

# Making sense of the COP9 signalosome

a regulatory protein complex conserved from *Arabidopsis* to human

The COP9 signalosome, once defined as a repressor complex of light-activated development in *Arabidopsis*, has recently been found in humans and is probably present in most multicellular organisms. The COP9 signalosome is closely related to the lid sub-complex of the 26S proteasome in structural composition and probably shares a common evolutionary ancestor. A multifaceted role of the COP9 signalosome in cell-signaling processes is hinted at by its associated novel kinase activity, as well as the involvement of its subunits in regulating multiple cell-signaling pathways and cell-cycle progression. The molecular genetic studies in *Arabidopsis* suggest that the complex functions as part of a highly conserved regulatory network, whose physiological role in animals remains to be determined.

The COP9 signalosome, also known as the COP9 complex and JAB1-containing signalosome, is a conserved nuclear protein complex found in plants and animals<sup>1-5</sup>. It is composed of eight distinct subunits, designated S1 (57 kDa) to S8 (22 kDa) according to the molecular weight of the mammalian complex subunits<sup>4,5</sup> (Table 1). Subunit composition and the subunit sequences are conserved between the mammalian and the plant complexes, implying that the complex has a conserved cellular function in higher eukaryotic organisms.

The initial discovery of the COP9 complex was a result of genetic analysis of light control of *Arabidopsis* seedling development. *Arabidopsis* seedlings have three organ types: cotyledon, hypocotyl and root (Fig. 1). Morphogenesis of

germinating seedlings is light dependent; light triggers and maintains the developmental process termed photomorphogenesis, whereas dark signals the seedlings to undergo etiolation (or skotomorphogenesis), as illustrated in Fig. 1. COP9, the gene encoding the first defined subunit, was initially identified in a genetic screen of dark-grown mutant seedlings that mimic the light-grown morphology<sup>6</sup>. Seedlings homozygous for *cop9* mutations exhibit a constitutive photomorphogenic phenotype in both dark and light (Fig. 1), including expression of light-activated genes, inhibited hypocotyl elongation, absence of an apical hook, and open and expanded cotyledons<sup>6</sup>. In addition, the mutant plants constitutively express stress/pathogen-activated genes, accumulate a high level of anthocyanin pigment, have

**TABLE 1. Summary of the COP9-signalosome subunits**

Subunit	Mammals		<i>Arabidopsis</i>		Homology (identity %)	Functional remarks
	Other names	MW (kDa)	Other names	MW (kDa)		
S1	GPS1	57	FUS6, COP11	51	42	Repressor of JNK and AP-1
S2	Trip15	51	—	54	60 <sup>b</sup>	Nuclear receptor interacting protein
S3	SGN3	46	—	46	46 <sup>a</sup>	—
S4	—	45	—	47	60 <sup>b</sup>	—
S5	JAB1	38	AJH1 AJH2	42 42	62 63	AP-1 coactivator
S6	hVIP	36	—	36	50 <sup>b</sup>	Cell-cycle regulator
S7a	—	30	—	—	—	—
S7b	—	30	FUS5	27	32	—
S8	hCOP9	23	COP9	22	32	—

<sup>a</sup>Tomato protein LC15 was used in sequence comparison and the percentage of identity was taken from Ref. 3.

<sup>b</sup>The plant sequence used for comparison are peptide sequences from cauliflower<sup>5</sup>. All other plant sequences used are full-length sequences from *Arabidopsis*. Abbreviation: MW, molecular weight.

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ectopically differentiated chloroplasts in the roots, and look stunted and die at the late seedling stage<sup>7-10</sup>. Similar pleiotropic phenotypes have been associated with at least 11 genetic loci collectively known as the pleiotropic *COP/DET/FUS* loci in *Arabidopsis*, most of which encode subunits of the COP9 complex (see below). The recessive nature of all these mutations suggests that the COP9 signalosome is a negative regulator of photomorphogenic development. On the other hand, mutations resulting in the phenotype opposite to the *cop9* mutants, that is, long hypocotyl and less anthocyanin accumulation in the light, have identified a number of plant photoreceptor loci as well as regulatory loci, such as *HY5*, which positively regulate photomorphogenesis in *Arabidopsis*<sup>11,12</sup> (Fig. 1).

The roles of these *Arabidopsis* genes in plant light responses and seedling photomorphogenesis have been reviewed<sup>13-15</sup>. Here, we focus primarily on recent findings on the COP9 signalosome, particularly the insights elucidated by subunit characterization and by the relevant knowledge gained from the *Arabidopsis* molecular genetic studies.

### Subunit composition of the COP9 signalosome

Human homologs corresponding to *Arabidopsis* COP9 signalosome subunit 1 and 8, or FUS6 and COP9, were reported in 1995 (Ref. 16). Yet the existence of the homologous protein complexes in plants and animals was demonstrated unambiguously only recently, following isolation of the mammalian COP9 signalosome independently from two research groups. Seeger *et al.* encountered the signalosome complex as contaminating components in a 26S proteasome preparation from human erythrocytes<sup>17</sup>, and was later able to separate the two complexes successfully<sup>3</sup>. Wei *et al.* purified the complex biochemically from pig spleen, based on the co-enrichment of subunit 1 and 8 (Ref. 4), and further confirmed the composition by immunoaffinity purification of the complex using antibodies against subunit 1 (or GPS1) (Ref. 5). Table 1 summarizes the subunit composition of the COP9 signalosome.

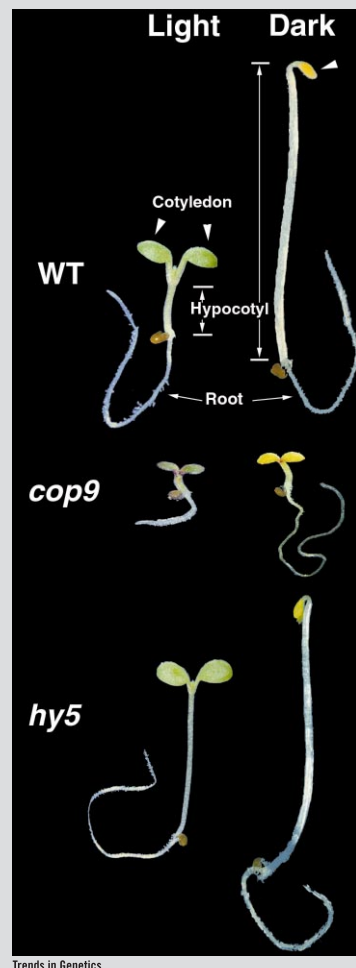
Subunit 1 (S1) was previously identified as GPS1, which was isolated by its ability to rescue the lethality of a *Saccharomyces cerevisiae* mutant deleted for the  $\alpha$  subunit of trimeric G protein<sup>18</sup>. Transient expression of full-length GPS1 in mammalian cells was shown to inhibit JNK1 [JUN (c-Jun) N-terminal kinase]. Consistently, expression of GPS1 was shown to repress JUN-dependent promoter activity<sup>18</sup>. Thus, this study supports the repressor hypothesis

proposed for the plant COP9 complex. The N-terminal region of subunit 2 (S2) is identical to Trip15, which was reported to interact with the thyroid hormone receptor and the retinoic acid X receptor in a ligand-dependent manner in a yeast two-hybrid screen<sup>19</sup>. S3 and S4 are novel proteins; S3 is also known as SGN3, subunit 3 of the JAB1-containing signalosome<sup>3</sup>.

Subunit 5 (S5) has been described previously as JAB1 (JUN activation domain binding protein 1), and was reported to interact with JUN and coactivate JUN mediated gene expression<sup>20</sup>. There are two highly homologous S5 proteins in *Arabidopsis*, AJH1 and AJH2 (Ref. 21, Table 1), which will be discussed in more detail later. Subunit 6 is identical to VIP (human HIV-1 Vpr protein interacting protein), which was postulated to represent a host target responsible, in part, for the viral protein Vpr-induced cellular differentiation and growth arrest<sup>22</sup>. Interestingly, the presence of Vpr in the cell redirects VIP from nuclear interior to nuclear periphery, resulting in colocalization of the two proteins. It was further shown that cells expressing antisense VIP were blocked at G2/M phase of the cell cycle, demonstrating the role of S6 in cell-cycle progression<sup>22</sup>. Subunit 7 (S7) has two isoforms in mammals, S7a and S7b. However, in *Arabidopsis*, S7 is encoded by a single gene, *FUS5* (D. Chamovitz, pers. commun.). The smallest subunit, S8, is COP9 in *Arabidopsis*, or hCOP9 in human.

Overall, the amino acid sequence identities of individual subunits from plants to mammals vary from 32% (S7 and S8) to over 60% (S2 and S5) (Table 1). Therefore, it is not surprising that homologs of the COP9 signalosome components also exist in many other organisms, such as *Drosophila* and *Caenorhabditis elegans*<sup>5</sup>. Interestingly, only S5 (JAB1) seems to have a putative homolog (YDL216c, about 30% identical) in the completely sequenced genome of *Saccharomyces cerevisiae*. The absence of homologous genes of all other subunits in *S. cerevisiae* suggests that the COP9 signalosome is not present in this single-cell organism.

**FIGURE 1. Light-dependent morphology of *Arabidopsis* seedlings**



Wild-type seedling development is drastically influenced by light. The *cop/det/fus* class of mutants, like *cop9*, is unable to undergo etiolation in the absence of light signals. While the mutants of opposite phenotype, such as *hy5*, are partially etiolated, even in the presence of light. These phenotypes led to the proposal that *COP/DET/FUS* gene products act as repressors, whereas *HY5* acts as an activator of photomorphogenic development.

### The COP9 signalosome is enriched in the nucleus and present ubiquitously in plant and animal cells

The COP9 signalosome has been detected in all of the organs examined in plants and animals, and seems to accumulate to slightly higher levels in flowers and roots of *Arabidopsis*<sup>2,23</sup> and in thymus, spleen and brain of mice<sup>4</sup>. The subcellular distribution of the COP9 signalosome complex has been reported in several studies. Antibodies to either S1 or S8 subunits revealed a predominantly

**TABLE 2. Three types of *Arabidopsis cop/det/fus* mutant**

Mutant	COP9 signalosome	Subunit 5 monomer	Subunit identity
<i>cop9</i>	—	+	S8
<i>fus6/cop11</i>	—	+	S1
<i>cop8</i>	—	+	N/A
<i>fus5</i>	—	+	S7
<i>fus8</i>	—	+	N/A
<i>fus11</i>	—	+	N/A
<i>fus12</i>	—	+	N/A
<i>cop16</i>	—	+	N/A
<i>cop1</i>	+	—	No
<i>det1</i>	+	—	No
<i>cop10</i>	+	+	N/A

Abbreviations: '+' or '—' denote normal or below detectable level of accumulation of the complex and the monomer S5, respectively (F.S. Kowk, 1998, PhD Thesis, Yale University); N/A, data not available; No, not a subunit of COP9 signalosome.

nuclear localization in plant and human cells<sup>2,4,23</sup>. Human S6 (VIP) was also shown to be a nuclear protein<sup>22</sup>. On the other hand, SGN3 (S3) was detected mostly in the cytosol, particularly around the nucleus<sup>3</sup>. However, only S1 and S8 have been reported so far to accumulate exclusively in the complex form, and so their localization patterns are more likely to reflect that of the COP9 signalosome. By contrast, *Arabidopsis* S5 and S7, and human S5, accumulate in complexed as well as the free monomeric form<sup>21</sup> (D. Chamovitz, pers. commun.; N. Wei, unpublished). Since the monomeric form of *Arabidopsis* S5 appears to be mostly cytosolic<sup>21</sup>, the cellular location of a given subunit in the cell might not necessarily represent that of the complex.

#### Most COP/DET/FUS loci are required for the formation or stability of the COP9 signalosome

Among 11 COP/DET/FUS loci of *Arabidopsis*, mutations in eight of them can lead to undetectable levels of the COP9 signalosome (Table 2)<sup>21</sup>. Most of these loci probably encode structural components of the complex. It appears that missing any one of the subunits can lead to structural destabilization of the entire complex<sup>1,21</sup>. Only three *cop/det/fus* mutants, *cop1*, *det1* and *cop10*, still accumulate the complex<sup>21</sup>.

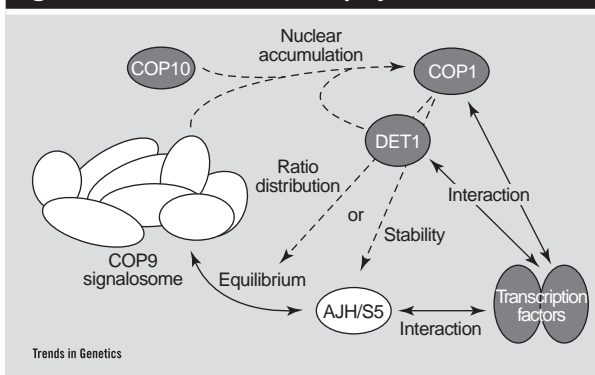
The exact correspondence between the mutant loci and the genes encoding the remaining subunits should be revealed soon following the molecular cloning of all of the *Arabidopsis* COP9 signalosome subunits. There is at least one exception, however, to this correlation between mutant and subunit: the two genes encoding S5 of *Arabidopsis*, *AJH1* and *AJH2*, do not correspond to any of the 11 COP/DET/FUS loci. Nevertheless, reduction of the overall amount of AJH proteins in transgenic *Arabidopsis* lines expressing antisense *AJH1* mRNA or by cosuppression of endogenous *AJH1* expression do lead to a weak photomorphogenic phenotype<sup>21</sup>. Because there are a total of eight subunits in the COP9 signalosome, at least one of the eight COP/DET/FUS loci that are required for the stability or formation of the complex does not encode a core subunit. Molecular characterization of this locus could be invaluable in understanding features of the molecular assembly and structural stability of the COP9 signalosome.

#### The networks of the COP/DET/FUS gene products

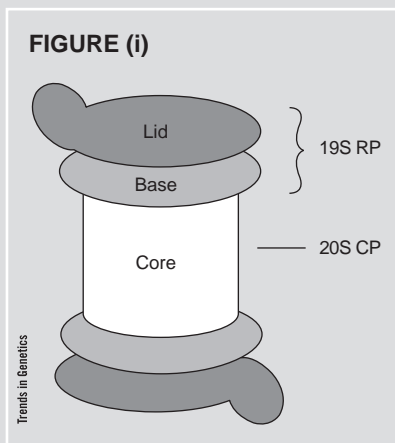
By size fractionation of crude cell extract using gel filtration, the complex (about 500 kDa) can be separated easily from its free subunits (less than 60 kDa). Using this technique in combination with immunoblot analysis,

Kwok *et al.* found that S5 accumulates in both complexed and monomeric forms<sup>21</sup>. Apparently, the equilibrium between these two forms might be physiologically relevant and subject to regulation (Fig. 2). This was suggested from the observation that the equilibrium of monomer versus complexed S5 is perturbed in *cop1* and *det1* mutants, in that the free monomeric AJH (S5) is missing while the AJH-containing COP9 signalosome complex is structurally normal (Table 2). One interpretation of this result is that COP1 and DET1 might have a role in stabilizing the S5 free form in the cell. Alternatively, COP1 and DET1 might be involved in controlling the ratio of complexed and monomeric S5. The absence of functional COP1 or DET1 in the mutants leads to all of the S5 proteins shifting to the complexed form. In either scenario, a regulatory relationship of the COP9 signalosome with COP1 and DET1 is implied.

On the other hand, the COP9 signalosome has been shown to be required for the nuclear accumulation of COP1 (Ref. 2, Fig. 2). COP1 normally accumulates in the nucleus in the dark, and quantitatively re-partitions towards the cytoplasm upon exposure to light<sup>24</sup>. In the *cop9* and other *cop/det/fus* mutants, however, COP1 could not be found in the nucleus in the dark<sup>2</sup>. At least three different mechanisms might account for this phenomenon. First, the COP9 signalosome might be involved in the nuclear import or nuclear retention of COP1, supporting a light-dependent COP1 nuclear/cytoplasmic shuttling model. Second, the COP9 signalosome might be involved in the protection of nuclear COP1 from degradation, which would suggest a degradation mechanism underlying the control of light-dependent COP1 nuclear abundance. Finally, the *cop9* mutations might simply mimic the effect of exposure of the cells to an extremely high intensity of light.

**FIGURE 2. Functional connections between the COP9 signalosome and the relevant players**

This summary is based on the reported genetic analysis in *Arabidopsis* and biochemical interaction studies. The solid lines indicate a demonstrated direct interaction either in animals or plants, while the dotted lines imply functional interaction. COP1 and DET1 are both nuclear proteins<sup>13–15</sup>. Light negatively regulates the accumulation of COP1 in the nuclei of wild-type seedlings<sup>24</sup>, while the mutants of COP9 signalosome, *cop10* and *det1* abolish nuclear accumulation of COP1 in darkness<sup>2</sup>. COP1 and DET1 seem to affect the equilibrium between monomer and the complexed form of S5 in the COP9 signalosome. *COP10* has not yet been cloned. COP1 has been shown to interact with transcription factors including b-ZIP protein HY5 (Ref. 12). The animal version of S5 (JAB1) has also been shown to interact with transcription factor JUN (Ref. 20). Mutations in the genes encoding COP1, DET1, COP10, and of the COP9 signalosome all result in constitutive photomorphogenic phenotype as detailed in the text.

**BOX 1. The 19S regulator of the 26S proteasome and its lid–base topology**

**FIGURE (i)**  
The 26S proteasomes can be dissociated into 20S core particles (20S CP) and 19S regulatory particles (19S RP). The 19S RP, at least in *Saccharomyces cerevisiae*, is composed of the lid and the base subcomplexes.

The 26S proteasome is a cellular protein-degradation device that plays an essential role in a diverse range of biological processes<sup>36,39</sup>. It can be dissociated into 20S and 19S particles: the 20S core catalytic particle (20S CP) is a cylinder-shaped structure with interior proteolytic sites<sup>40</sup>; the 19S regulatory particles (19S RP), composed of six ATPase and 11 or 12 non-ATPase subunits, cap the two ends of the 20S CP cylinder, and are essential for degradation of ubiquitinated proteins. In addition to substrate selection, the 19S RP is thought to be responsible for unfolding, deubiquitination, and finally injection of the substrates into the 20S CP (Ref. 36). Other regulators, such as PA28 or the 11S regulator, can also associate with the 20S proteasome, creating a proteasome with different substrate specificity and proteolytic activities<sup>36,40</sup>. The conformation and the dynamic structure endow the proteasome with the ability to act in coordination with cell-signaling activities and homeostatic mechanisms.

Recent studies of the *Saccharomyces cerevisiae* proteasome demonstrated that the 19S RP is composed of two subcomplexes, the base and the lid<sup>27</sup> (Fig. i). The base complex, comprising all of the six ATPases and three non-ATPase subunits, directly contacts the 20S CP. The lid complex, containing eight non-ATPase subunits, covers the 26S proteasome cylinders at the two ends. Rpn10p, a non-essential ubiquitin binding protein<sup>41</sup>, assists to strengthen the connection between the lid and the base. The lid-less proteasome isolated from the  $\Delta rpn10$  mutant, is specifically defective in the degradation of ubiquitinated proteins but not in peptidase activity or the degradation of a non-ubiquitinated substrate. These results indicate that the lid is an essential component linking the proteasome to the ubiquitin system. Given the extraordinary conservation of the 19S regulator from yeast to human<sup>30</sup>, the lid-base topology found with the yeast 19S RP is probably conserved in higher eukaryotes.

Under such conditions, COP1 would be completely depleted from the nucleus by a mechanism that might not relate directly to a primary function of the COP9 signalosome.

*Arabidopsis* COP1 and possibly DET1 have recently been shown to interact with HY5, a genetically defined positive regulator of photomorphogenesis<sup>12,25</sup> (Fig. 1). HY5 is a b-ZIP type of transcription factor that mediates light activation of transcription by binding to upstream regulatory elements including the G-box, a light-responsive element<sup>11,26</sup>. The data also suggest that COP1 binds HY5 to repress its ability to activate photomorphogenic responses<sup>12</sup>. Coincidentally, S5 (JAB1) was reported to interact with and act as coactivator to JUN, an oncogenic b-ZIP transcription factor in mammals<sup>20</sup>. It is conceivable that, like COP1, the COP9 signalosome and/or S5 monomer might regulate cellular transcription by modulating the activity or stability of transcription factors.

It is worthwhile to mention that, in addition to the conservation of the COP9 signalosome, COP1 and DET1 also have conserved counterparts in animals (N. Wei, unpublished). It is, therefore, reasonable to postulate that the regulatory network defined by this group of genes is highly conserved between plants and animals.

### The COP9 signalosome and the lid complex of the 26S proteasome

A database homology search with COP9 signalosome subunits identified a group of 26S proteasome regulatory subunits<sup>5</sup>. The 26S proteasome is an essential protein-degradation device and is responsible for the degradation of ubiquitinated proteins (Box 1). Notably, all of the proteasome subunits related to the COP9 signalosome are components of the lid<sup>27</sup>, a subcomplex of the 19S regulatory particle. Moreover, there is a one-to-one relationship between subunits of the COP9 signalosome and the lid<sup>5</sup> (Fig. 3). Subunit 5 of the COP9 signalosome, which is one of the most conserved COP9 signalosome subunits among different organisms, shares the highest sequence similarity to Rpn11p of the yeast lid complex (28% in identity). The two small COP9 signalosome subunits, S7 and S8, which

are the least conserved among different organisms, show weakest similarities to the corresponding yeast lid subunits, Rpn9p and Rpn12p, respectively.

The one-to-one correspondence between subunits of these two complexes implies that the COP9 signalosome and the proteasome lid are probably derived from a common ancestral protein complex. In one model (Fig. 4a), the 26S proteasome is a more ancient complex. The COP9 signalosome evolved from an ancestral version of the lid subcomplex and assumed a new function as a result of adaptation to the developmental complexity of multicellular eukaryotic organisms. In an alternative model (Fig. 4b), a protein complex ancestor gives rise to both the modern COP9-signalosome and the lid of the 26S proteasome. This model also implies that the lid was acquired by the proteasome as a preformed protein complex. Presumably, after a genetic duplication event, the two resulting complexes started to diverge, each optimizing for specialized functions through sequence modifications of their subunits. In either scenario, the COP9 signalosome and the lid complex of today are clearly distinct structural and functional entities.

### PCI and MPN signature domains

The PCI (for proteasome, COP9, initiation factor 3) and MPN (for Mpr1p and Pad1p N-terminal) domains are found exclusively in three large multiprotein complexes<sup>28,29</sup>: COP9 signalosome; the 26S proteasome lid; and translation initiation factor 3 complex (with one exception for human C6.1A). Either PCI or MPN domains is present in all eight subunits of the COP9 signalosome<sup>5</sup>, seven of eight subunits of the proteasome lid<sup>27</sup>, and five of about ten subunits of human eIF3 (Ref. 28). Identification of the two large protein domains is itself an indication of a close relationship among these proteins. However, the sequence similarities between the corresponding subunits of the COP9 signalosome and the lid of the proteasome extend beyond these two domains to most of the coding regions (Fig. 3).

The third protein complex involved, the eukaryotic translation initiation factor 3 (eIF3) participates in translational preinitiation complex formation by promoting the

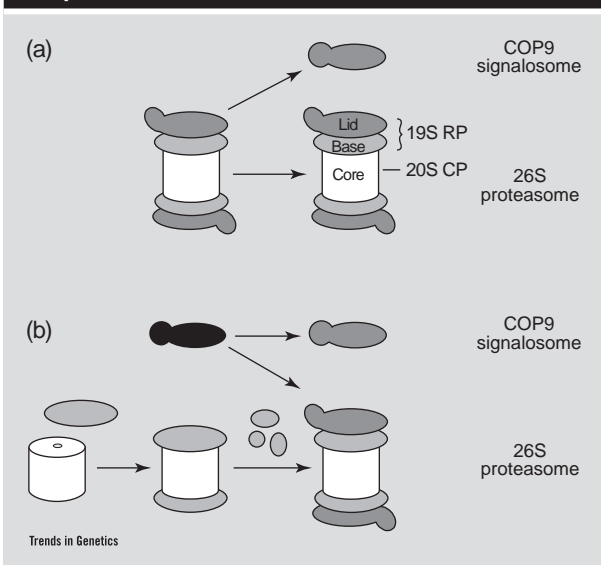
dissociation of 80S ribosome into 40S and 60S, and by mediating interactions between eIF2-GTP-Met-tRNA<sub>i</sub>, the 40S ribosome, and the mRNA. By contrast with the high conservation of the 26S proteasome from yeast to human<sup>30</sup>, five of about ten subunits of human eIF3 defined do not have yeast homologs<sup>31</sup>. The three eIF3 subunits [EIF3S6 (previously known as p48/INT6), p40 and p47]<sup>32,33</sup> exhibiting overall similarities to the COP9 signalosome subunits are among those that are unique to higher eukaryotes. Apart from these subunits, the PCI domain is also found in human p110/yeast NIP1p and mouse p162/yeast Rpg1p, the two conserved components of eIF3 apparently unrelated to COP9 signalosome subunits other than the presence of the PCI domain<sup>28,34</sup>.

The structural or functional role of the PCI and MPN domains are unknown. If these large protein domains have a structural role in macromolecular assembly, similar biochemical features in protein complex assembly would be expected in these three protein complexes. Alternatively, the PCI and MPN domains could represent docking sites of the complexes for interacting with common target or effector molecules, such as ubiquitin, 26S proteasome base subunits, or other substrates. In this case, the PCI and MPN domain subunits of eIF3 would represent regulatory modules through which the eIF3 activity could be regulated by a mechanism related to the COP9 signalosome and 26S proteasome.

**Functional implications**

The precise cellular activity of the COP9 signalosome remains enigmatic at present, but a few tantalizing clues might be inferred based on the data from genetic and biochemical studies. The apparent absence of the complex from the unicellular eukaryote *S. cerevisiae* indicates that the functions of the COP9 signalosome are not essential for the house-keeping activities of eukaryotic cells and is unique to higher eukaryotes. In *Arabidopsis*, mutant phenotypes suggest that the COP9 signalosome is essential for germinating seedlings to undergo etiolation in the

**FIGURE 4. Evolution of the COP9 signalosome and the 26S proteasome**



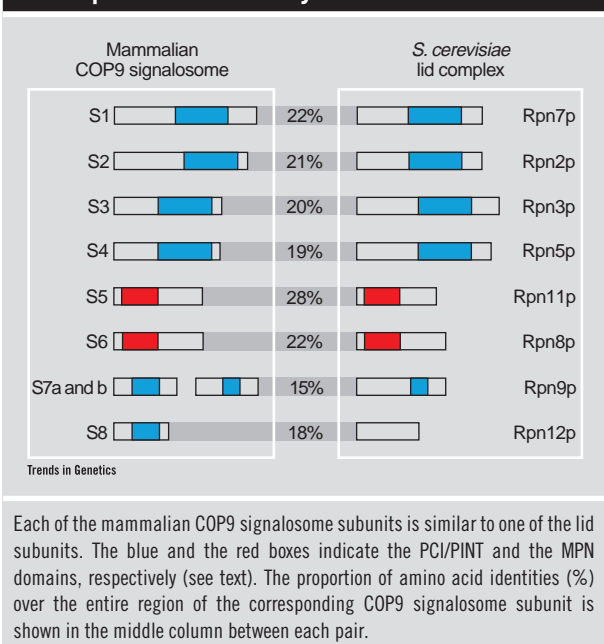
A diagram illustrating the two possible routes of evolution regarding the relationships between the COP9 signalosome and the 26S proteasome. The 20S proteolytic particles with similar general architectures are found in eubacteria, archaeobacteria and eukaryotes, whereas the complete 19S regulatory particle is only found in eukaryotes<sup>40</sup>. It is assumed that the 20S proteasome acquired sequentially the ATPases, the other non-ATPase subunits in the base subcomplex of the 19S RP, and then the lid subcomplex. See text for details.

absence of light signals and for normal plant cells to counteract the effects of multiple activating stimuli, including light.

Indeed, a number of subunits have been implicated in diverse signaling events in animal cells from regulation of the SAPK/JNK-mediated MAP kinase pathway (S1/GPS1 and S5/JAB1), nuclear hormone receptor-mediated functions (S2/Trip15), to cell-cycle regulation (S6/VIP). Most interestingly, the purified COP9 signalosome was shown to have kinase activities<sup>3</sup>. The purified complex was found to phosphorylate JUN at the sites (Ser63 and/or Ser73) overlapping with those phosphorylated by JNK, the major kinase responsible for JUN activation<sup>35</sup>. However, COP9 signalosome phosphorylates full-length JUN exclusively, whereas JNK phosphorylates both full-length and the amino-terminal (1-79) JUN fragment<sup>3</sup>. The signalosome was also shown to phosphorylate IκB and p105 (Ref. 3), the precursor of NFκB. These events lead potentially to the 26S proteasome-mediated processing/degradation of p105 and IκB and subsequent generation of active NFκB (Ref. 36). Yet, none of the subunits was found to contain any recognizable kinase domains. It is possible that the kinase domain in the components of the complex is unconventional, such as that found in TAF<sub>II</sub>250 subunit of the transcription factor TFIID complex<sup>37</sup>. Alternatively, the activity might come from a novel, low-abundance kinase that is not a structural subunit of the COP9 signalosome, but which associates tightly with the complex. In either case, the physiological relevance of this *in vitro* activity must be further substantiated to confirm the potential role of COP9 signalosome in cellular stress, immune and inflammatory responses.

As structurally closely related complexes, the COP9 signalosome and the proteasome lid might have similar modes of action. It has been suggested that the COP9

**FIGURE 3. The COP9 signalosome and the proteasome lid complex are structurally related**



signalosome could mediate interactions with another large structure, similar to the interaction of the lid with the base and 20S proteasome core<sup>27</sup>. Indeed, larger structures that associate weakly or transiently with the COP9 signalosome do seem to exist<sup>1,3</sup>. A major function of the proteasome lid is probably related to the ubiquitin system, such as recognition of ubiquitinated protein substrates and subsequent deubiquitination (Box 1). By analogy, it is plausible that the COP9 signalosome possesses an ability to recognize a group of cellular regulatory components through a tagging system, such as poly- or mono-ubiquitin, or ubiquitin-like proteins<sup>38</sup>, and to present them to a major cellular activity such as a transcription, chromatin remodeling or protein degradation. Given the similarity between the COP9 signalosome and the lid, and the apparent copurification of the COP9 signalosome with the 26S proteasome<sup>2,3</sup>,

it is not impossible that the COP9 signalosome might interact with the proteasome and act as a specialized proteasome regulator. Clearly, a better understanding of the function and the activity of the COP9 signalosome will illuminate an important aspect of cellular homeostasis, the basis of photomorphogenesis in plants, and probably much more besides.

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## A new section in *Trends in Genetics* starting in April – Genome Analysis

The purpose of the Genome Analysis section is to provide a forum for original observations concerning the function, organization and evolution of genomes. With the increasing quantities of genome maps and sequence data in public databases, genome analysis and bioinformatics are providing spectacular insights into fundamental biological questions, and this trend is set to continue. In Genome Analysis, *Trends in Genetics* will publish short articles based on the analysis of publicly accessible data. Articles coming up:

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**Errors in genome annotation** by Steven E. Brenner

**Molecular evolutionary evidence that *H19* mRNA is functional** by Laurence D. Hurst and Nick G.C. Smith