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Review

# Photoactivation of the cryptochrome/photolyase superfamily

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ABSTRACT

The cryptochrome/photolyase superfamily is a class of flavoproteins that can regulate the growth and development in plants, as well as the circadian clock and the potential magnetic navigation in animals, primarily by absorbing UV-A and blue light. It is generally agreed that these functions depend on the photochemical reaction of the flavin adenine dinucleotide (FAD) chromophore, non-covalently binding to cryptochromes or photolyases. Irradiation can initiate either photoreduction between FAD and certain electron donors or electron jumping in FAD, thereby leading to the generation of intermediates that activate the protein. This signaling process is known as photoactivation. Subsequently, the activated protein will interact with downstream receptors to transfer the photo and magnetic signals. Based on in-depth research on photoactivation, two photo-cycle mechanisms for the photoreception/photosignaling of the cryptochrome/photolyase superfamily, i.e., the photolyase model and the phototropin model, have been proposed. There is no apparent alternative to the photo-cycle of cyclobutane pyrimidine dimer (CPD) or (6-4) photolyase following the photolyase model. However, the mechanism is not clear for the photoactivation of cryptochromes and CRY-DASH, a new subcategory of photolyase. Since the photoactivation process is the first step for the physiological function of proteins, more and improved research efforts in this field have been widely developed. This review first briefly presents the structure, the photoactivation, and the repair mechanism of CPD and (6-4) photolyase. Next, we review in detail the photoactivation of cryptochromes and CRY-DASH by analyzing the current status of research, as well as the contradictions in the resting redox states of FAD, intermediates in photoreactions, the photo-cycle of FAD, the signaling state of proteins, and the necessity of given tryptophans for protein activity. Based on these studies, the correlations of photoactivation and photo-cycle mechanisms, as well as the correlations of photoactivation and magnetoreception of proteins, are discussed. Finally the crucial open questions regarding the photoactivation mechanisms of the cryptochrome/photolyase superfamily are outlined, considering the hypothesis for a cryptochrome-based model of avian magnetoreception.



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## 1. Introduction

At the beginning stage of life on earth, the atmosphere of the earth was not completely formed and could not shield off the astro-radiation and UV light from the sun that may have been able to cause great damage to the original species on the earth. Because of UV-light-induced photolesions, DNA could not replicate normally, leading to abnormalities and death during physiological development. UV light will induce two types of photolesions: cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone (6-4) photoproduct. These two types of photolesions can be repaired by DNA photolyase through absorbing blue light (300–500 nm) and undergo electron transfer (ET) [1]. According to their different binding substrates, photolyases have been classified into CPD photolyase and (6-4) photolyase; each of them specifically repairs the relevant photolesions. In addition, the CPD photolyase can be further divided into three categories: class I, class II, and class III.

Cryptochromes (Crys), a class of flavoprotein, can also absorb blue/UV-A light. Crys has highly conserved sequences and a crystal structure similar to those of DNA photolyase [2–13], which is considered to be the ancestor of Crys [14], but they perform distinct functions. Without a UV-damaged DNA-repairing function, Crys can regulate the growth and development in plants and the circadian clock in animals [14–19]. Crys has been found in many different species, including plants, algae [13,20–23], bacteria [24], insects [1,25–28], fishes [29,30], amphibians [31], birds [32–35] and mammals (e.g., mouse and human) [36–39]. Most of these Crys types are classified into two families: plant Crys and animal Crys. Fig. 1 shows the classification of the cryptochrome/photolyase superfamily.

Because Crys was first found in *Arabidopsis* [41], this class of protein has been studied the best. The genome of *Arabidopsis* encodes three cryptochrome members: *At*Cry1, *At*Cry2 and *At*Cry3 (Cry1, Cry2, Cry3 from *Arabidopsis thaliana*) [8,41–44]. However, only *At*Cry1 and *At*Cry2 belong to the family plant Crys. *At*Cry1 mainly regulates plant growth and development, such as photomorphogenesis [45,46], the inhibition of hypocotyl elgongation [41,42,47,48], the anthocyanin accumulation in leaves [49], cotyledon expansion [14,42,50], and the blue-light-dependent regulated gene expression [51]. *At*Cry2 is the regulator of flowering initiation [52]. Recently, another plant type cryptochrome, CPH1 (*chlamydomonas* photolyase homologue 1), has been identified in the unicellular green alga *Chlamydomonas reinhardtii*, a type of single-molecular *chamydomonas* [53], and is considered as the evolutionary ancestor of the plant Crys [54]. However, the physiological function of CPH1 is still not clear, even though light-induced proteolytic degradation has been found *in vivo* [53]. It is suggested that CPH1 may be related to the regulation of gene transcription and/or circadian phototaxis rhythms [55].

There are two main subfamilies in animal Crys: light-sensitive type-1 Crys (*Drosophila*-like Crys) and light-insensitive type-2 Crys (*vertebrate*-like Crys) [56]. Not all of the insect Crys variants belong to the type-1 Crys family, just as not all mammalian Crys variants belong to type-2 Crys. For example, bees only have type-2 Crys, and monarch butterflies have both [57,58]. Animal type-1 Crys, such as the cryptochromes of the fruit flies (*Drosophila*, *DmCry*) and the