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Authors: Fankhauser C, Ulm R

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A photoreceptor's on-off switch

By Christian Fankhauser[1] *and* Roman Ulm[2]
[1]Centre for Integrative Genomics, Faculty of Biology and Medicine, University of Lausanne, 1015 Lausanne, Switzerland. Email: christian.fankhauser@unil.ch
[2]Department of Botany and Plant Biology, Section of Biology, Faculty of Science, University of Geneva, 1211 Geneva, Switzerland

Photoreceptors are present in all kingdoms of life, fulfilling a broad range of functions, including vision, phototaxis, ensuring reproduction at the right time of the year, establishment of photoprotection, and regulating growth and development (*1*). Photoreceptor-mediated signaling must be turned on and off in a timely fashion. Light-induced structural modifications lead to the photoreceptor signaling state, which often engages in regulated protein-protein interactions. However, in order to maintain photosensitivity it is also important to turn the system off. For example, it has long been known that the signaling state of human visual rhodopsins is very short lived (*2*). Patients with defective rhodopsin inactivation suffer from severe dark adaptation problems illustrating the importance of inactivation mechanisms (*2*). On page … of this issue, Wang *et al.* (*3*) report that plant cryptochromes are activated through blue light-induced homodimerization. This dimerization and all subsequent signaling events are blocked by the interaction between light-activated cryptochrome and a novel protein coined BLUE-LIGHT INHIBITOR OF CRYPTOCHROMES 1 (BIC1) (*3*). This system is proposed to control the fraction of cryptochrome photoreceptors engaged in cellular signaling and thereby contributing to the maintenance of photosensitivity.

Cryptochromes are a family of blue light photoreceptors present in insects and throughout the green lineage. In contrast, mammalian cryptochromes do not function as photoreceptors but are part of the circadian oscillator (*4*). Presently there is no evidence that animal cryptochromes act as homodimers in vivo; however, they signal through protein-protein interactions, similar to plant cryptochromes. The model plant *Arabidopsis thaliana* has two cryptochromes

named cry1 and cry2 with the former primarily controlling blue light-regulated seedling establishment, while the latter controls photoperiod-mediated flowering (*4*). Plant cryptochromes have long been known to work as dimers (or oligomers) (*5, 6*). cry2 has a propensity of homo-oligomerizing in response to blue light, a feature that was exploited to design optogenetic tools (*7*). However, whether blue light-induced dimerization is a central event in the activation of cryptochrome signaling in plants has remained unknown. Wang and coworkers now provide several lines of evidence supporting this view. cry2 homodimerizes in response to blue light absorption in plants. Overexpression of BIC1 blocked light-regulated cry2 homodimerization, phosphorylation and degradation, as well as interaction with downstream signaling partners such as the transcription factor CRYPTOCHROME-INTERACTING BASIC-HELIX-LOOP-HELIX 1 (CIB1; (*8*)), thereby blocking physiological responses (*3*).

Light regulated dimerization has also been reported in several members of another blue light photoreceptor family. LOV (Light Oxygen Voltage) domain photoreceptors exist in plants, fungi, algae and numerous prokaryotes. The photosensory LOV domains are found in combination with various output domains including protein kinase domains or DNA-binding domains. Light activation leads to dimerization of several "LOV-DNA binding domain" photoreceptors. This initial light reaction enhances photoreceptor affinity to target sequences (*9-11*). Interestingly, light triggers LOV-mediated homodimerization of the fungal White Colar Complex (WCC) photoreceptor, a circadian transcription factor. This induces Vivid, a negative regulator that interferes with WCC activity by forming competing heterodimers with WCC (*11*). However, light-induced dimerization is not a prerequisite for all LOV domain photoreceptors (*12*) and whether this happens for plant LOV domain photoreceptors such as the phototropins and Zeitlupe remains unknown.

The UV-B photoreceptor UVR8 presents another example of regulation of the oligomeric state by light. In its ground state UVR8 is a homodimer and UV-B absorption leads to photoreceptor monomerization, a conformer that engages in subsequent signaling events through protein-protein interactions (*13*). The

return to the ground state of UVR8 is facilitated by the interaction of the UVR8 monomer with REPRESSOR OF UV-B PHOTOMORPHOGENESIS 1 and 2 (RUP1/2), a pair of UV-B-induced proteins (*14*). This negative feedback system ensures the presence of a pool of dimeric-inactive UV-B photoreceptors, which is probably essential to maintain UV-B sensitivity. The discovery of BIC1/2 as key regulators of the cryptochromes presents interesting analogies and differences with the UVR8-RUP system. By inhibiting cryptochrome dimerization BICs also prevent all subsequent signaling events (*3*). Given that expression of BIC1/2 is attenuated in cryptochrome mutants there is also some evidence for a possible negative feedback loop coupling crytochrome activation to the production of its negative regulators.

Light regulation of the oligomeric state and the regulation of this process by accessory proteins is crucial for the plant photoreceptors UVR8 and cryptochromes. Interestingly, in the former monomers signal while in the latter homodimers do. Understanding of how BIC expression and activity is regulated in vivo will be important to understand how the cryptochrome off-switch is wired, particularly whether it represents a node of cryptochrome signaling regulation modified by other environmental cues. It will be also exciting to learn about the exact mechanism of BIC action, in particular, are they preventing dimerization by interacting with cryptochrome monomers or promoting the return to a monomeric state. Outside of plants, the discovery of BIC1 may lead to further developments in the use of cryptochromes for optogenetics. Finally it will be interesting to test the evolutionary conservation of this newly discovered regulation of active dimer state for animal cryptochrome activity.

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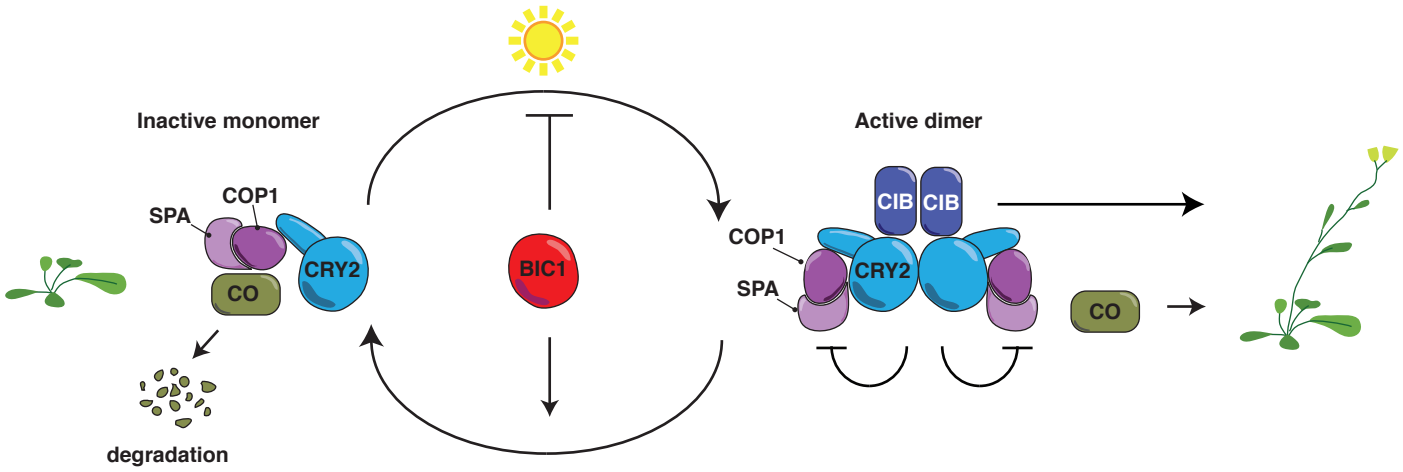
Figure legend

Light induces homodimerization of cry2 and subsequent signaling events including interaction with SPA proteins leading to stabilization of CONSTANS (CO) and interaction with CIB. Binding of BIC1 to cry2 prevents all light-induced signaling events.


Inactive monomer
SPA
COP1
CRY2
CO
degradation
BIC1
Active dimer
CIB
CIB
COP1
SPA
CRY2
CO