

Review

The phytochrome red/far-red photoreceptor superfamily

Robert A Sharrock

Address: Department of Plant Sciences and Plant Pathology, Montana State University, Bozeman, MT 59717-3150, USA.
Email: sharrock@montana.edu

Published: 28 August 2008

Genome Biology 2008, **9**:230 (doi:10.1186/gb-2008-9-8-230)

The electronic version of this article is the complete one and can be found online at <http://genomebiology.com/2008/9/8/230>

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Abstract

Proteins of the phytochrome superfamily of red/far-red light receptors have a variety of biological roles in plants, algae, bacteria and fungi and demonstrate a diversity of spectral sensitivities and output signaling mechanisms. Over the past few years the first three-dimensional structures of phytochrome light-sensing domains from bacteria have been determined.

Light is an important environmental factor in most ecosystems. Photosynthetic organisms in particular must sense and respond to light cues to optimize their growth and metabolism. The quantity, direction and spectral make-up (the color or 'quality') of the light sensed by an organism conveys information regarding the abiotic and biotic environment and can be used to control adaptive responses. One superfamily of photosensory receptors comprises the phytochromes ('plant color'), which absorb in the red/far-red part of the spectrum [1]. These receptors were first discovered in plants in the 1950s [2], but have more recently been identified in a broad spectrum of eukaryotic and prokaryotic phyla. In this brief overview I shall focus on recent advances relating principally to the understanding of phytochrome diversity and structure.

Phytochromes are reversibly transformed by red and far-red light between conformations with different absorption spectra. The light-sensing moiety in all phytochromes is a covalently attached bilin chromophore. Following synthesis in the cytoplasm, the phytochrome apoprotein binds chromophore and, in the absence of light, this holoprotein folds into a stable, red-light-absorbing conformation, Pr. Absorption of red light by Pr converts the protein to the far-red-absorbing conformation, Pfr. Absorption of far-red light by Pfr converts the conformation back to Pr (Figure 1). Hence, to a first approximation, phytochromes can be thought of as reversible red/far-red light-activated molecular switches.

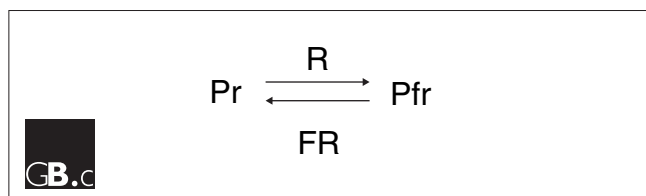
The absorption spectra of Pr and Pfr overlap to some extent and in the light an equilibrium between Pr and Pfr is

established that reflects ambient light conditions. This equilibrium responds rapidly to changes in the ratio of red to far-red light, making phytochromes useful as sensors of critical changes in light quality. The physiological and developmental responses regulated by phytochromes in plants and algae are very diverse, including seed germination, photomorphogenesis and chloroplast movement, shade avoidance, and photoperiodic time measurement [3]. In most cases, responses are induced by red light and cancelled by far-red, leading to the idea that Pfr is the active conformation and Pr is inactive. Phytochrome function in other organisms is less well understood, but it has been implicated in light regulation of motility and pigment synthesis in bacteria and sexual development and secondary metabolism in fungi.

The diversity of the phytochrome superfamily

Phytochromes in land plants and green algae act as dimers, with monomer molecular weights of around 120 kDa. They show extensive sequence conservation and a very similar, distinctly modular native structure consisting of amino-terminal photosensing and carboxy-terminal dimerization/signaling regions (Figure 2a); these two modules retain at least some of their individual activities when separated [4].

Angiosperms, gymnosperms, ferns, mosses and green algae usually contain small families of three to five phytochrome (*PHY*) genes [3]. Plant phytochromes (*Phy* proteins) have proved resistant to crystallization and structure determination, but structure prediction from the amino-acid sequences

**Figure 1**

Phytochrome acts as a molecular switch in response to red and far-red light. It occurs in two reversible conformations (Pr and Pfr), which absorb red light (R) and far-red light (FR) respectively.

indicates that the photosensing region is composed of three adjacent domains, PLD-GAF-PHY, where PLD is a PAS (Per/Arnt/Sim)-like domain (which acts as a signal-sensing domain in many different proteins), GAF is a cGMP phosphodiesterase/adenyl cyclase/*Fhl1* domain that is not associated with a specific enzymatic activity, and PHY is a phytochrome-specific PAS-related domain (Figure 2b). The absorption maxima of the Pr and Pfr forms of plant phytochromes are near 670 nm and 730 nm, respectively (Table 1). The chromophore is phytychromobilin (PΦB), a linear tetrapyrrole derived from the oxidation of heme to biliverdin IX α (BV) followed by enzymatic reduction [5]. PΦB is covalently linked to the apoprotein through a thioether bond to a cysteine side chain in the middle of the GAF domain. The lyase activity required to form this linkage resides in the apoprotein itself. Fragments of plant phytochromes that contain only the PLD-GAF domains bind chromophore and adopt a Pr conformation. However, the PHY domain is essential for the ability to photoconvert between Pr and Pfr.

The carboxy-terminal modules of plant phytochromes contain two predicted PAS domains followed by a sequence with apparent homology to two-component histidine kinases (TC-HKs) - the effector proteins in the 'two-component' environmental sensing systems common in bacteria, plants and fungi [6]. (Two-component systems typically comprise a receptor histidine kinase that receives the signal and relays it to a 'response regulator' protein that elicits the cellular

response.) However, in the plant phytochromes, amino acids critical to histidine kinase catalytic function are not conserved, and so these histidine kinase related domains (HKRDs) do not function via a typical TC-HK mechanism (Figure 2b). As we shall see later, bacterial and fungal phytochromes do contain functional histidine kinase domains and act via a two-component mechanism.

Exceptions to the conserved domain organization shown in Figure 2b for the plant phytochromes have been described in green algae and ferns, in which 'neochrome' photoreceptors combine a Phy-like PLD-GAF-PHY red/far-red sensing module with a flavin-binding LOV (light/oxygen/voltage) domain characteristic of cryptochrome and phototropin blue-light receptors [7].

In the late 1990s, phytochromes were discovered in cyanobacteria and other eubacteria. Genetic analysis of light-induced changes in the composition of phycobilisomes (large photosynthetic antenna complexes of phycobiliproteins anchored to thylakoid membranes) in *Fremyella* and the genome sequencing of *Synechocystis* first revealed the existence of prokaryotic cyanobacterial phytochromes (termed Cph to distinguish them from the plant Phy proteins) [8-10]. Cyanobacterial genomes contain small families of one to five Cph genes. The amino-terminal regions of Cph proteins contain Phy-related PLD-GAF-PHY regions but the carboxy-terminal sequences lack the tandem PAS and HKRD domains of Phy proteins and instead contain a prototypical TC-HK domain with characteristic amino acid motifs and the substrate histidine residue that is autocatalytically phosphorylated on activation of the kinase (Figure 2b).

Synechocystis Cph1 uses phycocyanobilin (PCB) rather than PΦB as its chromophore, and autocatalytically attaches the chromophore to the GAF domain as in the Phy proteins [8]. Cph1 undergoes reversible photoconversion, but with Pr and Pfr absorption spectra shifted towards the blue end of the spectrum compared with the plant phytochromes (Table 1). Most notably, recombinant *Synechocystis* Cph1 shows red/far-red differential histidine kinase autophosphorylation,

Table 1**Generalized properties of major groups of phytochromes**

Group	Organisms	Approximate MW (kDa)	Chromophore	Pr λ_{max} (nm)	Pfr λ_{max} (nm)
Phy	Plants and green algae	120-130	PΦB	670	730
Cph	Cyanobacteria	80-115	PCB	650	705
Bph	Eubacteria	80-100	BV	700	750
Fph	Filamentous fungi	130-205	BV	705	760

Representative values for the properties are given to illustrate fundamental differences and similarities among these groups. Only a limited number of members of each group have been directly analyzed for their chromophore specificity and spectral properties. The molecular weight (MW) ranges reflect sequences currently available in public databases.

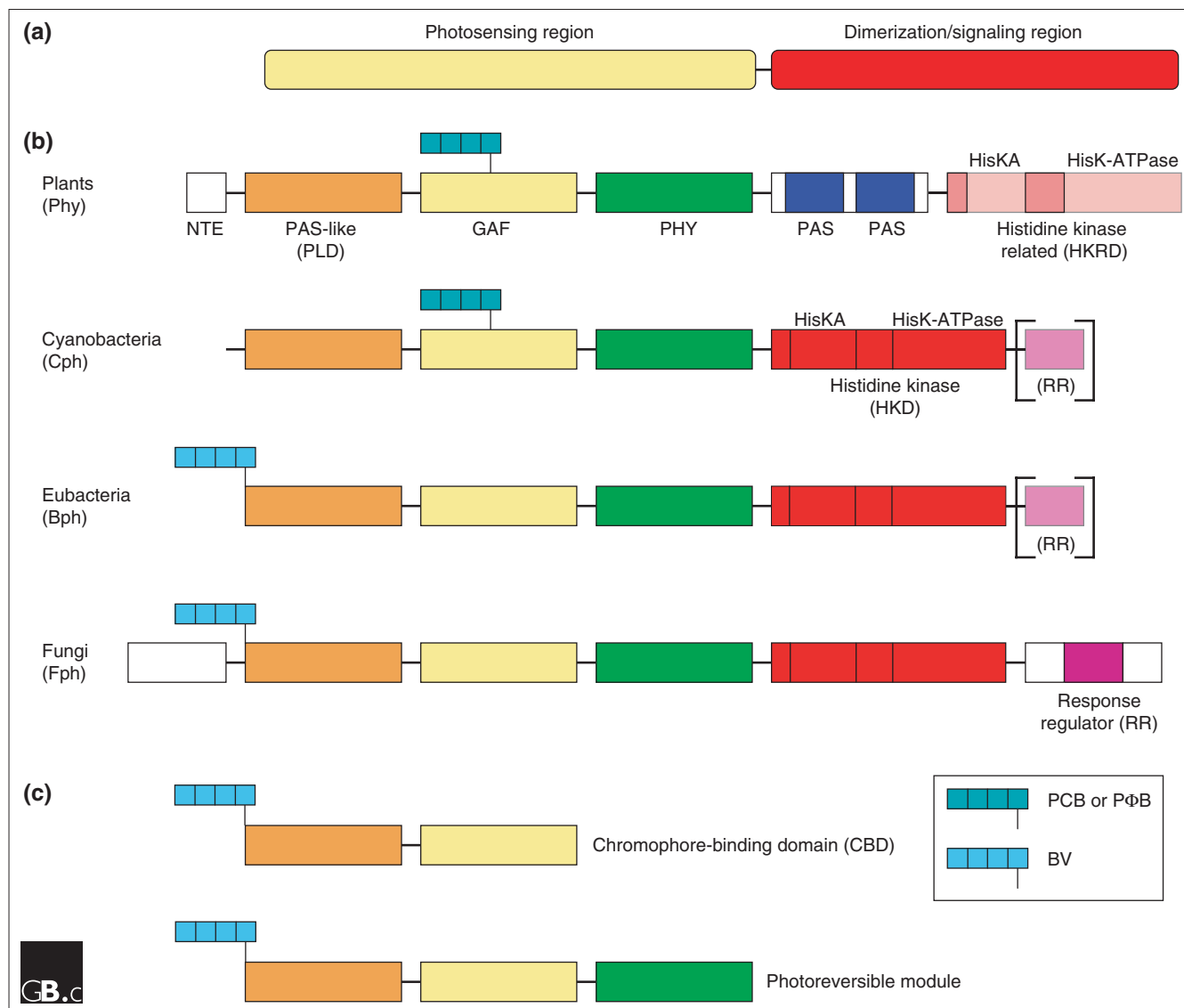


Figure 2
 Domain structures of phytochromes. **(a)** The modular nature of phytochromes. Phytochromes consist of two functionally separable regions: an amino-terminal photosensing domain and a carboxy-terminal domain that is involved in dimerization of phytochrome polypeptide chains and in generating the output signal. **(b)** Conserved phytochrome domains: NTE, plant-specific amino-terminal extension; PLD, PAS-like domain; GAF, a domain distantly related to PAS and found in phytochromes and cGMP-specific phosphodiesterases; PHY, a domain distantly related to PAS and specific to phytochromes; HKD, histidine kinase domain containing a phosphoacceptor His residue and motifs characteristic of functional histidine kinases; HKRD, histidine kinase related domain lacking a phosphoacceptor His residue and motifs characteristic of histidine kinases; HisKA, histidine kinase A domain-related; HisK-ATPase, histidine kinase ATPase superfamily domain. The response regulator (RR)-like domain shown bracketed in Cph and Bph is found in a minority of these proteins but is common in Fph proteins. **(c)** The non-photoreversible chromophore-binding fragment of Bph that was used for determination of the three-dimensional structures published in [25,29,30]. Its structure determines the absorption spectrum of the Pr form. For comparison, the photoreversible fragment containing the PHY domain is also diagrammed. Its structure will provide information about the nature of the conformational change between Pr and Pfr.

with Pr more active than Pfr, and histidine-to-aspartate phosphorelay to a *Synechocystis* response regulator protein [8]. This demonstration that Cphs are light-regulated two-component histidine kinases led to a reassessment of phytochrome function and evolution, and moved the evolutionary context of the origin of bilin-containing photosensing

pigments back many hundreds of millions of years. It also encouraged searches for Phy-related gene sequences in the genome databases of diverse organisms.

Phy-related coding sequences have now been found in the genomes of nonphotosynthetic bacteria, including *Deinococcus*,

Pseudomonas and *Agrobacterium*, the purple photosynthetic bacterium *Rhodospirillum*, and the symbiotic photosynthetic bacterium *Bradyrhizobium* [11-15]. These genomes contain from one to six eubacterial phytochrome (Bph) genes. Bph proteins attach biliverdin (BV), the precursor to PΦB and PCB, as their chromophore and, like other phytochromes, have photoreversible Pr and Pfr conformations. Attachment of BV occurs autocatalytically via a thioether linkage to a cysteine side chain near the Bph amino terminus, rather than in the GAF domain [14] (Figure 2b), and the absorbance maxima of Bph Pr and Pfr forms are red-shifted relative to Phys and Cphs (Table 1). Bph proteins have canonical TC-HK domains at their carboxyl termini and function as red/far-red light-regulated histidine kinases [11]. The fact that diverse heterotrophic nonphotosynthetic bacteria contain phytochromes raises many questions about the possible roles of red and far-red light as environmental signals in these organisms, but the biological functions of most of the Bph proteins are not yet known.

The genome sequences of the filamentous fungi *Neurospora* and *Aspergillus* also revealed coding sequences for PLD-GAF-PHY-HKD proteins [16,17] (Figure 2b). Like Bphs, these fungal phytochromes (Fphs) attach a BV chromophore at the amino-terminal end of their PLD domains and their red/far-red conformations are spectrally red-shifted (Table 1). From one to several Fph sequences have also been identified in the genomes of other ascomycete and basidiomycete fungi, but not in those of yeasts such as *Saccharomyces* or *Candida*. The carboxy-terminal output modules of the Fphs so far characterized also carry a response regulator domain, forming a 'hybrid' TC-HK structure in which autophosphorylation of the substrate histidine residue is followed by intramolecular phosphotransfer to an aspartate in the response regulator region. Hybrid TC-HK architectures are also found among a small number of Cphs and Bphs (Figure 2b).

Comparison of phytochrome function in different organisms

In green plants, phytochromes have very diverse regulatory functions throughout the entire life cycle, mediating light effects on seed germination, the switch from nonphotosynthetic growth in dark-grown seedlings to photoautotrophy, neighbor sensing, and timing of flowering. In seedlings, for example, phytochrome activation regulates approximately 10% of plant genes [18], and controls cell growth and division, chloroplast development, and circadian rhythms [3]. Plant Phys assembled as Pr in the dark are localized to the cytoplasm, but undergo red/far-red light-regulated translocation to the nucleus, where they accumulate in sub-nuclear foci [19]. Although a complete signal transduction pathway for a plant phytochrome response has not yet been described, both cytosolic and nuclear mechanisms are implicated. There is evidence that plant Phys have serine/threonine kinase activity [1]. In addition, upon movement to

the nucleus, they bind to a subfamily of plant basic helix-loop-helix (bHLH) transcription factors [20]. Several bHLH proteins are rapidly phosphorylated and degraded following their interaction with phytochrome, suggesting that one major rapid Phy signaling mechanism involves targeted turnover of transcriptional regulators [21].

In cyanobacteria and eubacteria, phytochromes function in the regulation of phototaxis, pigmentation, and synthesis of the photosynthetic apparatus [1,22]. In fungi, Fph phytochromes have roles in the control of sexual development and mycotoxin production. In contrast to plant Phy proteins, fungal phytochromes were initially observed to localize exclusively to the cytosol, irrespective of light conditions [16,17]. This conclusion has been challenged recently by the finding that *Aspergillus* FphA binds to and forms a complex in the nucleus with the LreA and LreB proteins, homologs of the *Neurospora* zinc-finger transcription factors WC-1 and WC-2 [23]. WC-1 functions as both a flavin-containing blue-light photoreceptor and a DNA-binding transcription factor, and a WC-1/WC-2 protein complex is involved in setting the *Neurospora* circadian clock. Direct physical interaction between *Aspergillus* Fph and the blue-light photosensing/response proteins opens up new and exciting possibilities for cross-talk in light signal transduction in fungi.

More structurally divergent phytochrome-related proteins have been identified in prokaryote sequence databases. These contain recognizable bilin-binding GAF domains but lack PLD and/or PHY domains, have various non-HK-related carboxy-terminal signaling domains, or lack cysteine residues at either of the typical locations for chromophore attachment [22]. It was suggested that these proteins be grouped as 'phytochrome-like' gene products. Moreover, among the more structurally typical Bph receptors, some are unusual with respect to classical concepts of phytochrome activity and function. The 'bathyphytochromes' identified in *Bradyrhizobium* and *Agrobacterium* adopt a Pfr conformation rather than Pr as their ground state in the absence of light and work 'backwards', in that it is the Pr conformation that induces biological responses, such as the synthesis of the photosynthetic apparatus, and conversion to Pfr that cancels them [15,24]. Some Bphs of *Rhodospseudomonas* and *Bradyrhizobium* photoconvert between Pr and a near-red 'Pnr' or orange 'Po' conformation [25,26]. A distantly related phytochrome-like GAF domain from the cyanobacterium *Anabaena* reversibly photoconverts between a relatively standard Pr form and a green-light-absorbing (Pg₅₄₃) form [27]. Finally, a chromophore-less achromo-Bph found in some *Rhodospseudomonas* strains is postulated to function as a redox sensor rather than a light sensor [28]. It appears that, since its very early origins, the bilin-binding GAF domain has been spectrally and biologically highly adaptable and in the world of non-plant phytochromes many of the old expectations must be put aside.

The three-dimensional structures of bacteriophytochrome photosensory modules

Photoconversion between the Pr and Pfr conformations differentially affects the enzymatic activities of Cphs and Bphs [8,11], while the plant phytochromes function by interacting with a large number of proteins, including bHLH transcription factors, substrates for phytochrome-associated serine/threonine kinase activity, cryptochrome blue light receptors, and other proteins, which bind differentially to the Pr and Pfr forms [20]. Hence, a molecular understanding of the three-dimensional structures of phytochromes and of the very rapid photochemical and slower protein conformational changes that occur upon red or far-red photoconversion will be crucial to understanding their mechanisms of action. Attempts to crystallize plant phytochromes or their truncated domains have not been successful. The prokaryotic phytochromes have, however, proved more amenable.

Wagner *et al.* [29,30] crystallized the PLD-GAF chromophore-binding domain (see Figure 2c) of *Deinococcus* Bph in the Pr conformation and determined its three-dimensional structure by X-ray analysis at 2.2 Å and 1.45 Å resolution, while Yang *et al.* [25] determined the structure of a similar region of *Rhodospseudomonas* BphP3. These fragments assemble with chromophore and fold into a Pr conformation but are not capable of photoconverting to Pfr. Nevertheless, this work provided critical three-dimensional structural information and resolved several longstanding questions. As expected for PAS-related domains, PLD and GAF in these proteins fold into five- or six-stranded antiparallel β -sheets, flanked by bundled α -helices. The BV chromophore, in the C5-Z,*syn*/C10-Z,*syn*/C15-Z,*anti* configuration, sits in a hydrophobic pocket formed from GAF domain elements. The chromophore A, B and C rings are nearly co-planar and the D ring is 40-45° out of that plane. This structure is consistent with the Z-to-E isomerization of the C₁₅=C₁₆ double bond and rotation of the D ring that is proposed to be the initial photoreaction induced by absorption of red light [5]. Surprisingly, the refined 1.45 Å structure of the *Deinococcus* Bph chromophore-binding domain indicates that, on linkage to the apoprotein, the BV chromophore adopts a configuration more similar to PCB and PΦB than previously thought [29]. Whether this chemistry is characteristic of other BV-containing Bphs and Fphs will need to be resolved. The crystal structures also confirm that the chromophore in the Pr conformation is completely protonated and that photoconversion between Pr and Pfr probably involves a deprotonation/reprotonation cycle [31].

All currently characterized phytochromes act as dimers. Plant Phy proteins form homo- or heterodimers as a result of interactions between their carboxy-terminal ends [32,33]. This is in line with the fact that prototypical TC-HKs are homo- or heterodimers, an interaction mediated by α -helices in their HisKA domains [34], although it is not known whether the HisKA-related sequences in plant Phys play a

similar role. It has been noted that the Bph and BphP3 PLD-GAF crystal structures contain buried contact surfaces between monomer symmetry mates and that these surfaces may represent biologically relevant subunit-interaction sites [29]. However, *in vivo* expression of truncated Phy proteins shows that the PLD-GAF-PHY regions do not dimerize [4]. Further analysis of phytochrome quaternary structure determinants will resolve this point and determine what functional role, if any, dimerization plays in regulating photosensing activity.

In summary, the phytochrome 'light switch' has been revealed in many of its details over the past few years and much more information is on the way. References to unpublished crystal structures for the Pr forms of larger regions of Bph and Cph sensory modules, including the full PLD-GAF-PHY domains (Figure 2c), have appeared [35,36]. These structures will show how the three domains surrounding the chromophore-binding pocket interact in Pr and may suggest roles for the PHY domain in photoconversion and conformational stability. This new and exciting atomic-level picture of phytochrome structure and function is poised to be rapidly expanded by the application of solution structure methods such as small-angle X-ray scattering, nuclear magnetic resonance (NMR), and resonance Raman spectroscopy [36,37]. For example, the isolated GAF domain from a thermostable *Synechococcus* Cph, lacking both PLD and PHY sequences, photoconverts between Pr and Pfr conformations and is small enough for NMR analysis [38]. These approaches will be particularly relevant to determining structural changes associated with the phytochrome photo-transformation cycle. The roles of individual amino-acid residues in bilin binding, spectral integrity and photo-conversion can then be probed by structurally guided site-directed mutagenesis [25,39].

Origins and evolution

The expanded phylogenetic distribution of phytochromes clearly has implications for understanding their origins and evolution. Bilin-binding photosensor proteins in eubacteria, cyanobacteria and fungi are of ancient origin and have adopted diverse functions in regulating motility, sexual development, metabolic adaptation and probably many other behaviors. Published phylogenetic trees, based on alignments of GAF, PLD-GAF, or PHY domain sequences, lack sufficient information to develop strong hypotheses for the relationships among prokaryotic and eukaryotic phytochromes, although the Phy, Cph, Bph, Fph and Phy-like sequences form five distinct clusters in these analyses [22,26].

The advent of the blue-shifted Cph and Phy forms, which use PCB or PΦB rather than BV as chromophore and a GAF domain attachment site rather than a more amino-terminal site, gave rise to photoreceptor systems better tuned to detecting the red wavelengths that efficiently drive chlorophyll

and phycobiliprotein-mediated photosynthesis. Plant and algal phytochromes, with their unique carboxy-terminal PAS-PAS-HKRD modules, may have arisen via transfer of a Cph gene from an endosymbiotic cyanobacterium and subsequent divergence from the typical Cph structure [22]. Interestingly, Jaubert *et al.* [26] observed that a genomic island encoding PCB chromophore synthesis enzymes and a novel Bph phytochrome that binds PCB rather than BV as its chromophore has been acquired by the genome of the plant symbiont *Bradyrhizobium* via lateral gene transfer. Alternatively, it has been argued from phylogenetic analysis that the plant Phy proteins are more likely to have evolved from a progenitor *PHY* gene that existed in the ancestral eukaryotic cell before endosymbiosis of a photosynthetic cyanobacterium [40]. Further study of phytochrome lineages will be useful in resolving these questions. It is notable that sequences encoding phytochrome-related bilin-binding GAF domain proteins have not been found in many groups of organisms for which there are extensive genomic databases, including animals and yeasts, although there is one preliminary finding of a possible archeal PLD-GAF protein [22].

The signature phytochrome GAF bilin-binding domain has been fused to and regulates many different output protein modules with many biological roles. Analysis of these output mechanisms in experimentally accessible prokaryotes and fungi should help to elucidate their transduction pathways. Indeed, a TC-HK mechanism for Bph regulation of photosynthetic gene transcription in *Rhodospseudomonas* [28] and Fph interaction with well known fungal transcription factors [23] have been reported. However, plant Phys evolved as proteins with a conserved and unique carboxy-terminal domain structure that does not immediately suggest a signaling mechanism and has not been readily dissected by genetic and molecular approaches. Many questions downstream of the recent elegant analyses of phytochrome structure and photochemistry remain.

Acknowledgements

This work was supported by grant IBN-0348913 to RAS from the National Science Foundation.

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