

cells (reviewed in ref. 13), a variety of approaches are now available to make progress in this area. Eventually, knowledge gained from these studies may be exploited in the development of more specific and efficient cancer therapies. □

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1. May, P. & May, E. *Oncogene* **18**, 7621–7636 (1999).
2. Ollman, M. et al. *Cell* **101**, 91–101 (2000).
3. Brodsky, M. H. et al. *Cell* **101**, 103–113 (2000).
4. Kaelin, W. G. *Oncogene* **18**, 7701–7705 (1999).
5. Rubin, G. M. et al. *Science* **287**, 2204–2218 (2000).
6. Brodsky, M. H., Sekelsky, J. J., Tsang, G., Hawley, R. S. & Rubin, G. M. *Genes Dev.* **14**, 666–678 (2000).
7. Hari, K. L. et al. *Cell* **82**, 815–821 (1995).
8. McCall, K. & Steller, H. *Trends Genet.* **13**, 222–226 (1997).
9. Nordstrom, W., Chen, P., Steller, H. & Abrams, J. M. *Dev. Biol.* **180**, 213–226 (1996).
10. Wang, S. L., Hawkins, C. J., Yoo, S. J., Müller, H.-A. & Hay, B. A. *Cell* **98**, 453–463 (1999).
11. Goyal, L., McCall, K., Agapite, J., Hartwig, E. & Steller, H. *EMBO J.* **19**, 589–597 (2000).
12. Hawkins, C. J., Wang, S. L. & Hay, B. A. *Proc. Natl Acad. Sci. USA* **96**, 2885–2890 (1999).
13. Song, Z. & Steller, H. *Trends Cell Biol.* **9**, M49–M52 (1999).
14. Rodriguez, A. et al. *Nature Cell Biol.* **1**, 272–279 (1999).
15. Zhou, L., Song, Z., Tittel, J. & Steller, H. *Mol. Cell* **4**, 745–755 (1999).

# COP1 patrols the night beat

Raymond J. Deshaies and Elliot Meyerowitz

**Light regulates the behaviour of many organisms. New data indicate that the greening of plants is facilitated by light-dependent stabilization of a transcription factor that is rapidly degraded in darkness. Thus, photomorphogenesis joins cell division and circadian rhythm as another critical biological process that is governed by proteolysis.**

**P**hotomorphogenesis refers to the constellation of morphogenetic and biochemical changes that occur when a seedling breaks through the soil to be greeted by the sun. Over the past decade, plant geneticists have harvested a bumper crop of regulatory proteins involved in this process. These include the HY5 transcription factor, which promotes photomorphogenesis in the light, and COP1, which represses photomorphogenesis in the dark. Now, in a recent issue of *Nature*, Osterlund et al.<sup>1</sup> report that COP1, under the cloak of darkness, directs HY5 to be degraded by the proteasome. These observations suggest a specific biochemical function for COP1, and demonstrate that photomorphogenesis, like the cell cycle, circadian rhythm and the innate immune response, is governed by regulated proteolysis.

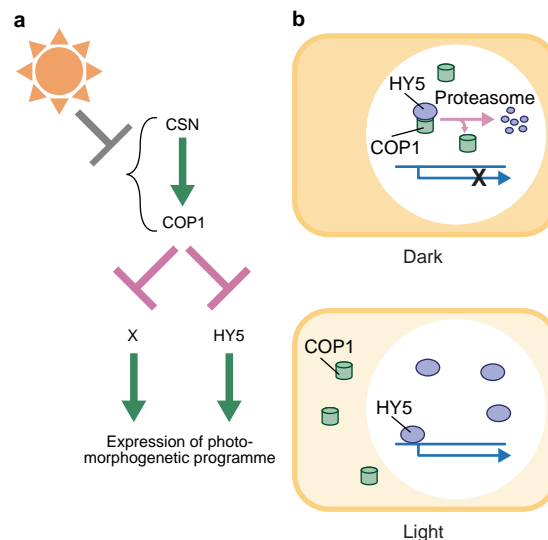
Plants sense a broader range of light wavelengths than humans and respond to light in various ways. Underlying these responses are several light-sensing systems. *Arabidopsis thaliana* possesses five different photoreceptors for red and far-red light, at least two different classes of proteins that serve as receptors for blue light and a poorly understood set of ultraviolet receptors. The long-wavelength receptors are phytochromes, proteins attached to tetrapyrrole chromophores, that act as photon-activated protein kinases. One class of blue-light receptors, the cryptochromes, is composed of flavoproteins that are homologous to regulators of circadian rhythms in animals.

Plants grown in the dark are spindly, contain undifferentiated (white) chloroplasts and fail to express light-induced genes. Once a seedling breaks through the ground and is exposed to sunlight, however, its activated photoreceptors provoke marked changes in development. The illuminated seedling assembles mature chloroplasts, turns green, and grows in a more compact manner. These changes are brought about by light-activated expression of entire suites of genes, resulting in a broad spectrum of changes collectively referred to

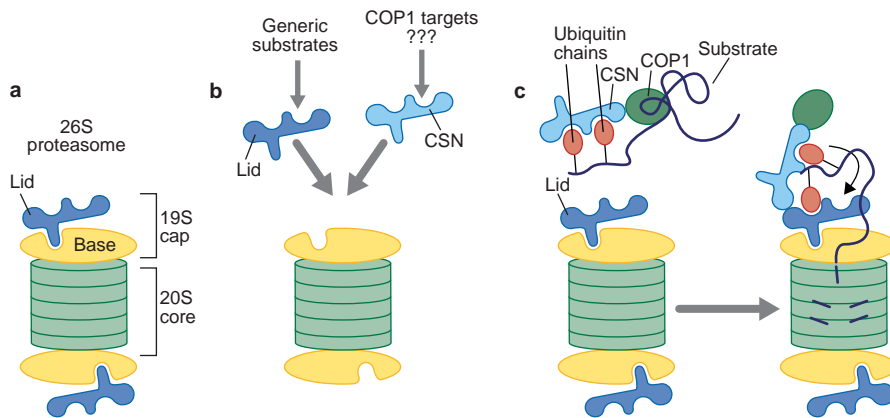
as photomorphogenesis.

Many mutations affect the ability of plants to detect and respond to light. Among these are recessive mutations in the *cop* (constitutive photomorphogenic), *det* (de-etiolated) and *fus* (*fusca*) loci, which lead to photomorphogenic development in the dark. The existence of such mutations implies an active mechanism that represses photomorphogenesis in the dark, as opposed to a mechanism that activates greening in the light. Mutant analysis and molecular cloning of many of the *cop*, *det* and *fus* genes has given rise to a model for how the photomorphogenic switch is thrown once a plant is exposed to the sun (Fig. 1).

Two central components of the photomorphogenic switch are the products of the *HY5* and *COP1* genes. *HY5* encodes a bZIP transcription factor that binds to the promoters of light-induced genes<sup>2,3</sup>. *hy5* loss-of-function mutants fail to execute some aspects of the photomorphogenic programme in the light, indicating that HY5 may facilitate photomorphogenesis by promoting the transcription of light-inducible genes<sup>4</sup>. *COP1*, by contrast, encodes a protein of unknown biochemical function; *cop1* loss-of-function mutants constitu-



**Figure 1 Genetic model for control of photomorphogenesis. a, Proposed epistatic relationships of CSN, COP1, HY5, and X, a hypothetical regulator of photomorphogenesis. Sunlight stabilizes HY5 by interfering with the CSN-dependent function of COP1. b, In darkness, nuclear COP1 promotes turnover of HY5 by the proteasome. In sunlight, COP1 is redistributed to the cytoplasm. This leads to accumulation of HY5, which in turn activates transcription from HY5-dependent promoters. Maintenance of a nuclear pool of COP1 in darkness requires CSN.**



**Figure 2 Putative functions of CSN in protein degradation. a, Structure of the 26S proteasome. The 19S cap is composed of two subcomplexes – the lid and the base. b, Proposed model for CSN function. CSN and the lid serve as interchangeable substrate-recruiting modules that dock upon the base. c, Alternative model for CSN function. CSN captures ubiquitinated substrates and passes them to the lid, thereby facilitating substrate destruction. Interaction between COP1 and nuclear CSN may facilitate retention of COP1 in the nucleus.**

tively activate the photomorphogenic programme in the dark. COP1 binds directly to HY5, and a HY5 mutant (HY5( $\Delta$ 1–77)) that is unable to bind to COP1 induces a hyper-photomorphogenic phenotype in plants grown in the light<sup>5</sup>. Interestingly, unlike *cop1* mutants, HY5( $\Delta$ 1–77) mutants are not constitutively photomorphogenic in the dark, indicating that COP1 may repress the activity of several photomorphogenesis-promoting proteins (Fig. 1a).

How does light modulate the ability of COP1 to repress HY5? In the dark, COP1 polices the nucleus, where it prevents HY5 from activating downstream genes. In the light, however, COP1 is redeployed to the cytoplasm, allowing HY5 activity and subsequent photomorphogenesis (Fig. 1b). Nuclear accumulation of COP1 in the dark depends on several genes, including *DET1*, *COP8*, 9 and 10 and *FUS4*, 5, 6, 11 and 12 (ref. 6). Most of these genes encode subunits of a nuclear protein complex called the COP9 complex or signalosome, which has now been renamed CSN (for COP9/signalosome)<sup>7</sup>. Homologues of all eight subunits of CSN exist in mammals and in *Drosophila*, and a similar complex is found in fission yeast, indicating that CSN may function in a conserved cellular process.

Several clues point to a key role for proteolysis in the regulation of photomorphogenesis. First, all CSN subunits have distant relatives within the 19S cap of the 26S proteasome. The 19S cap contains two subcomplexes — the ‘base’ and the ‘lid’<sup>8</sup>. The base is comprised of eight subunits and directly abuts the 20S proteolytic core (Fig. 2a). The lid, also comprised of eight subunits, sits upon the base and renders proteolysis by the 20S core dependent upon the prior attachment of a multi-ubiquitin chain

onto a substrate protein. Strikingly, every CSN subunit has a homologous counterpart in the lid, indicating that these complexes may share a common ancestor and may possess related functions<sup>8,9</sup>. A further link between proteolysis and photomorphogenesis is suggested by the sequence of COP1, which contains both a RING finger and WD-40 repeats. Over the past year, RING-finger domains have been shown to be essential for the functions of several ubiquitin ligases, including APC, SCF, Ubr1 and Cbl<sup>10</sup>. In addition, WD-40 repeats serve as substrate-recruiting modules for both the SCF and APC families of ubiquitin ligases.

Osterlund and colleagues have now obtained concrete evidence that photomor-

phogenesis is governed by regulated proteolysis. HY5 is not abundant in dark-grown plants, but accumulates to high levels in the light. In contrast, *cop1* mutants contain abundant HY5 in both light and darkness. How does COP1 control HY5 accumulation? Whereas the concentration of HY5 protein increases ~20-fold upon illumination, that of HY5 mRNA increases only ~3-fold, implying a post-transcriptional regulatory mechanism. Indeed, HY5 is stable in the light but turns over in dark-grown plants. In extracts prepared from dark-grown seedlings, HY5 is rapidly degraded, but it can be stabilized by compounds that inhibit the peptidases of the 26S proteasome. Like *cop1* mutants, CSN-deficient mutants also accumulate HY5 inappropriately in the dark. These data argue that in the dead of night, COP1, with the help of CSN, specifies the turnover of HY5 by the proteasome system. The activity of COP1 or CSN, however, is somehow curbed by light, allowing HY5 and other photomorphogenic proteins to accumulate. Although the data presented by Osterlund and colleagues is tantalizing, there is, as yet, no direct evidence that HY5 degradation is ubiquitin-dependent, or that either COP1 or CSN are components of the ubiquitin/proteasome pathway.

If COP1 is in fact a ubiquitin ligase, the next important question rising over the horizon is this — how does CSN enable COP1 to annihilate HY5? Although CSN influences the intracellular partitioning of COP1, its biochemical function remains unknown. Two competing hypotheses can explain how CSN controls the COP1-mediated elimination of HY5. First, CSN and the lid may serve as interchangeable substrate receptors for the proteasome (Fig. 2b), much as F-box proteins serve as inter-

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changeable substrate receptors for SCF ubiquitin ligases<sup>10</sup>. The hypothetical 'CSN proteasome' may recognize a subset of proteins, including COP1 targets such as HY5. However, a subunit of the lid was recovered in a two-hybrid screen for *Arabidopsis* proteins that bind to CSN1 (ref. 11). Thus, rather than replacing the lid, CSN may in fact bind to the intact 26S proteasome. This observation supports the second hypothesis, that CSN and the 26S proteasome may act in series to mediate the degradation of specific substrates.

How might CSN facilitate the destruction of COP1 targets? CSN and the lid each contain two subunits containing MPN domains and six subunits possessing PCI motifs<sup>8,9</sup>. We propose that one of these domains comprises a tetra-ubiquitin-binding motif (tetra-ubiquitin is the shortest multi-ubiquitin chain that efficiently targets a substrate to the 26S proteasome)<sup>12</sup>. According to this view, both the lid and CSN may bind to several tetra-ubiquitin chains (or to several tetra-ubiquitin segments within a single chain). We envision the following sequence of events (Fig. 2c): COP1 binds to and catalyses the assembly of multi-ubiquitin chains on HY5. Either

before or after the ubiquitination step, the COP1–HY5 complex interacts with CSN through direct contacts between CSN, COP1 and ubiquitinated HY5. CSN loaded with the ubiquitin-ligase–ubiquitinated-substrate complex then binds to the lid of the 26S proteasome to deliver its cargo for destruction. If tetra-ubiquitin dissociates quickly from CSN but slowly from the lid, the multi-ubiquitinated substrate could be transferred vectorially from CSN to the lid. Thus, CSN serves to collect ubiquitinated proteins within the nucleus for delivery to the proteasome, possibly protecting them from de-ubiquitination before they can be destroyed. Although this model is highly speculative, it is consistent with all of the available data and is readily testable.

What is next for COP1 and CSN? The biochemical functions of both COP1 and CSN remain to be identified. It also remains unclear how signals from activated photoreceptors impinge on the COP1–CSN axis to relieve repression of HY5. Lastly, it is likely that both COP1 and CSN have other targets and physiological functions in plants and other organisms (for example, a related circuit may control the turnover of TIM and PER during circadian oscillations in

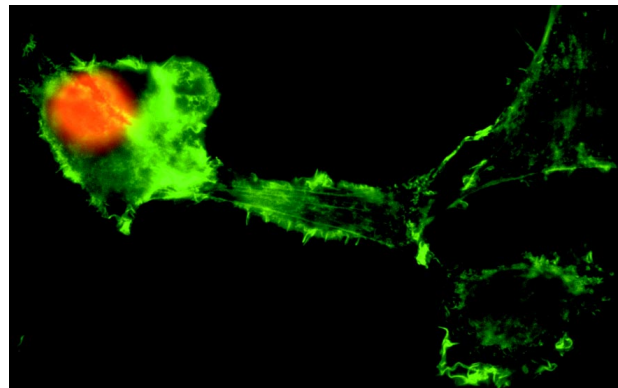
animals<sup>13</sup>), but these remain to be discovered. As more and more researchers are beginning to prowling this beat, further suspects should be apprehended shortly. □

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- Osterlund, M. T., Hardtke, C. S., Wei, N. & Deng, X. W. *Nature* **405**, 462–466 (2000).
- Oyama, T., Shimura, Y. & Okada, K. *Genes Dev.* **11**, 2983–2995 (1997).
- Chattopadhyay, S., Ang, L.-H., Puente P., Deng X. W. & Wei N. *Plant Cell* **10**, 673–683 (1998).
- Koornneef, M., Rolff, E. & Spruit, C. J. P. *Z. Pflanzenphysiol.* **100**, 147–160 (1980).
- Ang, L.-H. *et al. Mol. Cell* **1**, 213–222 (1998).
- Von Arnim, A. G., Osterlund, M. T., Kwok, S. F. & Deng, X. W. *Plant Physiol.* **114**, 779–788 (1997).
- Deng, X. W. *et al. Trends Genet.* **16**, 202–203 (2000).
- Glickman, M. H. *et al. Cell* **94**, 615–623 (1998).
- Wei, N. & Deng, X. W. *Trends Genet.* **15**, 98–103 (1999).
- Deshaies, R. J. *Annu. Rev. Cell Dev. Biol.* **15**, 435–467 (1999).
- Kwok, S. F., Staub, J. M. & Deng, X. W. *J. Mol. Biol.* **285**, 85–95 (1999).
- Thrower, J. S., Hoffman, L., Rechsteiner, M. & Pickart, C. M. *EMBO J.* **19**, 94–102 (2000).
- Naidoo, N., Song, W., Hunter-Ensor, M. & Sehgal, A. *Science* **285**, 1737–1741 (1999).

## "Eat me" signals of apoptotic bodies

One of the characteristics of apoptotic cell death is the rapid removal of cell corpses, which are engulfed by macrophages or by non-professional phagocytes. This is because induction of cell apoptosis leads to the exposure of "eat me" signals on the cell surface before the late apoptotic event of cell lysis. Thus, apoptosis is a 'clean' process that does not normally lead to spillage of cell contents or to inflammation. Exposure of phosphatidylserine (PS) residues, which are normally asymmetrically distributed and restricted to the inner leaflet of the plasma membrane, has been identified as both an early event in apoptosis and a prerequisite for engulfment, as PS-containing liposomes can inhibit phagocytosis of apoptotic bodies. But what is the receptor for PS on phagocytic cells? Although several cell-surface molecules were proposed to contribute to the recognition of apoptotic cells, none of them seems to bind specifically to PS residues. An alternative model is that recognition is based on homophilic interactions, as exposure of PS on the surfaces of both apoptotic and phagocytic cells has recently been reported to be required for engulfment (Marguet *et al.*, *Nature Cell Biol.* **1**, 454–456; 1999). Now, in a recent issue of *Nature* (**405**, 85–90; 2000), Valerie Fadok and colleagues at the National Jewish Medical and Research Center in Denver, Colorado report the cloning of a PS receptor (PSR), using an antibody raised against activated macrophages, which they found to inhibit engulfment of apoptotic cells. PSR is expressed on macrophages and on certain epithelial cells and fibroblasts. Transfection of the gene encoding PSR confers T and B cells with the capacity to recognize and engulf



apoptotic cells, which is inhibited by anti-PSR antibodies and by PS-containing liposomes. The picture shows a 3T3 fibroblast (labelled in green), transfected with complementary DNA encoding PSR, extending a protrusion and engulfing a Jurkat T cell that has been induced to die by ultraviolet irradiation (labelled in red). Interestingly, the PSR gene is conserved in *Caenorhabditis elegans* and *Drosophila*, indicating that, as is the case for the apoptotic programme, the mechanisms of engulfment may be evolutionarily conserved.

VALERIE DEPRAETERE

VALERIE FADOK