Light sensing and responses in fungi

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Abstract | Light controls important physiological and morphological responses in fungi. Fungi can sense near-ultraviolet, blue, green, red and far-red light using up to 11 photoreceptors and signalling cascades to control a large proportion of the genome and thereby adapt to environmental conditions. The blue-light photoreceptor functions directly as a transcriptional regulator in the nucleus, whereas the red-light-sensing and far-red-light-sensing phytochrome induces a signalling pathway to transduce the signal from the cytoplasm to the nucleus. Green light can be sensed by retinal-binding proteins, known as opsins, but the signalling mechanisms are not well understood. In this Review, we discuss light signalling processes in fungi, their signalling cascades and recent insights into the integration of light signalling pathways with other regulatory circuits in fungal cells.

Chromophore
An organic molecule that absorbs light in the visible spectrum. Photoreceptors are proteins containing a chromophore, which upon light absorption cause structural changes of the attached protein.

Flavin
An organic molecule with a characteristic tricyclic heterocycle (isoalloxazine).

Linear tetrapyrrole
An organic molecule composed of four five-atom rings. They can be cyclic, as in haemoglobin, or linear, like in biliverdin.

Phytochrome
A protein that contains a linear tetrapyrrole as a chromophore and absorbs red and far-red light. It is the main photosensor of plants and controls morphogenesis.

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Most animals use light to obtain crucial information about their environment, including information about their orientation as well as visual information obtained through highly sophisticated sensory organs. Plants use light to optimize the exposure of their leaves for photosynthesis and to control the flowering period or seed formation. Many microorganisms, such as filamentous fungi, use light as a source of information. They are equipped with several photosensory systems and can respond to different light intensities and wavelengths (colours)[1–5] (FIG. 1).

Fungi have a crucial role in the remineralization of organic matter, are important plant and animal pathogens and are frequently used in industry, for instance, in the production of secondary metabolites or catalytic enzymes. Hence, advances in the study of fungal biology should help to further our understanding of their pathogenicity and improve their application to biotechnology[6].

Although fungal light responses have been studied for more than 50 years, the availability of hundreds of fungal genome sequences and the recent developments of novel experimental approaches, such as genome-wide expression analyses or whole-genome sequencing to identify mutations, have provided novel insights into fungal light sensing and signalling pathways. It was shown that in several fungi the expression of a large proportion of the genome is regulated by light and that, thus, light affects many aspects of fungal life. Furthermore, light signalling may be tightly linked with other pathways such as sporulation, primary metabolic pathways or the production of secondary metabolites or hydrolytic enzymes[7–15].

Only a few different photoreceptors developed during evolution. Such photoreceptor proteins always contain an organic molecule as the chromophore, which absorbs visual light. There are flavin-binding blue-light receptors, retinal-containing green-light sensors and proteins with a linear tetrapyrrole as the chromophore that function as red-light sensors. Most fungi contain at least two types of photoreceptors, and some even contain all three. Some blue-light photoreceptors reside in the nucleus and can directly control gene expression, whereas the red-light receptor phytochrome has nuclear and cytoplasmic functions and is linked to the transcriptional machinery through other signalling modules. Both blue-light and red-light receptors also control the DNA structure of certain target genes and thereby their transcription. The green-light photoreceptor is a transmembrane protein, and it is still unclear how signalling occurs. There is also evidence that a particular blue-light receptor (an orthologue of white collar 1 (WC-1)) can sense green light[16]. In all cases, light causes primary changes of the attached chromophore, which in turn lead to conformational changes of the proteins and changes in their activities. Thereby, light controls the activity of many genes and metabolic and morphogenetic pathways. One question that arises is why fungi use such complex photosensory systems.

Fungi live in many different habitats, ranging from the desert to the tropics, and their environment changes frequently and often drastically. Even in moderate zones, the soil conditions may change dramatically over the course of a day. There are two strategies to cope with this challenge: adapt physiologically or escape and conquer new habitats. Many fungi produce spores for dispersal, and light is a reliable informational source to indicate air exposure, which in some fungi is required to induce sporulation and/or the formation of a fruiting body[17,18] (FIG. 2). Spores have a thick, pigmented cell wall for protection and may be covered with very resistant hydrophobins[19]. Once spores germinate, hyphae may be fully exposed to harmful ultraviolet light, and

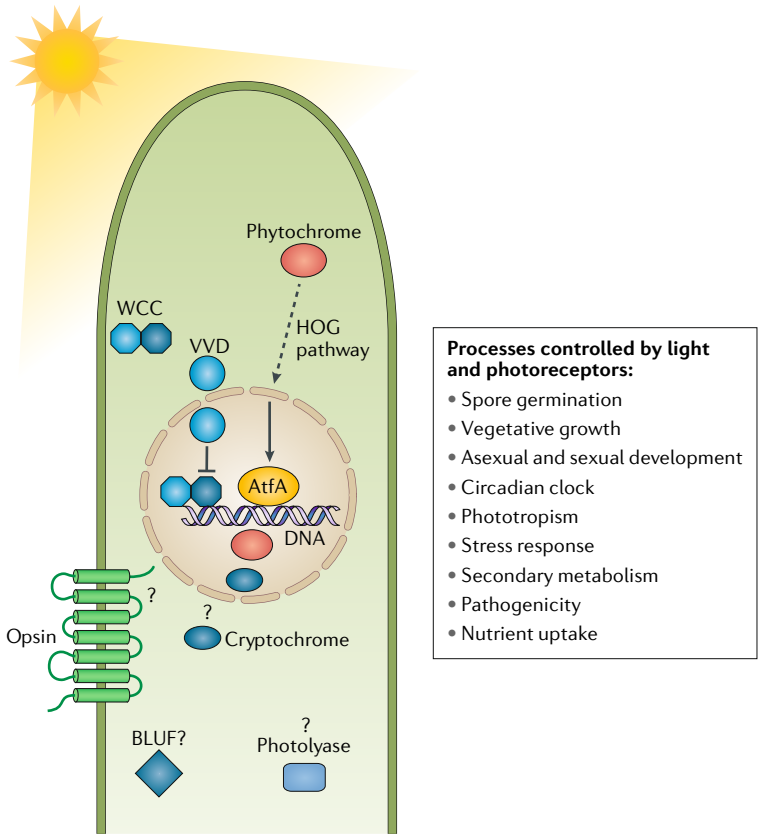

Fig. 1 | **Photoreceptors in filamentous fungi and overview of light-controlled processes.** Fungi contain flavin-binding blue-light receptors, retinal-containing green-light sensors, known as opsins, and proteins with a linear tetrapyrrole as a chromophore that function as red-light sensors (phytochromes). Three major classes of blue-light receptors are distinguished: the light, oxygen and voltage (LOV) domain-containing proteins such as white collar 1 (WC-1) or vivid (VVD), the blue-light sensor using FAD (BLUF) proteins and the cryptochrome and photolyase protein family. Those photoreceptors can be found in both the cytoplasm and the nucleus, and the green-light photoreceptor is a transmembrane protein. One of the main response outputs of light signalling is the control of gene expression, and hence the light signal has to be transmitted into the nuclei. In the case of blue-light signalling through the white collar complex (WCC) (comprising WC-1 and WC-2), the WCC resides in the nucleus and directly regulates gene expression. For clock functioning, shuttling of the WCC between the cytoplasm and the nucleus is important[147]. By contrast, cytoplasmic phytochromes use the high osmolarity glycerol (HOG) signalling module for signal transduction from the cytoplasm to the nucleus. At the end of the HOG pathway is the AtfA transcription factor, which induces gene expression. However, a fraction of phytochrome is also found in nuclei, where it controls the activity of the chromatin-remodelling machinery (not shown), which also contributes to gene expression. In *Aspergillus nidulans*, the phytochrome interacts in the nucleus with the WCC, but the functional role of the interaction remains to be determined. Opsin resides in the cytoplasmic membrane, and the signalling mechanism is not yet known (indicated by the question mark). The blue-light receptor VVD interacts with the WCC and functions as a negative regulator of WCC-regulated genes[98,148]. The signalling pathways for cryptochrome and photolyases are not clear (indicated by the question marks). In *Botrytis cinerea*, one cryptochrome resides in the cytoplasm and one in the nucleus[55]. Processes that are controlled by light and photoreceptors include spore germination, vegetative growth, the circadian clock, stress responses, metabolism, nutrient uptake and pathogenicity.

germination after sunset would be advantageous. Indeed, in *Aspergillus nidulans, Aspergillus fumigatus* and *Fusarium oxysporum*, light delays germination[13,20]. However, spore formation and germination may be the result of the integration of many internal and external cues, such as light, air exposure or the nutritional stage of the mycelium. Hence, light signalling must be tightly connected to other signalling cascades, developmental pathways and metabolic networks.

Fungi may also adapt their physiology in addition to developmental programmes. If their habitat dries out, fungi respond by producing compatible solutes to prevent water loss[21]. This occurs frequently if fungi approach the surface of organic substrates and are exposed to light. Therefore, light can be regarded as an alerting system to prepare fungi for stressful conditions before they arise. Such changes in the environment also occur during the day–night cycle, and many fungi use a circadian clock system to foresee regularly changing environments and be prepared for the upcoming day or night[22,23]. Among other factors, light is an important input into the clock system, and in *Neurospora crassa* and other fungi, the light-sensing and circadian clock systems share the blue-light photoreceptor WC-1 (REF.[24]). Nevertheless, genes can be independently regulated by light, by the clock or by both[25].

Finally, some fungi can not only detect differences in the colour (wavelength) and intensity of light but also sense the direction of illumination, as exemplified by the phototropism of the sporangiophore of *Phycomyces blakesleeanus*[26,27] (FIG. 2).

The numerous examples of light responses in fungi indicate the complexity of light sensing and signal transduction and a crucial role in regulating fungal life (FIGS 1,2). Because fungi are amenable to most molecular, genetic, cell-biological, physiological and biochemical methods, they serve as model systems to understand regulatory networks in eukaryotic cells.

In this Review, we summarize the structural basis for light sensing in filamentous fungi and explore the light signalling mechanisms for blue-light, green-light and red-light photoreceptors. Finally, we review our current understanding of crosstalk of the light signalling pathways with other cellular pathways.

The structural basis for light sensing

Most cellular pathways are driven by proteins, and thus physical signals need to be transmitted to the protein level. In the case of light sensing, signal amplification and decoding of small conformational changes in the chromophore (which sometimes occurs in the range of picoseconds) into a code that cells can understand are required. Proteins without chromophores absorb ultraviolet light through aromatic amino acids. Likewise, the photoreceptor UVR8 in *Arabidopsis thaliana* contains specific tryptophan residues, and ultraviolet-light absorption by those residues leads to the conversion of a UVR8 dimer into monomers that shuttle into nuclei[28]. In comparison, visible-light sensing depends on a chromophore with aromatic residues or other systems with conjugated π-electrons. Such chromophores include the isoalloxazin ring systems in flavins, the retinal molecule or linear tetrapyrroles such as biliverdin (FIG. 3).

Blue-light photoreceptors. Flavin chromophores can be bound to different domains in a photoreceptor protein, and three major classes of blue-light receptors are distinguished: the light, oxygen and voltage (LOV) domain-containing proteins, the blue-light sensor

Circadian clock
Describes a stable oscillation synchronized by light. The period is approximately (circa) a day (diem).

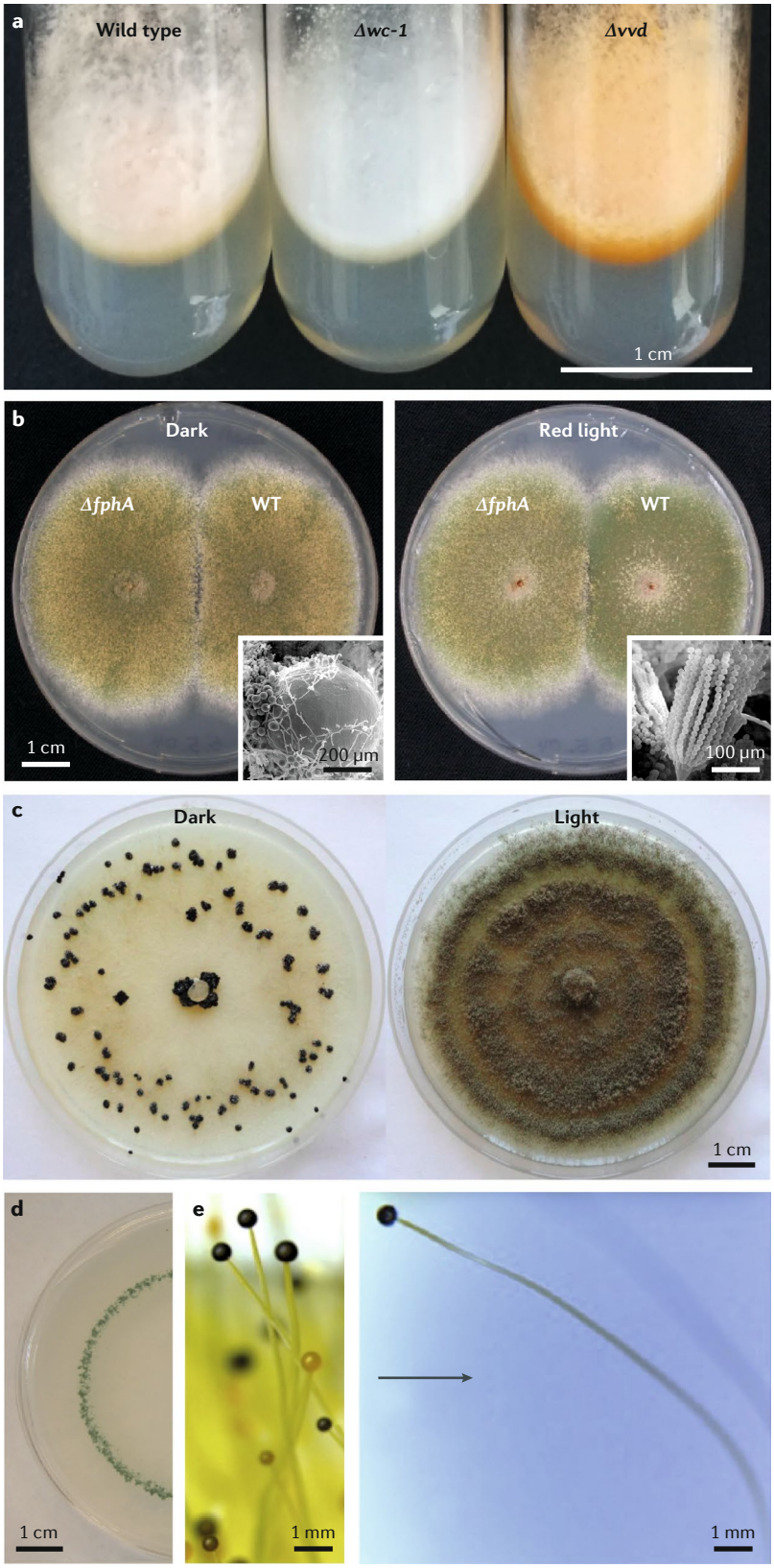

Fig. 2 | **Light responses in model fungi. a** | *Neurospora crassa* strains were grown in test tubes on an agar surface in light at 25 °C for 5 days. The orange colour indicates the production of carotenoid. Mutant cells lacking the blue-light photoreceptor white collar 1 (WC-1) (Δ*wc-1* mutant) produce less carotenoid than the wild type (WT). By contrast, cells that lack the small light, oxygen and voltage (LOV) domain-containing photoreceptor protein vivid (VVD) (denoted Δ*vvd*) produce more carotenoid than the WT, which is indicative of the loss of photoadaptation. **b** | *Aspergillus nidulans* strains were grown on agar plates in the dark or under red-light illumination at 37 °C for 5 days. The WT forms more cleistothecia (yellow structures) and less green conidia in darkness than in red light. Light represses the formation of cleistothecia. In a strain that lacks the phytochrome FphA (Δ*fphA*), red light suppresses cleistothecia formation much less than in the WT. The exact mechanisms as to how phytochrome controls genes required for cleistothecia formation are not known. The scanning electron microscopic pictures show a cleistothecium (left; 500 μm diameter) surrounded by Hülle cells and a conidiophore (right; spores are 3 μm in diameter). **c** | Agar plates grown with *Botrytis cinerea* in the dark or with a rhythm of 12 h dark and 12 h light are shown. In the dark, sclerotia (hardened fungal hyphae for survival) are formed, whereas in the presence of light, green conidia are produced. **d** | An agar plate grown with *Trichoderma atroviride* and illuminated for 5 min with blue light and further grown in the dark is shown. Green conidia formed at only the growth front at the time of illumination. **e** | Sporangiophores of *Phycomyces blakesleeanus* (left) and illuminated with light from the left (right picture) are shown. The phototropic response depends on the WC-1 photoreceptor MADA[51]. Part **a** image courtesy of Z. Yu. Part **b** adapted with permission from REF.[69], Elsevier. Part **c** images courtesy of J. Schumacher, University of Münster, Germany. Part **d** adapted with permission from REF.[133], Elsevier. Part **e** adapted with permission from REF.[102], Elsevier.

Sporangiophore
The morphological structure of fungi that produce (resistant) spores, which are small entities for dispersal or for survival.

using FAD (BLUF) proteins and the cryptochrome and photolyase protein family. The reaction mechanism for LOV domains, which were first described in plant phototropins[29], is not fully understood. In the dark state, the flavin (flavin mononucleotide (FMN) or FAD) is embedded into a pocket of the photoreceptor protein without further interactions. The chromophore is fully oxidized, and illumination causes a covalent adduct formation between a carbonyl group of the isoalloxazin ring system in the flavin and the thiol group of a cysteinyl residue of the photoreceptor protein. Although not completely resolved, evidence suggests that electron transfer occurs between the cysteine residue and the flavin, which results in the formation of a thioether[30,31]. Returning the protein to the dark leads to a reversion of all processes, including cleavage of the covalent bond. The series of events is called photocycle. Further insights into the mechanism of blue-light perception and dark reversion came from the study of the fungal small LOV domain-containing protein vivid (VVD)[32,33]. In addition to the critical cysteine residue, several amino acids in the protein are important for function. Those residues determine the lifetime of the photoadduct, which is important for the biological function of VVD[34,35]. The crystal structures of VVD were obtained in both the dark and the light states. Surprisingly, illumination of the protein caused dimerization of two subunits into a homodimer[36]. VVD can also interact with the white collar complex (WCC) (see below)[37,38]. A prerequisite for VVD dimerization is a glutamine residue, which flips its amide side chain owing to altered hydrogen

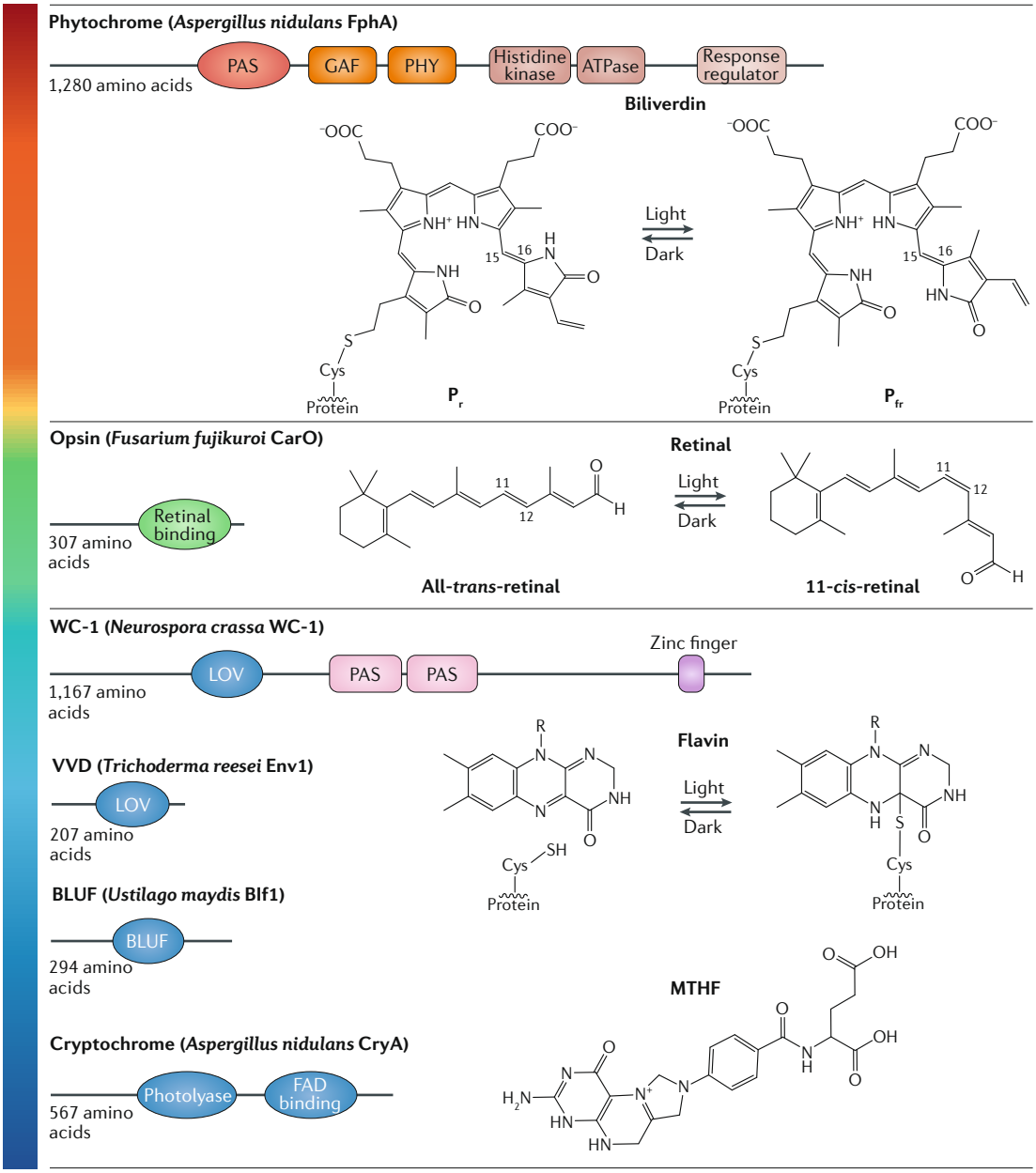

Fig. 3 | **Structure of fungal photoreceptors and their chromophores.** For each photoreceptor type, one representative is shown. Phytochrome consists of a photosensory domain composed of a PAS, a GAF and a PHY domain. In fungi, the chromophore, a linear tetrapyrrole, is bound to a cysteine in the PAS domain. The second half of the protein consists of a signal output domain composed of a histidine kinase and a response regulator domain. The chromophore absorbs red light and undergoes isomerization and a conformational change. The nature of the chromophore is not known yet, but *Aspergillus nidulans* phytochrome assembles in vitro with biliverdin. Opsin is a transmembrane protein with retinal as chromophore. Upon absorption of green light, the retinal undergoes a *cis–trans* isomerization. The white collar 1 (WC-1) protein and vivid (VVD) contain light, oxygen and voltage (LOV) domains where an FAD is covalently bound to a cysteine upon illumination. The WC-1 protein also contains two PAS domains for protein–protein interaction and a zinc-finger domain for DNA binding. The blue-light sensor using FAD (BLUF) protein contains flavin, and cryptochrome additionally contains a methyltetrahydrofolate (MTHF) molecule. FAD is bound differently from LOV domains. The size of the photoreceptors is indicated in amino acids. VVD, vivid.

Cryptochrome
A flavin-binding protein that senses blue light and is involved in circadian rhythms in higher eukaryotes.

Photolyase
An enzyme that repairs DNA damage caused by ultraviolet light. The enzyme contains flavin as cofactor and itself requires blue light for activity.

Photoadduct
A chromophore that attaches covalently to a protein.

Photoadaptation
The phenomenon in which after light signalling the system becomes insensitive for a certain time.

bonding interactions after protonation of the flavin chromophore[39]. VVD is important for photoadaptation and inhibits WCC activity[40,41] (FIG. 2).

The first fungal LOV domain-containing protein identified was the white collar (WC) protein WC-1 in *N. crassa*, and the discovery of FAD as a chromophore was a true breakthrough in the fungal field[42–44]. A crucial cysteine and approximately 11 other amino acids are important for blue-light sensing[45]. The 127 kDa WC-1 protein contains PAS domains for protein interaction, transcriptional activation domains and a zinc-finger DNA-binding domain (FIG. 3). A putative

Rhodopsins
The photosensors of the retina. Rhodopsins contain retinal as a chromophore. Rhodopsins are also found in lower eukaryotes and in archaea.

nuclear localization domain was later shown to be involved in DNA binding, but this domain is not required for nuclear import[46]. A second protein essential for blue-light sensing was cloned shortly after WC-1 and named WC-2. WC-2 is a 57 kDa protein that lacks a LOV domain[47] and can localize in nuclei despite the lack of a functional nuclear localization signal[48,49]. WC-1 and WC-2 form the heterodimeric WCC, which can induce transcription, but the nuclear import mechanisms for both proteins remain elusive. The fact that WC-1 is a transcription factor and contains a flavin for light perception suggests that the light signal transduction cascade is minimalistic. The WCC functions as a transcriptional regulator and a photosensor at the same time. If WC-1 or WC-2 are lacking, *N. crassa* cannot sense blue light, and light-dependent pigment formation is inhibited (FIG. 2). The two zygomycetes *Mucor circinelloides* and *P. blakesleeanus* display a much larger variety of WC orthologues than *N. crassa*. *P. blakesleeanus* contains three WC-1 proteins along with four WC-2 orthologues, and *M. circinelloides* contains three WC-1 and two WC-2 proteins[16,50]. They are structurally similar but have distinct functions. In *M. circinelloides*, one WC-1 protein controls blue-light-dependent carotenogenesis in hyphae, whereas a second one is involved in the phototropic response. Interestingly, phototropism is controlled by blue and by green light, and both responses require the blue-light receptor WC-1 (REF.[16]). In *P. blakesleeanus*, the WC-1 orthologue MADA as well as the WC-2 orthologue MADB are involved in both carotenogenesis and phototropism[50,51].

Another blue-light-perceiving protein family is composed of photolyases and cryptochromes[52]. They typically bind FAD with an additional folate or a riboflavin derivative. The chromophores are non-covalently bound. Both photolyases and cryptochromes are found in fungi, and evidence suggests that they may have a role in DNA repair and sexual development[53–55]; however, the signalling mechanisms are still poorly understood.

BLUF proteins were described in bacteria and exist in several fungi[56]. However, mechanistic studies of those photoreceptors are still lacking.

Green-light photoreceptors. Green light can be sensed by retinal-binding proteins, known as opsins, which are found in the retinal rod cells of vertebrates[57]. Archaea and bacteria harbour channel rhodopsins, which are seven-transmembrane proteins, and the all-*trans*-retinal form is covalently linked to a lysine residue in the seventh helix of the proteins. The activated protein translocates protons or chloride ions across a membrane[58]. Several amino acids, which can be reversibly protonated, are important for activity. Originally discovered in archaea, proton-pumping channel rhodopsins were also found in fungi[59–62]. Three different classes are distinguished: the first class has a slow photocycle with low proton-pumping activity. An example is *N. crassa* NOP-1 (REFS[60,63,64]). The second class is characterized by strong green-light-dependent proton-pumping activity[62]. The genomes of many fungi encode further opsin-related proteins lacking the lysine residue for chromophore binding. The function of this third class is still enigmatic[65].

Evidence suggests that one of the WC-1 orthologues in *M. circinelloides* is involved in green-light-mediated phototropism[16]. Deletion of the gene encoding WC-1a also affected blue-light phototropism, suggesting that this WC-1 orthologue may have a role in phototropism rather than green-light perception per se.

Red-light and far-red-light photoreceptors. Red-light and far-red-light sensing in phytochromes depends on a linear tetrapyrrole (bilin), autocatalytically bound to the apoprotein via a conserved cysteine residue. Phytochromes were discovered in plants, where they are well studied[66–68]. In fungi, this photoreceptor type was first discovered in the two model fungi *A. nidulans* and *N. crassa*[69,70]. The nature of the bilin chromophore derivative in fungal phytochromes has yet to be determined, although it was shown that *A. nidulans* FphA is able to use biliverdin[69,70] (FIG. 3). The chromophores exist in two interchangeable conformations that are well distinguished by their spectral properties. The P_r form absorbs red light, thereby changing the conformation and shifting the absorption maximum into the far-red spectrum; this new form is called P_{fr}. On absorbing far-red light, the chromophore reverts to the P_r form. Phytochromes are large proteins that consist of a photosensory region with a bound chromophore and a signal output domain. The sensory region is composed of three domains: the PAS domain, the GAF domain and the PHY domain, whereas the signal output domain has similarity to prokaryotic histidine kinases. It has been speculated that plant phytochromes have a prokaryotic origin, with an amino terminus from cyanobacteria and a carboxyl terminus from proteobacteria[71,72]. The chromophore is bound to the PAS or the GAF domain (FIG. 3).

The crystal structure of the photosensory domain in the bacterium *Deinococcus radiodurans* revealed a very unusual deep trefoil knot between the GAF and the PAS domains[73]. As of yet, no structure of any fungal phytochrome has been determined. The signal output region is characterized by an ATPase and a histidine kinase domain. The histidine in the histidine kinase domain can be phosphorylated in bacteria and fungi; the kinase activity was lost during evolution in plants, and the histidine was replaced by an arginine or a glutamate. In some bacteria and in fungi, another domain is attached to the histidine kinase[72], which shows similarity to prokaryotic response regulator domains and contains an aspartate for phosphorylation. As in prokaryotic two-component systems, a phosphate can be transferred from the histidine of the histidine kinase domain to the aspartate of the response regulator domain. However, the phosphotransfer has been observed between different phytochrome molecules only in vitro[74].

Light signalling mechanisms

Different photoreceptors vary considerably in structure and locate either to the cytoplasmic membrane (opsins) or to the cytoplasm and to nuclei (phytochrome and WC proteins). In all photoreceptors, light causes primary conformational changes of the protein, followed

FRQ
A negative regulator of the circadian clock in fungi. Oscillation of transcription of clock-controlled genes requires the positive element, white collar 1 (WC-1), and the negative FRQ protein.

Cleistothecia
The fruiting body of ascomycetes. Spores are produced after meiosis.

Conidiation
The process of the formation of vegetative (asexual) spores. Usually special morphological structures, the conidiophores, are produced, which generate the conidia.

by different output mechanisms, such as control of protein–protein interactions or control of phosphorylation events leading to different signalling mechanisms. Most light responses ultimately depend on gene regulation. For instance, the production of reproductive, spore-producing structures from simple hyphae requires the control of hundreds, or even thousands, of genes at specific points in time. This is achieved by transcription factors that control certain steps in development[75]. Linking their expression to light control thus enables coupling of the entire morphogenetic pathway to light[7]. Likewise, metabolic processes may be controlled in a similar manner. Depending on the location of the photoreceptor, different signalling cascades are required (see below). In addition to their photosensory function, it seems that some of the receptors also have a role in the dark (BOX 1).

Blue-light signalling mechanisms. The mechanism of gene activation upon blue-light exposure has been studied in great detail. Blue light controls all photoresponses in *N. crassa* and also has a role in other fungi with a pronounced red-light response[8]. WC-1 and WC-2 form a heterodimer (the WCC), bind to the promoters of light-activated genes and after illumination activate gene expression[8]. Approximately 400 direct target genes of the WCC were identified after 15 minutes of illumination, many of which encode transcription factors such as SUB-1. After this first wave of gene activation, SUB-1 together with the transcription factor FF-7 (which contains a putative *O*-acetyl transferase domain) and the WCC activate downstream genes. Hence, a transcriptional hierarchy controls a large proportion of the genome[8,76–78] (FIG. 4). The activity of WC-1 and WC-2 seems to be regulated through multiple complicated post-translational phosphorylation events[79–82]. In the case of circadian clock regulation, the WCC induces the production of the clock protein FRQ, which subsequently inhibits the activity of the WCC by recruiting kinases CKI and CKII to phosphorylate and inactivate the WCC, thus providing a negative feedback loop[83]. Protein kinase A (PKA) and protein kinase C (PKC) also inhibit the activity of the WCC, whereas PP2A and PP4 dephosphorylate and activate the WCC[81,84,85]. Recent studies have revealed that light-regulated genes are induced in bursts, followed by a period in which the promoters are refractory to stimulation[86,87].

The WCC also controls gene expression through chromatin remodelling. In *N. crassa*, the WCC binds to the promoters of light-regulated genes in the dark and interacts with a histone acetyl transferase, NGF-1, which is stimulated by the WCC upon illumination. NGF-1 mediates the acetylation of lysine residue 14 of histone H3, which increases the accessibility of genes to RNA polymerase II and leads to gene activation[88,89]. By contrast, methylation of lysine 9 and lysine 4 by the methyltransferases DIM-5 and SET-1 represses gene expression expression. Methylation requires the function of the heterochromatin protein HP-1 (REFS [90,91]). In addition to the nuclear functions (that is, transcriptional activation and chromatin remodelling), evidence suggests that the WCC has cytoplasmic functions during circadian clock regulation[81]. Moreover, the regulatory role of the WCC in the circadian clock in the absence of light indicates that this complex also has a function in the dark[92]. Similarly, in *A. nidulans*, LreA (the orthologue of WC-1) is required for full induction of cleistothecia production in the dark[93]. Finally, in *Trichoderma atroviride*, the WC-1 orthologue Blr-1 seems to control the growth rate of hyphae in the dark and seems to be required for starvation-induced conidiation[94–96].

An important negative regulator of the WC light-regulatory system is the VVD protein of *N. crassa*[32,41,97] (FIG. 2). VVD is a repressor of light-controlled and clock-controlled genes and interacts directly with the WCC[98]. Activated WCC induces the expression of *vivid*, and VVD then inhibits WCC activity by binding to the WCC[99]. Hence, VVD is important for photoadaptation[34]. In addition to WC-1, RCO1 and RCM1, the homologues of the co-repressor complex Tup1–Ssn6 in yeast, are required for the proper induction of *vivid* in response to light and thus indirectly for photoadaptation[100].

After the discovery of the blue-light-sensing genes in *N. crassa*, these were partially characterized in many different fungi[51,93,94,101–104]. The VVD protein has been well studied in *Trichoderma reesei* (termed ENVOY, Env1), but it is not found in all fungi, and the mechanisms of photoadaptation in those fungi remain elusive[5,65]. Although the WC proteins are well conserved, studies in *A. nidulans* point to different regulatory cues. Whereas the WCC is bound to the promoter and activates gene expression in *N. crassa*, this complex dissociates from the promoter upon illumination in *A. nidulans*[105]. This could be related to the fact that gene activation in *A. nidulans* primarily depends on phytochrome. The exact mechanism by which the WCC is released from the promoters is not clear yet, and it would be interesting to determine whether WCC dissociation from light-activated promoters after illumination

Box 1 | **Light sensing as a novel function for old proteins?**

Evidence suggests that photoreceptor proteins also fulfil functions in the dark and that some photoreceptors may also have roles in signalling pathways other than light signalling. Those non-canonical functions of photoreceptors may shed light on the evolution of the sophisticated photoreceptors that exist today. In the case of phytochromes, evidence suggests that they developed from histidine hybrid kinases, which are typical sensors that respond to specific signals. Hence, light perception could have developed as a secondary feature of such a histidine hybrid kinase, and the question is what the primary function could have been. It has been suggested that plant and bacterial phytochromes are involved in temperature sensing[140–143]. This mechanism is not yet entirely clear, but it is likely that changes in temperature cause conformational changes in the phytochrome and thereby initiate a signalling cascade. Introduction of the bilin chromophore into the protein and a reaction with light could induce the same conformational changes as in the case of temperature. Similarly, rhodopsin may function as a temperature sensor in *Drosophila melanogaster*[144]. Hence, temperature sensing could be the original function of phytochromes. In agreement with that, it was speculated that a bacterial blue-light sensor using FAD (BLUF) protein functions as a temperature sensor, and for a plant phototropin, such a function was shown[145,146]. This could point to the possibility that light responses could be properties acquired during evolution. It is also well known that the WC proteins have functions in the dark, for example, for clock functioning in *Neurospora crassa*[93,96]. The clock can be entrained by light but also by temperature cycles, and one may speculate that temperature sensing was also the ancient function in this case.

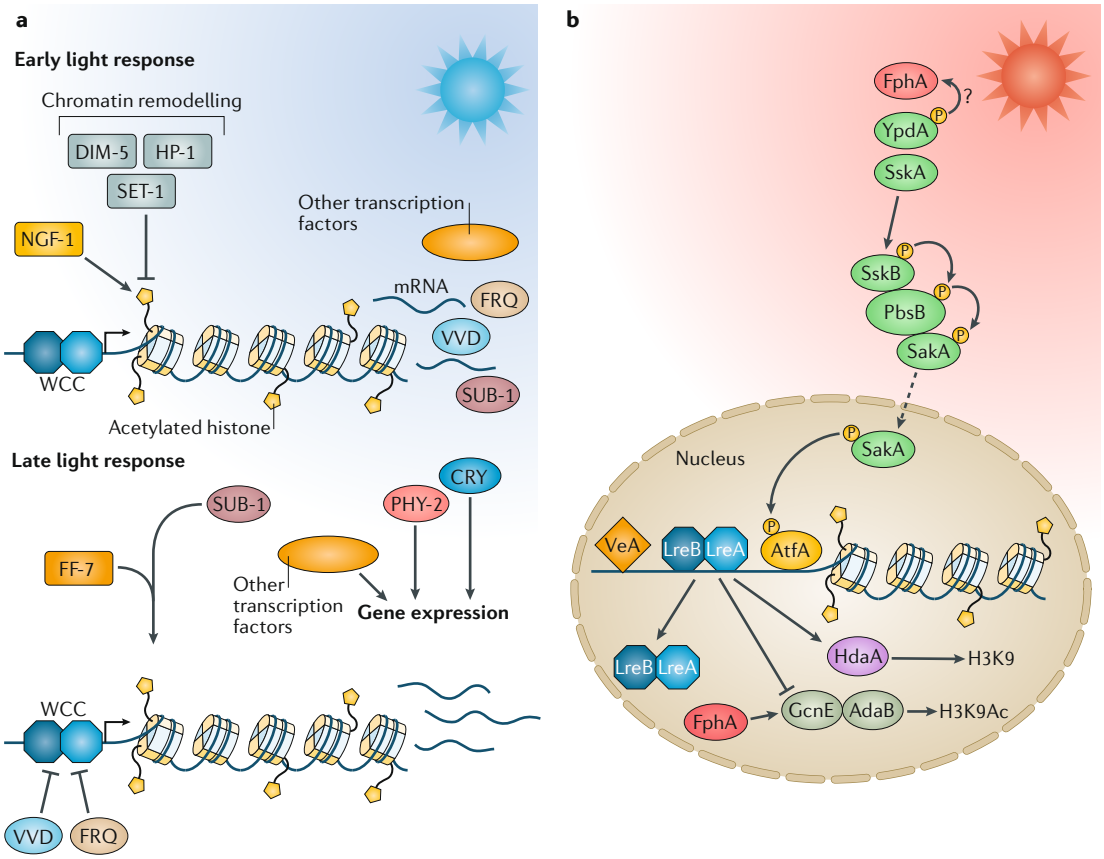

Fig. 4 | **Current model of light responses in fungi. a** | In *Neurospora crassa* — and probably in other fungi as well — the blue-light response involves a hierarchical expression of light-responsive genes. As a first response, light-activated white collar complex (WCC) binds to the promoters of early light-responsive genes and transiently induces their expression. WCC interacts with and stimulates the histone acetyl transferase NGF-1; histone acetylation promotes gene expression. By contrast, histone methylation by DIM-5, SET-1 and HP-1 represses gene expression. Among the early induced genes are *frq*, *vivid* and six transcription factor-encoding genes such as *sub-1*. After the first wave of gene induction, SUB-1 together with the transcription factor FF-7, the WCC and other transcription factors activate the expression of late light-responsive genes. Cryptochrome CRY and phytochrome PHY-2 were shown to regulate a small subset of genes. Vivid (VVD) (which is encoded by *vivid*) interacts with the WCC and inactivates it. Therefore, the light-induction does not persist. The phenomenon is called photoadaptation. FRQ protein accumulates in a circadian manner and inhibits the activity of the WCC rhythmically. Both WCC and FRQ are central elements of the circadian clock. **b** | In *Aspergillus nidulans*, red light is perceived by the phytochrome FphA. In the cytoplasm, light-dependent activation of FphA probably leads to dephosphorylation of the phosphotransferase protein YpdA, causing activation of the high osmolarity glycerol (HOG) pathway and, via phosphorelay, activation of the MAP kinase stress-activated kinase (SakA). Phosphorylated SakA shuttles into the nucleus to phosphorylate the transcription factor AtfA, which activates gene expression. Chromatin remodelling through acetylation of lysine 9 in histone H3 (H3K9Ac) is also involved in light signalling. LreA (the orthologue of WC-1) interacts with the histone acetyltransferases GcnE and AdaB and the histone deacetylase HdaA. In the dark, LreA and VeA (which is an NF-κB-related master regulator of development and secondary metabolism) are bound to the promoters of light-inducible genes. LreA is released from the promoter in light. LreA inhibits GcnE activity and promotes HdaA activity, and gene repression is promoted by LreA–LreB–VeA. Following illumination, FphA stimulates GcnE activity, which leads to the acetylation of H3K9 and gene expression. However, the interaction between FphA and GcnE and an effect of light on GcnE activity have not been verified.

is conserved in other fungi in which phytochromes seem to have an important role in light signalling, such as *Botrytis cinerea* or *Alternaria alternata*.

In comparison, there is very limited evidence for signalling related to blue-light perception through the photolyase or cryptochrome blue-light receptors[53,106]. The best evidence for a regulatory role comes from work in *B. cinerea*, which develops asexual sclerotia in the dark and asexual conidia after illumination with near-ultraviolet light (FIG. 2). Blue light inhibits both processes, and one cryptochrome (BcCRY2) is required for the blue-light repression of conidiation[55], whereas it is not required for the induction of conidiation with near-ultraviolet light.

Sclerotia
A multicellular structure used for survival of some fungi. In *Botrytis cinerea*, it is the prerequisite for sexual fruiting body (apothecia) formation.

Green-light signalling mechanisms. Green-light sensing and signalling are much less understood than blue-light sensing. There is good evidence that the green-light photoreceptor NOP-1 in *N. crassa* is involved in the regulation of developmental processes, possibly through the control of the oxidative state of the cell[107,108].

High osmolarity glycerol pathway
(HOG pathway). A signalling pathway that is required for the adaptation of yeast and other organisms to high osmolarity conditions.

These findings suggest a signalling cascade from the membrane-bound protein to the nucleus. However, how this is achieved remains unknown. Currently, it is difficult to speculate about a signalling cascade because the primary action of NOP-1 is not well understood, owing to its low proton-pumping activity and because it is not coupled to a G protein[64]. In *F. oxysporum*, the proton-pumping channel rhodopsin, CarO, localizes to the plasma and internal membranes, and the light-activated protein contributes to the generation of a membrane potential or controls the ionic balance of the cell[109]. There is evidence that CarO retards spore germination in light. This effect resembles the role of phytochrome in *A. nidulans* and *A. fumigatus*[13,20]. It is probably advantageous that spores germinate after sunset when humidity increases at night.

It has been hypothesized that changes in the pH gradient trigger a signalling cascade through the well-studied pH signalling pathway[110]. Interestingly, these opsins, like CarO, seem to be present in only plant-interacting fungi[109]. In the pathogenic fungus *Colletotrichum gloeosporioides*, it was shown that pH-controlled genes are required for colonization[111]. Such genes are under the control of the PacC transcription factor and were activated under alkaline conditions. The light-dependent activation of opsin should lead to an acidification of the microenvironment at the cytoplasmic membrane. Hence, during the day, when the opsin is activated, colonization of the host could be reduced. Another effect of proton pumping by opsins is the generation of a membrane potential, which could be important for uptake processes, and thus the nutritional status may change in the dark or upon mutation of the opsin function.

An interesting case of green-light signalling was observed in *Blastocladiella emersonii*. This chytrid fungus is characterized by motile zoospores that exhibit a phototactic swimming behaviour. In this case, rhodopsin is fused with a guanylyl-cyclase catalytic domain. Upon light stimulation, the enzyme is activated and produces cGMP as a second messenger. cGMP levels control ion channels and thereby membrane polarization[112,113]. This, in turn, modulates Ca^{2+} homeostasis and most likely controls the behaviour of the flagellum.

Red-light signalling mechanisms. Red-light and phytochrome signalling have been mainly studied in *A. nidulans, A. fumigatus* and *B. cinerea*[3,4]. Some major phenomena controlled by red light in *A. nidulans* are the balance between asexual and sexual development and the germination process[20,69]. Phytochromes were characterized by reverse genetics after their discovery in bacteria and the identification of partial sequences in fungal genome projects[69,70,114]. Similar to blue-light signalling via the WC proteins, a phytochrome-dependent signalling cascade could be very short because red light also penetrates the cytoplasm and reaches the nucleus. However, phytochrome does not contain features of a transcriptional regulator[69], but although the protein was found in the cytoplasm, interaction studies clearly showed the occurrence of a nuclear fraction. The *A. nidulans* phytochrome contains two nuclear localization signals[93], but there is no evidence yet for light-dependent shuttling of the protein as described for plant phytochromes[115]. In *A. nidulans*, the phytochrome FphA interacts in the nucleus with both the WCC and an NF-κB-related master regulator of development and secondary metabolism, VeA[93,116,117]. In addition, it was reported that FphA interacts with chromatin-remodelling enzymes, such as histone deacetylases and histone acetyltransferases[105] (FIG. 4b). The role of the protein interactions and whether light induces those interactions remain elusive. In addition to those interactions in the nucleus, there is recent evidence that the cytoplasmic fraction of phytochrome is crucial for red-light signalling. In a mutant screening for mutants that do not respond to red light (blind mutant), the MAP kinase stress-activated kinase(SakA; also known as HogA) was identified as a possible signalling factor downstream of red-light sensing[11] (FIGS 4b,5). The high osmolarity glycerol pathway (HOG pathway) (which regulates the hyperosmotic stress response) consists of a two-component signalling module and a MAP kinase module. It was shown that the cascade was activated at the level of the phosphotransfer protein YpdA. The phosphorylation status of YpdA triggers downstream signalling, but it is not entirely clear how YpdA is controlled by FphA. FphA harbours an active histidine kinase, the activity of which is stimulated by light, suggesting that the protein could phosphorylate target proteins[74]. By contrast, it was shown that purified FphA can accept a phosphate from YpdA[118]. The aspartate residue in the response regulator domain of FphA was crucial for the reaction, whereas the histidine residue was not required. In vivo, it was shown that both the histidine residue of the histidine kinase domain and the aspartate residue of the response regulator domain were essential for phytochrome activity[105]. One possibility is that histidine phosphorylation is required to expose the response regulator in a way that it can be phosphorylated by YpdA. Histidine phosphorylation of FphA may also enable other proteins to interact with FphA and, for example, dephosphorylate the aspartate in the response regulator domain.

N. crassa harbours two phytochromes (PHY-1 and PHY-2), and PHY-2 may modulate the activity of the WCC, is upregulated during sexual development and is involved in the control of the expression of early sexual developmental genes[70,107,119]. This points to a complex regulatory network in *N. crassa*, as found in *A. nidulans*. *A. fumigatus* also contains two phytochromes[13], and similarly to *A. nidulans*, one of them seems to control germination, surprisingly, in the dark. In contrast to *A. nidulans*, asexual sporulation in *A. fumigatus* does not require red light and thus does not necessitate a phytochrome[13,120].

The two fungi *B. cinerea* and *A. alternata* also react to red light, suggesting that they harbour functional phytochromes[4,121,122]. Interestingly, whereas the genome of *A. alternata* encodes one phytochrome, the genome of *B. cinerea* was found to encode three phytochromes. However, the exact functions of the phytochromes and the interplay with other light-sensing systems need to be further investigated. *B. cinerea* contains 11 putative photoreceptor proteins for different wavelengths[4].

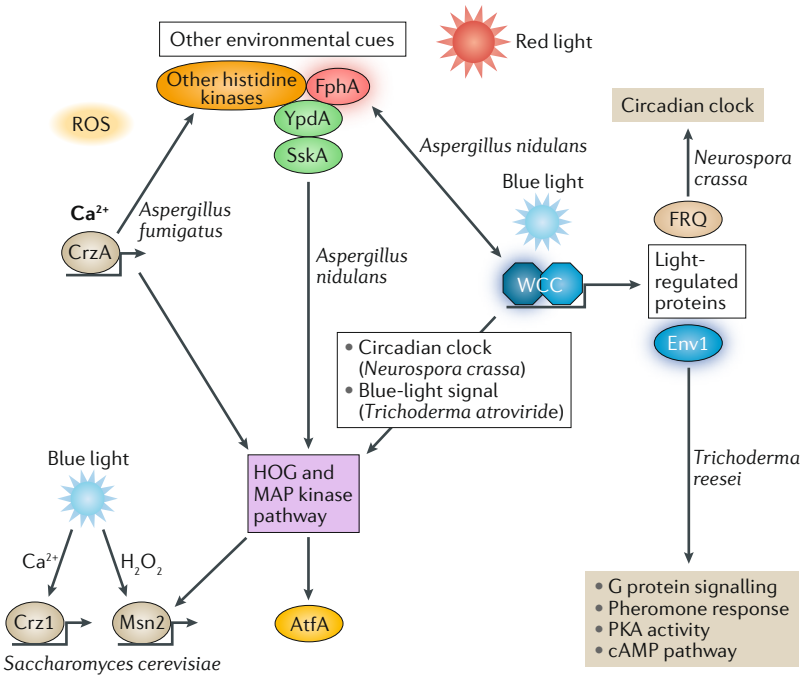

Fig. 5 | **Links between light signalling pathways and other cellular pathways.** In *Aspergillus nidulans*, red-light signalling via the phytochrome FphA requires the high osmolarity glycerol (HOG) MAP kinase pathway to transmit the light signal into the nucleus, where the AtfA transcription factor activates light-inducible genes. The HOG pathway is the central stress signalling module and is required for sensing of oxidative (reactive oxygen species (ROS)) or osmotic stress. In addition to FphA, different hybrid histidine kinases control the phosphorylation status of YpdA and thus signalling via the HOG pathway. In *Aspergillus fumigatus*, it was shown that the Ca^{2+} concentration affects the expression level of SskB (not shown). CrzA is the orthologue of the Crz1 transcription factor of *Saccharomyces cerevisiae*. Thus, Ca^{2+} signalling seems to be interlinked with light and stress signalling. In *S. cerevisiae*, which lacks photoreceptor proteins, blue light can cause an increase of hydrogen peroxide (H_2O_2), which in turn induces downstream signalling processes through the transcription factor Msn2. Blue light also activates the Crz1 transcription factor in a Ca^{2+}–calcineurin-dependent, but protein kinase A (PKA)-independent, manner. Thus, light leads to gene induction even in the absence of photoreceptors. This mechanism could also be active in other fungi that contain photoreceptors. Blue-light signalling has been studied best in *Neurospora crassa* but also in *Trichoderma atroviride* and *Trichoderma reesei*. The white collar complex (WCC) induces light-regulated genes, including the *frq* gene. The FRQ protein is the negative element and the WCC the positive element in the *N. crassa* circadian clock system. The clock system and blue-light signalling are also interlinked with the HOG pathway. In *T. reesei*, a role of the blue-light receptor Env1 (the VVD orthologue) in controlling metabolic pathways through different signalling pathways has been unravelled.

Light, stress and development

Fungi may use light – perhaps in combination with a circadian clock – to adapt to stressful conditions and for orientation in the environment to produce reproductive structures at the right place and the right time[1] (FIG. 2). As, for example, the production of spore-producing structures may depend on many internal and external factors, such as the nutritional status of the fungus, salt concentration in the environment or the availability of a mating partner, it is clear that light is only one of the parameters that need to be integrated to regulate biological processes under distinct conditions. This raises the question of how the light-sensing pathways or molecules are interlinked with stress signalling or developmental pathways. Such a link seems apparent for ultraviolet light stress, which causes DNA damage. The damage is repaired by photolyases, which are activated by blue light[56,123]. The WCC may also be connected to DNA damage repair through an endonuclease; for example, in *Cryptococcus neoformans*, it was shown that the WCC controls the expression of the Uve1 endonuclease[124]. Spores of the insect pathogenic fungus *Metarhizium robertsii* were less sensitive to ultraviolet-B light when grown under continuous visible light[125], further providing evidence that light signalling and the DNA damage repair pathways are coordinated.

A link between light and stress signalling was discovered in *B. cinerea* and *A. nidulans*[11] (FIGS 4,5). In *B. cinerea*, deletion of one of the three phytochromes led to increased sensitivity to cell wall stress[126]. In *A. nidulans*, it was found that the red-light signal initiates the HOG pathway via the phosphotransfer protein YpdA. However, it remains to be shown whether phytochrome signalling occurs exclusively via the HOG pathway or whether phytochromes control gene expression independent of the MAP kinase SakA and vice versa. Furthermore, in *Beauveria bassiana*, it was found that phytochrome regulates multi-stress responses in the fungus and that key proteins in the HOG pathway are transcriptionally modulated by activated phytochrome. Interestingly, resistance against osmotic stress was shown to be decreased in a phytochrome mutant, whereas the mutant strain was more tolerant towards oxidative stress[127]. In addition to phytochromes, *A. nidulans* and other filamentous fungi contain almost 20 putative sensory histidine kinases but only one more phosphotransfer protein besides YpdA[118,128]. What the other input signals are and how they are integrated are largely unknown, but the existence of other sensors suggests a much more complex situation than the one in *Saccharomyces cerevisiae*, which has only one osmosensor kinase.

Similarly, WC-dependent blue-light signalling is connected to stress signalling[10]. In *T. atroviride*, light upregulates the expression of at least two genes of the HOG pathway, and light induces phosphorylation of the HOG MAP kinase Tmk3. Phosphorylation of the MAP kinase did not occur in a *wc-1* (*blr-1*) mutant. This example suggests two layers of regulation: a fast one involving post-translational modification of the MAP kinase and a slower regulatory pathway through the transcriptional upregulation of components of the HOG pathway. However, not all light-responsive genes required Tmk3 for their expression[10].

The coupling of light with stress responses was found for Env1, the VVD orthologue in *T. reesei*[5]. In this case, one cysteine residue in the LOV domain of VVD is required for flavin binding, and a second one responds to oxidative stress[97].

The HOG pathway is also linked to the Ca^{2+} signalling pathway, which is a second stress-activated signalling module. In *A. fumigatus*, some genes encoding proteins of the HOG pathway are direct targets for the central transcription factor of this pathway, CrzA[129]. In addition, it could be that the HOG pathway signals into the Ca^{2+} signalling pathway, which could link light sensing to polar growth. It was shown that light delays germination and reduces the growth rate of

hyphae and that Ca^{2+} is important for the coordination of actin polymerization and vesicle secretion[13,20,130,131]. Furthermore, in *T. reesei*, Env1 controls cAMP levels, which could provide another link between blue light and polar growth[132,133].

It seems that fungi can also perceive light and adapt to stressful conditions without the described photoreceptors[134,135]. In *S. cerevisiae*, a peroxisomal oxidase converts blue light into hydrogen peroxide, which is transduced by the peroxiredoxin Tsa1 to cytosolic thioredoxin. Oxidized thioredoxin represses the PKA-dependent phosphorylation of Msn2, enabling nuclear accumulation of the general stress response transcription factor Msn2, which affects gene expression[136]. In addition, blue light can activate the transcription factor Crz1 in a Ca^{2+}–calcineurin-dependent, but PKA-independent, manner. It is likely that similar mechanisms exist in filamentous fungi as well.

Light also controls developmental decisions of the mycelium. Two examples are *A. nidulans* and *T. atroviride*[7,94] (FIG. 2).The formation of reproductive structures in response to light requires reprogramming of the cells and is another example of how light can be transmitted into differential gene expression[17,75]. It was shown that central regulators of asexual development of *A. nidulans* are controlled by light[7]. One of the regulators is VeA[116,117]. VeA interacts with FphA, and the activity of VeA is controlled through multiple phosphorylation events[93,137,138]. However, there is currently no evidence that those phosphorylation events are mediated by FphA, and it remains to be elucidated how the light-sensing machinery and transcription of developmental genes by VeA are linked.

Future perspectives and conclusions

Fungal photoreceptors and connected signalling cascades have been described in recent years, and an unexpected complexity has emerged. However, our current knowledge does not yet allow us to present a unified picture of light signalling in fungi. One major disadvantage may be our limited knowledge of the biology of fungi, as most molecular analyses are restricted to laboratory conditions. Therefore, the role of photoreceptors may be overlooked or misinterpreted, as in the case of the two phytochromes in *N. crassa* or the role of opsin-related proteins. For opsins with proton-pumping activity, it remains unknown how they might control developmental or other morphogenetic pathways.

One question that arises is relevance of the number of photoreceptors present in one fungus. All the light effects described thus far could be fulfilled with just one photoreceptor to perceive the light signal. Why then would fungi need to see different colours or have up to 11 photoreceptors, as does, for example, *B. cinerea*, which contains 6 blue-light receptors, 2 opsins and 3 phytochromes[2]? As stress adaptation and reproduction are such important processes, one possibility is that the use of different photosystems is advantageous in evolution and provides backup systems. However, it is possible that the lack of our understanding of this complexity may again be due to our limited knowledge of the biology of fungi. For instance, phytochrome signals not only indicate a 'yes' or 'no' in regard to inducing a certain biological programme; the ratio between the P_r and the P_{fr} forms of phytochrome provides information about the time of the day, as the spectral properties change throughout the day. Perhaps that is important for competing in nature. The use of different photoreceptors is also useful in different habitats. For example, in forest canopy environments, green light dominates, and hence, many plant pathogenic fungi seem to have functional opsin proteins[108]. Likewise, it has been shown that red light penetrates soil deeper than blue light[139]. Moreover, it seems that photoreceptors are under constant pressure to evolve. For example, all photoreceptors seem to have undergone gene duplications in certain fungi, enabling them to fulfil slightly different functions, such as the two phytochromes in *N. crassa* or the WC orthologues in *P. blakesleeanus* and *M. circinelloides*. Furthermore, *Sclerotinia sclerotiorum* was shown to have three phytochromes, although one of those lacks the crucial histidine residue and thus may not exhibit kinase activity.

Fungi such as *B. cinerea, A. alternata* and *A. nidulans*, in which all photoreceptors seem to fulfil some functions under laboratory conditions, seem to be appropriate models for future analyses.

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