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Current Opinion in Microbiology

# Fungal development and the COP9 signalosome

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The conserved COP9 signalosome (CSN) multiprotein complex is located at the interface between cellular signaling, protein modification, life span and the development of multicellular organisms. CSN is required for light-controlled responses in filamentous fungi. This includes the circadian rhythm of *Neurospora crassa* or the repression of sexual development by light in *Aspergillus nidulans*. In contrast to plants and animals, CSN is not essential for fungal viability. Therefore fungi are suitable models to study CSN composition, activity and cellular functions and its role in light controlled development.

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**Current Opinion in Microbiology** 2010, **13**:672–676

This review comes from a themed issue on
Growth and development: eukaryotes
Edited by José Pérez-Martín

Available online 9th October 2010

1369-5274/$ – see front matter


**DOI** 10.1016/j.mib.2010.09.011

## Introduction

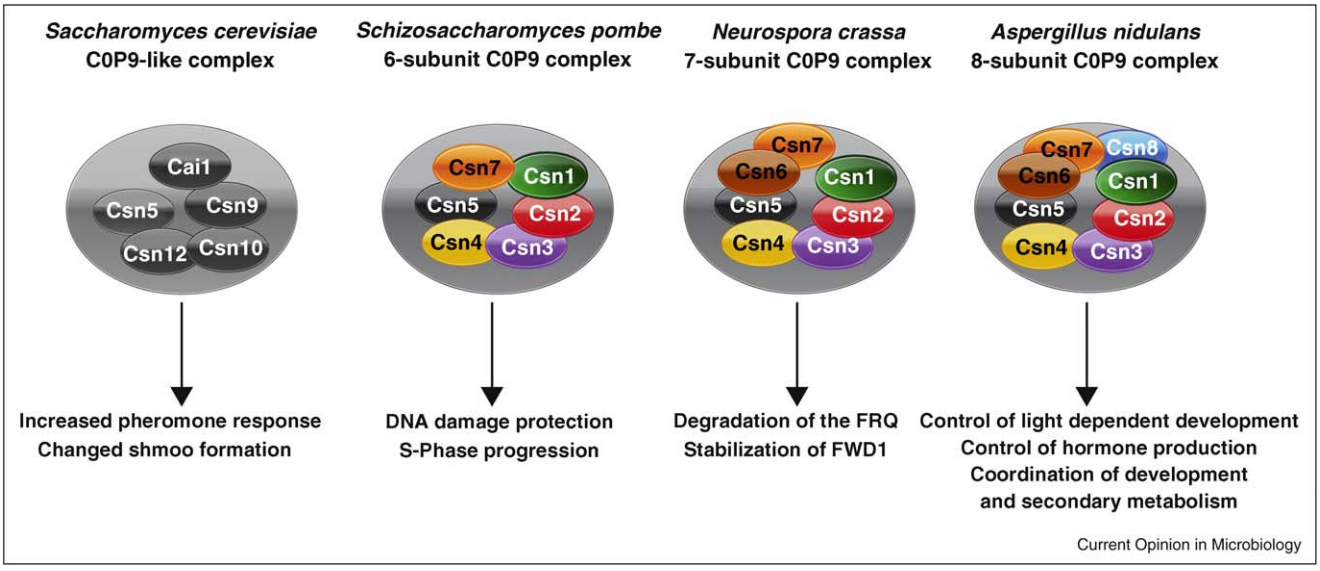
The COP9 signalosome, also known as CSN, is a protein complex found in most eukaryotes from yeast to human [1,2]. CSN was originally identified by its role in light response in plants where mutants showed a *constitutively photomorphogenic/de-etiolated/fusca* (COP) phenotype [3,4]. CSN defective plants growing in the darkness display a development pattern normally seen in the light. In addition, plant CSN is required for the survival of seedlings and is involved in pathogen response [2]. In mice and flies, the absence of CSN causes embryonic death, whereas aberrant expression has been associated with tumour growth [5–7]. CSN is a platform for associated proteins and plays a central role in regulating post-translational processes as protein ubiquitination/deubiquitination, neddylation/deneddylation and phosphorylation. These properties directly affect enzymatic activities, protein stability and subcellular trafficking. Therefore CSN impinges on numerous signaling pathways affecting transcriptional regulation, DNA repair, cell cycle, cell differentiation, and development [1,8,9]. The archaetypal COP9 signalosome comprises the eight subunits CSN1–CSN8 and shares structural features with the lid of the 26 proteasome or translation factor eIF3. These complexes are summarized as Zomes and usually contain six PCI (proteasome/COP9/initiation factor: approximately 200 amino acids) domain proteins and two MPN (Mpr1p and Pad1p N-terminal) domain proteins. eIF3 contains four additional subunits. Additional MPN proteins include AMSH1 involved in endocytosis, or Prp8 protein functioning in RNA splicing. CSN and the lid share the highest homology, because a corresponding paralogue for each gene encoding a subunit of one complex can be assigned in the other complex. The Zomes control cellular protein levels by affecting the synthesis and the stability of proteins. Whereas eIF3 is involved in protein synthesis and the lid in protein degradation, there are various functions which are associated with CSN at the interface between protein synthesis and degradation [10].

## CSN organisation and intrinsic function

CSN has been identified in various fungal species. It is dispensable for the growth of unicellular yeasts and of filamentous fungi [11•,12•,13]. This is in contrast to the slime mold *Dictyostelium discoideum* which requires CSN for growth [14]. Some fungi show significant differences in subunit composition in comparison to the eight-subunit CSN of higher organisms (Figure 1). Smaller versions of CSN are present in *Neurospora crassa* with seven [15,16] or in the fission yeast *Schizosaccharomyces pombe* with six subunits [13,17]. The budding yeast *Saccharomyces cerevisiae* possesses an alternative CSN complex. This includes as the only significantly conserved subunit the homolog of Csn5 [18]. Csn5 is the intrinsic CSN enzyme activity including MPN and a JAMM domain for a metalloprotease activity. This activity triggers the cleavage of the ubiquitin-related Nedd8/Rub1 from CSN target proteins, a process known as deneddylation. Consistent with its function, Csn5 displays homology to the subunit of the proteasome lid that cleaves ubiquitin from proteins. *Aspergillus nidulans* possesses the classical eight-subunit CSN as plants or animals. The fungal Csn5 homolog CsnE is able to recruit the whole CSN complex but only when the other subunits are present [11•,12•].

The best characterised substrates of CSN are cullins, which represent stalk-like eukaryotic scaffold proteins. They serve as platform for the formation of various multisubunit complexes [19]. Fungi possess the minimal eukaryotic set which are the three cullins Cul1, Cul3 and Cul4; humans express seven cullins and there are additional proteins with a cullin homology domain [20,21]. Cullins are subunits of cullin-based Ring finger ubiquitin ligases (CRL). SCFs, the largest group of CRLs

**Figure 1**



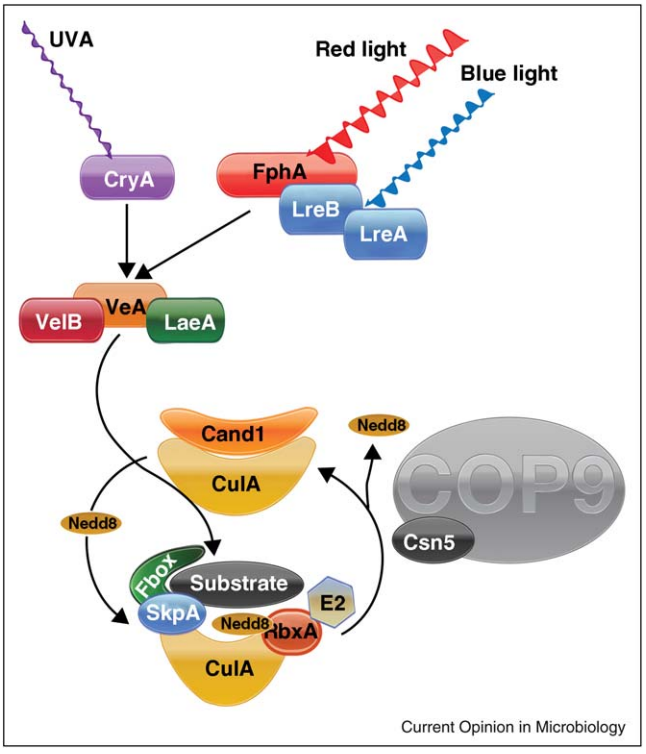

Architecture and developmental functions of fungal COP9 signalosomes (CSN).

contain Skp1 linker proteins which connect cullin-1 to one of numerous F-box proteins, the adaptors for substrates to be ubiquitinated (Figure 2). Cullins themselves can be modified by Nedd8 and this neddylation activates CRL ubiquitin ligases. Ring proteins and the neddylated region of the cullin provide a surface for the E2 ubiquitin conjugating enzyme to ubiquitinate a substrate. K48 polyubiquitination is a marker for proteolysis. CSN cleaves Nedd8 from cullins, which leads to inactivation of CRLs. Thus, a major role of CSN is the regulation of ubiquitination, thereby affecting the stability of proteins.

## Fungi and the CSN paradox

The *csn* mutants of the fission yeast *S. pombe* have moderate phenotypes as delayed progression through S-phase or hypersensitivity to radiation [17,22]. This fungus has contributed to clarify the conflicting role of CSN *in vitro* or *in vivo* on the activity of CRLs. CSN inhibits CRL *in vitro*, but promotes the activity of ubiquitin ligases *in vivo*. CSN mediated deneddylation increases *in vivo* the stability of specific F-box proteins by preventing autoubiquitination when substrate is absent. Without CSN several F-box-proteins are autocatalytically destructed which results in decreased CRL activity *in vivo*. There are two classes of F-box proteins: only those F-box proteins containing a characteristic proline residue in the F-box domains are incorporated into CRL complexes and only those adaptors are stabilised in *csn* mutants [23••]. This leads to the CSN cycle of CRL control. In the absence of substrate, CSN forms a safe

**Figure 2**




Model of COP9 signalosome (CSN) and light response in *A. nidulans*. Light receptors FphA, LreA, LreB and CryA transmit the light signal to the velvet complex VelB/VeA/LaeA which interacts to SCF complexes controlled by the CSN and the Cand1 cycle.

platform for the assembly of CRLs with specific adaptors, by preventing autoubiquitination. If substrate is present, deneddylation is inhibited, thereby substrates are ubiquitinated. As long as sufficient substrate is present, ubiquitination of the F-box adapters is prevented, probably because substrates outcompete the adaptors.

A rather small fraction of unneddylated subcomplexes is sequestered by Cand1 which can be replaced by Skp1 for a new round of CRL assembly and a substrate recognition subunit when a new substrate becomes available [24,25]. Therefore the composition of CRLs can also be regulated by cycles of assembly and disassembly of active neddylated or inactive unneddylated cullin-RING subcomplexes. Cand1 (cullin-associated Nedd8-dissociated protein 1) acts as inhibitor of CRLs *in vitro*, because it stably binds to the deneddylated cullin-RING subcomplex. The protein is necessary to trigger the exchange of F-box proteins of CRLs [26]. This explains what had been termed the *CSN paradox*: CSN and Cand1 are inhibitors of CRLs *in vitro*, but are necessary for CRL assembly and disassembly and therefore CRL activity *in vivo*. Replacement of Cand1 by the substrate adaptors may be facilitated by additional factors or the neddylation of Cand1 itself [25]. Availability of substrates transfers CRLs from the Cand1 cycle back to the CSN cycle starting with substrate binding followed by cullin neddylation. The importance of the Cand1 cycle thus seems to lie in the incorporation of rare adapters into CRL complexes [23••,27]. Fungal Cand1 comes also in different versions. *N. crassa* possesses the classical Cand1 of plants or animals, *A. nidulans* a split version of two smaller CandA polypeptides and the recently discovered Cand1/Lag2 of *Saccharomyces cerevisiae* differs in sequence and in a much smaller size [10,25].

## CSN and light response

*N. crassa csn* mutants are impaired in controlling the circadian clock that adapts conidiation to the day and night rhythm and requires the *frequency* (FRQ) protein as essential compound of the oscillator [28]. *csn* mutant strains are also characterised by growth defects and reduction in aerial hyphae and conidia [15]. CSN regulates the circadian rhythm by stabilising a specific CRL complex which triggers ubiquitination of the FRQ oscillator [16]. FRQ ubiquitination requires the F-box protein FWD1 as substrate receptor. In *csn* mutants, FRQ is stabilised, because the FWD1 levels are reduced. Thus, CSN maintains stability and activity of SCF-FWD1, thereby enabling the proper proteolytic destruction of FRQ protein.

Light control of development is impaired in the absence of CSN in the filamentous fungus *A. nidulans* [29•,30•]. This fungus produces sexual ascospores within closed fruiting bodies in darkness. These cleistothecia consist of several different cell types as Hülle cells nursing the young fruiting body [31,32]. In light, the sexual cycle is inhibited and the formation of condiophores is favoured, which results in the production of air-borne asexual spores [29•,30•,33,34••,35]. *A. nidulans* senses light by red light receptors and blue light receptors [34••,36•,37••]. *csn* mutants are blind to light and initiate constitutively the sexual cycle even in the presence of light [11•]. This depends on the intrinsic CSN deneddylase activity, because single amino acid exchanges within the JAMM domain of the Csn5 homolog are sufficient to provide the phenotype [12•].

The fungal phenotype is reminiscent to *csn* mutants in plants where the light-induced genes are expressed in the dark [3,38–40]. About 15% of all genes were differentially expressed in a *csn* mutant during *A. nidulans* development. The light-independent development could be a consequence of an inadequate production of the *psi* (precocious sexual inducer) factors which act as pheromones [41••]. The proportion of *psi* factors derived from linoleic acid control the ratio of asexual and sexual development [42]. Plant *csn* mutants are impaired in gibberellic acid (GA) and SCF (SLY-1)-dependent germination and elongation [43–45]. Fungi and plants might share that CSN plays a key role in light response by controlling appropriate hormone production during development.

## CSN and the velvet complex

*A. nidulans csn* mutants are blind, not only compromised in the DNA damage response [46], but also impaired in coordinated sexual development and secondary metabolism. Mutants constitutively initiate sexual development but are blocked in cleistothecia maturation at the primordia state. Red coloured hyphae reflect impaired secondary metabolism [11•] reminiscent to plant mutants which accumulate the red pigment anthocyanin [3,38–40].

An antagonist of CSN in coordinating fungal development and secondary metabolism is the velvet complex VelB/VeA/LaeA [47••]. VeA serves in velvet complex as a light-sensitive bridging protein between VelB and LaeA and might require CSN function to be degraded (Figure 2). Remarkably, *velvet* is present only in fungi, whereas CSN is conserved among eukaryotes. In addition, defects in both complexes result in opposite phenotypes. Defects in VeA and CSN simulate illumination and darkness, respectively. VeA carries a PEST region which is a typical feature of protein stability control, and a *veA/csn* double deletion strain exhibits the *veA* phenotype. VeA has been shown to be a highly phosphorylated protein [48]. It is tempting to speculate that a CSN-controlled VeA degradation pathway is initiated by phosphorylation. ImeB is a candidate kinase which is involved in light control of *A. nidulans* and whose substrates are yet unknown [49]. It will be interesting to explore the relationship between VeA and CSN and compare the findings to plants and animals.

## Conclusion

The identification of developmental-specific CRL ubiquitin-ligases will be one of the major tasks of the future research to unravel the role of CSN in development. Filamentous fungi are reliable model systems. Only the adaptors of cullin-1 represent approximately 70 F-box protein encoding genes in *A. nidulans* [50]. A first developmental CRL has been found for this fungus with the F-box protein GrrA for an SCF required during late fruit body maturation [51]. The involvement of CSN in the light response pathway requires to explore CSN control of hormone production and the interaction to subunits of the *velvet* complex as VeA. Ongoing research should help to understand the molecular mechanism of the CSN-mediated control of ubiquitin-ligases affecting fungal development, light response and secondary metabolism.

## Acknowledgements

Research funding was provided by the Deutsche Forschungsgemeinschaft, DFG priority program SPP 1365, the Volkswagen-Stiftung, and the Fonds der Chemischen Industrie.

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