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Review

Many jobs for one good cop – The COP9 signalosome guards development and defense

Johannes W. Stratmann[a,*], Giuliana Gusmaroli[b,1]

[a] University of South Carolina, Department of Biological Sciences, Coker Life Science Bldg., 715 Sumter Street, Columbia, SC 29208, USA
[b] University of South Carolina Beaufort, Department of Science and Mathematics, Science and Technology Bldg., 1 University Boulevard, Bluffton, SC 29909, USA

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ABSTRACT

The COP9 signalosome (CSN) is a multiprotein complex that regulates the activity of CULLIN-RING E3 ubiquitin ligases (CRLs). CRLs ubiquitinate substrate proteins and thus target them for proteasomal degradation. This post-translational modification of proteins is arguably as important as reversible protein phosphorylation. The number of putative CRLs that recognize specific substrate proteins is vast, and known CRL substrates are involved in many cellular plant processes such as hormone signaling, the cell cycle, and regulation of growth, development, and defenses. By controlling the activity of CRLs, the CSN may integrate and fine-tune all of these processes. Recent research has unraveled in great mechanistic detail how the two multiprotein complexes CSN and CRL interact. As a consequence of CSN pleiotropy, complete loss of *CSN* function results in seedling lethality. However, recent work on plants that exhibit a partial loss of *CSN* function, has uncovered a role of the CSN during later life stages in processes such as development and defenses against pathogens and herbivorous insects. Not all aspects of development and defense are affected equally by *CSN* silencing, probably due to the differential participation and importance of CSN-regulated CRLs in these processes. This review will provide an overview of the highly complex regulation of CRL activity by CSN, and the many roles of the CSN in plant development and defense.

Contents

Abbreviations: CSN, COP9 signalosome; CRL, CULLIN-RING E3 ubiquitin ligase; FBP, F-box protein; E3, E3 ubiquitin ligase; JA, jasmonic acid; SA, salicylic acid.

* Corresponding author. Tel.: +1 803 777 5730; fax: +1 803 777 4002.
E-mail addresses: johstrat@biol.sc.edu (J.W. Stratmann), gusmaroli@uscb.edu (G. Gusmaroli).
[1] Tel.: +1 843 208 8266.

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Nomenclature

CSN1-8	COP9 signalosome subunits 1–8
CRL	CULLIN-RING E3 ubiquitin ligase
MPN	Mpr1-Pad1-N-terminal domain. This domain characterizes the two CSN subunits CSN5 and CSN6
PCI	Proteasome, COP9 signalosome and eIF3 domain. This domain characterizes the 6 CSN subunits CSN1–4, CSN7, and CSN8
CUL	CULLIN; the scaffold protein on which a CRL is assembled
RBX1	RING-box domain protein; binds to CULLINs; mediates interaction of CRL and E2 ubiquitin conjugating enzyme
SKP1	Adaptor protein that connects CUL1 and FBPs
FBP	F-box protein; substrate receptor protein of CUL1-based CRLs; binds to SKP1-type adaptor proteins
SCF	SKP1-CUL1-F-box-type CRLs
DDB1	Adaptor protein that connects CUL4 and DWD-repeat proteins
DWD-repeat protein	Substrate receptor protein of CUL4-based CRLs; binds to DDB1-type adaptor proteins
BTB/POZ	Protein that combines function of adaptor protein and substrate receptor protein of CUL3-based CRLs
NEDD8/RUB1	Neural precursor cell-expressed developmentally downregulated-8 (in metazoans) and RELATED TO UBIQUITIN 1 (in plants); ubiquitin-like protein covalently attached to CULLINs
Neddylation/rubylation	Covalent attachment of NEDD8 or RUB1 to CULLINs
Deneddylation/derubylation	Removal of NEDD8 or RUB1 from CULLINs by isopeptidase activity of CSN5
CAND1	CULLIN-ASSOCIATED AND NEDDYLATION-DISSOCIATED 1; binds to CULLINs and prevents reassembly of CRLs
UPS	Ubiquitin-proteasome system; protein ubiquitination by the concerted action of an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and E3 ubiquitin ligase, and the subsequent proteolytic degradation of the polyubiquitinated protein by the proteasome.

1. The COP9 signalosome is a component of the ubiquitin-proteasome system and regulates the CULLIN-based E3 ubiquitin ligases superfamily

1.1. Brief historical overview

The COP9 signalosome (CSN) was initially discovered during genetic screens for constitutive photomorphogenic development in darkness, which led to the identification of 10 non-allelic *cop*/*det*/*fus* mutants (reviewed in [1]). While dark-grown wild type *Arabidopsis* seedlings undergo skotomorphogenesis, a developmental program leading to elongated hypocotyls and closed, unexpanded cotyledons, the *cop*/*det*/*fus* mutants display a constitutive photomorphogenic phenotype, characterized by the deregulated activation of light-induced development (photomorphogenesis), even when grown in the absence of light. These mutants display short hypocotyls and open cotyledons, along with the deregulated expression of light-inducible genes and multifaceted defects in several cellular and developmental pathways that ultimately result in lethality at the seedling stage. The cloning and biochemical analyses of six of the *COP*/*DET*/*FUS* loci led to the identification of 6 PCI domain-containing subunits of a novel protein complex, which was subsequently named COP9 signalosome (CSN) after its involvement in signaling processes during plant development. The discovery of the CSN in *Arabidopsis* in 1994 [2] is one of the inspiring examples of an important discovery first made in plants. It triggered a wealth of research on the CSN in fungal and animal systems, including human health. Later, the CSN was identified in several model organisms across the evolutionary scale, and we now know that the CSN is a nuclear enriched and evolutionary conserved multiprotein complex, composed of eight subunits (termed CSN1 to CSN8), 6 containing a PCI (Proteasome, COP9 signalosome and eIF3) domain, and two (CSN5 and CSN6) containing a MPN (Mpr1-Pad1-N-terminal) domain [1].

The biochemical analyses of all eight *csn* loss of function mutants in *Arabidopsis* indicates that PCI and MPN subunits are structurally interdependent during the formation of the COP9 complex, which explains why all *csn* mutants share an identical phenotype. In fact, lack of either a PCI (CSN7 or CSN8) or an MPN (CSN5 or CSN6) subunit triggers the destabilization of other CSN components, indicating that several CSN subunits, including CSN1, CSN6 and CSN8 are unstable as free forms, and that their accumulation depends upon the formation of an intact complex [3–7]. Moreover, the complete depletion of either CSN5 or CSN6 results in the loss of the entire complex and redistribution of some subunits into smaller subcomplexes [3].

PCI and MPN domain containing proteins are also found in two other multisubunit protein complexes, the eukaryotic translation Initiation Factor 3 (eIF3) and the lid subcomplex of the proteasome 19S regulatory particle, which regulate the first and last step of the life of a protein. This suggests that the three complexes might have diversified from a common ancestor.

1.2. The CSN is an integral part of the ubiquitin proteasome system through modulation of E3 ubiquitin ligase activity

The COP9 signalosome is involved in the control of multiple signaling processes in probably all eukaryotic organisms. For instance, in plants the CSN regulates a plethora of cellular processes including hormone signaling and development [3,8–11], cell cycle progression [12], photomorphogenesis [13], and stress responses [14,15]. In fungi, the CSN carries out functions that are reminiscent of its role in plants, such as light-controlled development [16]. In animals, a wide range of processes require a functional CSN, such as development, regulation of transcription, cell cycle progression, cell proliferation, hormonal responses, angiogenesis, DNA repair,