assembled from [35••]).

domain, WC–1 forms a complex with the PAS domain of WC–2 [8,9]. This complex acts as transcriptional activator of light-regulated genes (Figure 2). Direct involvement of WC–1 in light perception has been shown by two different approaches. Dunlap and colleagues [10] characterized light-response elements (LRE) in the promoter of the frequency gene and showed that WC–1 binds to flavin adenine-dinucleotide (FAD) as a cofactor, forms a complex with WC–2 (the WCC) and hence confers light-regulation to the *frq* (or *frequency*) gene (see below). Liu and colleagues [11] purified the WCC and identified FAD in this protein fraction by fluorescence spectroscopy.

WC–1 and WC–2 are both nuclear-localized, but a fraction of WC–2 is also detected in the cytoplasm. Both proteins undergo light-dependent phosphorylation, but neither light nor phosphorylation has an effect on their localisation pattern [12]. One of the best-known examples

of blue light regulated gene expression in *N. crassa* is the transcriptional activation of the gene encoding the FRQ protein, the central component of the circadian clock (Figure 2). It was shown that the WC–1 protein concentration is regulated by protein kinase C (PKC) [13] and that hyperphosphorylation of WCC changes its binding activity to the target promoters, and thus is important for photoadaptation [14]. Not only is modification of the WCC at the protein level important for regulation of its activity but is also important for regulation of the complex at the transcriptional level. Kaldi *et al.* [15] recently showed that three promoters drive the expression of *wc–1*. In *Trichoderma atroviride*, a link to protein kinase A (PKA) was shown [16]. Abolishment of functional PKA resulted in a non-sporulating phenotype, whereas overexpression of PKA also induced conidiation in darkness. In *N. crassa*, apparently at least one additional circadian oscillator exists that also depends on WC–1 and WC–2 for activity and is temperature-entrainable [17,18].

A second blue-light receptor, named VIVID, was discovered recently in *N. crassa*. It consists of just one LOV domain and binds non-covalently to flavin (FAD or FMN [flavin mononucleotide]). It is hypothesized that VIVID senses changes in light intensity [19], and it is also involved in the modulation of the circadian clock [20]. Once WC–1 undergoes the dark–light transition, WC–1, in combination with WC–2, stimulates the expression of VIVID. In *vvd* mutants, the circadian gating of light responses is partially lost, which leads to a circadian shift.

Meanwhile, WC–like blue-light receptors have also been described in the ascomycetes *T. atroviride* (see above) [21], the rice blast fungus *Magnaporthe oryzae* [22], and *Aspergillus nidulans* (H Haas, personal communication; Fischer *et al.* unpublished results), as well as basidiomycetes and zygomycetes [23•,24,25••,26]. The zygomycete *Phycomyces blakesleeanus* produces up to 10 cm high sporangiophores that bend towards near-UV light and away from far-UV light. In the 1960s, the Nobel Laureate Max Delbrück had already isolated diverse *Phycomyces* strains with defective phototropism, of which the corresponding *madA* gene was recently discovered to encode a WC–1-like photoreceptor [25••].

The red-light response

Phytochromes were discovered in plants on the basis of the observation that seed germination of *Lactuca sativa* is inhibited by far-red light, and this effect is reversed by subsequent illumination with red light [27]. Phytochromes are a family of red/far-red-responsive photoreceptors using a linear tetrapyrrole (named bilin) as the chromophore for light sensing [28]. The attachment of the chromophore is an autocatalytic process resulting from an intrinsic bilin lyase activity of the phytochrome protein. Phytochromes switch between two stable conformations: a red-absorbing (Pr) form and a far-red-absorbing (Pfr) form. This so-called photoconversion involves a $Z \rightarrow E$ isomerisation in one double bond of the bilin, resulting in a conformational change in the phytochrome protein. All phytochromes share a common or general structure consisting of an N–terminal input module and a C–terminal regulatory module. The photosensory input domain comprises PAS, GAF (cGMP-specific phosphodiesterases; cyanobacterial adenylate cyclases; formate hydrogen lyase) and PHY (phytochrome) subdomains and harbours the chromophore attachment site, which is, depending on the organism, localized in the GAF or in the PAS domain. In the case of fungi and eubacteria, the output module is comprised of a histidine kinase domain (HKD) and a response regulator domain (RRD), whereas plant phytochromes possess only the HKD separated by two PAS domains from the photosensory module (Figure 2). Recently, a breakthrough was achieved with the crystal structure of the chromophore-binding domain from the *Deinococcus radiodurans* phytochrome with a 2.5 Å resolution [29••] and the structures of two phytochrome-related response regulators (with a resolution below 2 Å) from the cyanobacterium *Calothrix* PCC7601 [30].

In several fungi, red-light responses — reminiscent of the plant phytochrome response — have been reported, for example in *A. nidulans*. This fungus reproduces asexually with conidiospores and sexually with ascospores. Whereas asexual reproduction occurs at wavelengths of 680 nm, sexual spore formation is favoured at wavelengths of 740 nm, or in the dark [31]. Surprisingly, the peaks in the difference spectrum obtained with purified FphA expressed in *Escherichia coli* (at 705 nm and 758 nm) are slightly distinct from the peaks in the action spectrum. Whether this is because of different chromophores in *E. coli* and in *A. nidulans* has yet to be analyzed.

Another example of a phytochrome response related to the fungal phytochrome response is found in the true slime-mould *Physarum polycephalum*, where fragmentation of the plasmodium and sporulation can be induced by far-red light and the induction of sporulation can be suppressed by a red light pulse [32,33]. Thus, the *Physarum* phytochrome appears to act in reverse when compared to classical phytochrome effects, and is reminiscent of the high-irradiance response in *Arabidopsis*.

In filamentous fungi, phytochromes were identified in the genomes of several species, but were only analyzed in some detail in *N. crassa* and *A. nidulans*. The presence of a response regulator domain in the fungal proteins points to a bacterial origin of phytochromes from an ancient two-component system. In *N. crassa* two phytochrome-coding genes were identified, *phy-1* and *phy-2*. The expression of both *phy* genes is not regulated by light, but the transcription of *phy-1* appears to be under the control of the circadian clock. The function of the phytochromes in

N. crassa remained unclear, because the *phy*-deletion strains displayed no abnormalities in any known photoresponses [34]. By contrast, deletion of the single phytochrome gene, *fphA*, in *A. nidulans* caused a developmental phenotype [35••]. Corresponding deletion strains produce more ascospores under light conditions than did the wild type, indicating that the repression of sexual development is overcome. However, the de-repression is not complete, showing that *A. nidulans* is still able to sense and react to red light. This result points to additional photoreceptors, which remain to be discovered. Meanwhile, we have preliminary results suggesting cross-talk occurs between the phytochrome and the blue-light sensing *white collar* system (Purschwitz *et al.*, unpublished results).

In *A. nidulans*, phytochrome appears not to be the only component used for red-light sensing; *A. nidulans* laboratory strains harbour another mutation, which makes them light-insensitive. The gene was named *velvet*. This mutation is very useful, because corresponding strains conidiate well in the dark, and thus light is not required during growth and spore production. It was only recently that the gene was cloned and analyzed [36]; it doesn't display any significant sequence homology or domain conservation, but is conserved among filamentous fungi. Very recently it was shown that Velvet (VeA) shuttles in a light-dependent manner between the cytoplasm and the nucleus (A Calvo, personal communication). However, there is no evidence that it could also act as a light-sensor, and thus it is conceivable that it interacts genetically or even physically with the phytochrome. The first hints for such an interaction were obtained in our laboratory (Kastner *et al.*, unpublished results). VeA not only regulates the balance between asexual and sexual development but also the production of secondary metabolites [37].

A role for opsins in fungi?

Opsins are retinal-binding proteins, with seven transmembrane helixes (7TM), capable of absorbing light, either for signalling (e.g. visual rhodopsins of animal eyes) or for energy-conservation purposes (e.g. archaeal rhodopsins). Although fungi do not have eyes and are not able to use light for energy conservation, they do contain proteins with similarities to opsin. In the *N. crassa* opsin NOP–1 the chromophore is buried in a pocket within the 7TM structure, and bound by a protonated Schiff base to a lysine. The absorption of green light (λ_{max} 534 nm) leads to an all-*trans* → 13-*cis* isomerisation of retinal, followed by the deprotonation of the Schiff base, resulting in a near-UV-absorbing intermediate. Archaeal rhodopsins employ this mechanism in order to pump protons over the plasma membrane and act predominantly as light-driven ion transporters. By contrast, the reaction cycle of NOP-1 is far too long (up to seconds) to operate as an effective ion pump, suggesting rather that it has signalling functions. However, deletion of *nop-1* does not cause any discernible phenotype [38,39].

Conclusions

Although it has been known for a long time that fungi sense and react to light, it is only recently that the molecular machinery has been studied in some cases. So far, only very few components have been characterized and the availability of several fungal genome sequences, in combination with the steadily increasing toolbox for the manipulation of fungi, promises a fruitful future for the investigation of light sensing in fungi. Because light not only controls developmental decisions but also the production of secondary metabolites, the results might have implications for biotechnological processes, in which fungi play increasing roles in the production of low-molecular weight, as well as high molecular weight compounds.

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