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Review

The COP9 signalosome (CSN): an evolutionary conserved proteolysis regulator in eukaryotic development

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Abstract

The COP9 signalosome (CSN) is a multiprotein complex of the ubiquitin–proteasome pathway. CSN is typically composed of eight subunits, each of which is related to one of the eight subunits that form the lid of the 26S proteasome regulatory particle. CSN was first identified in *Arabidopsis* where it is required for the repression of photomorphogenic seedling development in the dark. CSN or CSN-related complexes have by now been reported from most eukaryotic model organisms and CSN has been implicated in a vast array of biological processes. It is widely accepted that CSN directly interacts with cullin-containing E3 ubiquitin ligases, and that CSN is required for their proper function. The requirement of CSN for proper E3 function may at least in part be explained by the observation that CSN subunit 5 (CSN5) is the isopeptidase that deconjugates the essential ubiquitin-like Nedd8 modification from the E3 cullin subunit. In addition to its interaction with E3s, CSN may also regulate proteolysis by its association with protein kinases and de-ubiquitylating enzymes. This review provides a summary of the role of CSN in regulating protein degradation and in eukaryotic development.

Keywords: 26S proteasome; COP9 signalosome; E3 ubiquitin ligase; Proteolysis; Ubiquitin; Development

1. Introduction

The COP9 signalosome (CSN) was initially identified from *Arabidopsis thaliana* mutants with a light-grown seedling phenotype when grown in the dark [1–4]. The cloning of the *constitutive photomorphogenesis 9 (cop9)* mutant from *Arabidopsis* was followed by the biochemical purification of a COP9-containing multiprotein complex from cauliflower, a species closely related to *Arabidopsis* [3,4]. Purified CSN has eight subunits and five additional *Arabidopsis* mutants with *cop* mutant phenotypes were found to carry mutations in CSN subunits (Table 1) [5–9]. Common to all of these *Arabidopsis* mutants is the fact that loss of one subunit results in the loss of the entire protein complex.

The presence of sequences in the databases that were related to *Arabidopsis* CSN subunits indicated that CSN may be an evolutionary conserved protein complex. This triggered the interest of various laboratories to isolate or define CSN complexes from most eukaryotic organisms ranging from the fission yeast *Schizosaccharomyces pombe* to human [10–16]. The absence of apparent *Saccharomyces cerevisiae* orthologues for all but CSN subunit 5 (CSN5), suggested that CSN may not be conserved in this budding yeast. However, the verification of results from large-scale genomics and proteomics studies has recently resulted in the isolation of a CSN-related complex from this organism [17,18]. CSN subunit nomenclature has been unified and, with the exception of the subunits of the budding yeast CSN-related complex, the individual CSN subunits are

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Table 1
CSN subunit composition and nomenclature

CSN subunit[a]	*Arabidopsis*[b]	Mammalian[b]	*S. cerevisiae*[c]	Domain	19S Lid paralogue[d]	Homology (%)[d]
CSN1	COP11/FUS6	GPS1		PCI	RPN7p	22
CSN2	FUS12	TRIP15		PCI	RPN6p	21
CSN3	FUS11	SGN3		PCI	RPN3p	20
CSN4	COP8/FUS4			PCI	RPN5p	19
CSN5	AJH1, AJH2	JAB1	YDL216C/Rri1	JAMM/MPN$^+$	RPN11p	28
CSN6		VIP		MPN	RPN8p	22
CSN7	FUS5			PCI	RPN9p	15
CSN8	COP9/FUS7	COP9		PCI	RPN12p	18
CSN9			YDR179C	PCI		
CSN10			YOL117W/Rri2	PCI		
CSN11			YIL071C/Pci8	PCI		
			YMR025W/Csi1	none		
			YDL147W/RPN5/Nas5	PCI	RPN5	100

[a] Unified nomenclature for CSN1 through CSN8 that are subunits of the CSN proper [19]. The nomenclature of the CSN-related complex from *S. cerevisiae* is defined in Refs. [17,18].
[b] Alternative nomenclature for *Arabidopsis* and mammalian CSN subunits based on genetic data.
[c] The *S. cerevisiae* CSN-related complex has a distinct subunit composition [17,18]. As yet, it has not been possible to clarify the relationship between the *S. cerevisiae* subunits and CSN1 through CSN8 from higher eukaryotes and *S. pombe*.
[d] The individual CSN subunits and their paralogues of the 19S regulatory particle lid share significant sequence identities (*S.cerevisiae* 19S RP lid subunit against mammalian CSN subunit, except RPN5).

now being referred to as CSN1 through CSN8 (Table 1) [19].

2. Biochemical functions of the CSN

2.1. CSN and the 26S proteasome

In eukaryotes, the specific elimination of regulatory proteins is mediated by the 26S proteasome, which can be dissected into the proteolytic 20S core particle (CP) and two presumably identical 19S regulatory particles (RP) positioned at either end of the 20S CP [20]. The 19S RP consists of a base and a lid, and the eight subunits that form the lid are paralogues of the eight CSN subunits (Table 1) [21]. Based on this apparent evolutionary relationship, it is thought that CSN and the 19S RP lid have a common ancestor and possess similar biochemical properties.

Both CSN and the 19S RP lid, contain six subunits with a PCI (*p*roteasome, *C*OP9, e*I*F3) domain and two subunits with a MPN (*M*OV34, *P*AD *N*-terminal) domain [22–24]. These domains are also present in subunits of one other multiprotein complex, the translation initiation factor 3 (eIF3) [22–24]. However, the similarity between CSN and the proteasome lid is by far greater than the similarity between the two complexes and eIF3. This is also reflected at the level of subunit–subunit interactions within CSN and the proteasome lid [25]. Within these complexes, it is believed that the PCI domain subunits have a predominantly scaffold function while the MPN domain proteins bring about biochemical activities such as the reported isopeptidase activities of CSN5 in CSN and RPN11 in the 26S proteasome (discussed below) [26–28].

2.2. CSN and E3 ubiquitin ligases

Protein degradation by the 26S proteasome is generally preceded by protein ubiquitylation, a process mediated by an E1 ubiquitin activating enzyme, an E2 ubiquitin conjugating enzyme, and an E3 ubiquitin ligase [29]. While E1 and E2 enzymes have no specificity towards proteolysis substrates, E3 ubiquitin ligases interact directly with these substrates to mediate their ubiquitylation together with associated E2s [30]. SCF complexes represent one family of E3 ubiquitin ligases. They consist of a cullin 1 subunit, the RING domain protein RBX1, a SKP1 adaptor protein, and an F-box protein. F-box proteins bind to the SKP1 adaptor with their N-terminal F-box domain and directly recognize degradation substrates by a C-terminal protein–protein interaction domain [30]. To date, several E3 complexes with a similar subunit composition have been described (Fig. 1). All of these complexes consist of a cullin-RBX1 core that interacts with an adaptor–receptor protein or subcomplex (Fig. 1).

The observation that affinity-purified cullin 1 from human and fission yeast interacts with CSN was the initial breakthrough finding that linked CSN to E3 ubiquitin ligase function (Fig. 1) [31]. In support of this observation, the SCF subunits cullin 1 and RBX1 were found to co-purify with CSN from cauliflower and *Arabidopsis* [32,33]. In *Arabidopsis*, similar phenotypes were observed in transgenic plants with decreased CSN levels and mutants of SCF^{TIR1}, an SCF complex required for proper response to the phytohormone auxin [32].

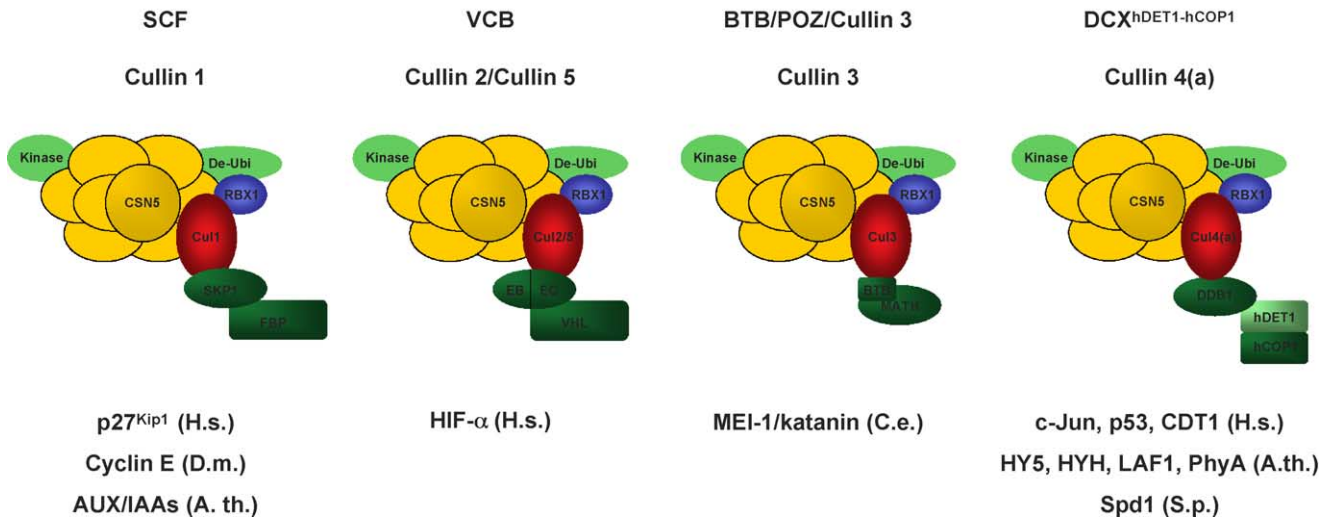

Fig. 1. CSN interacts with cullin-containing E3 ubiquitin ligase complexes or is required for the degradation of specific E3 targets. To date, four types of cullin and RBX1-containing E3 complexes have been described. Direct interactions between CSN and these E3s or a requirement of CSN for the degradation of their substrates have been demonstrated. Substrates are indicated below the E3 complexes. H.s., *Homo sapiens*; A.t., *A. thaliana*, C.e., *C. elegans*, D.m., *Drosophila melanogaster*; S.p., *S. pombe*; S.c., *S. cerevisiae*. Protein kinases (Kinase) and de-ubiquitylating (De-Ubi) activities have been found to be associated with CSN and may represent an additional level of regulation at the CSN. The figure depicts reported interactions between CSN and other protein (complexes) and not interactions between individual complex subunits.

Furthermore, the degradation of the SCF^{TIR1}-substrate PsIAA6 was increased in CSN mutants indicating that PsIAA6 proteolysis requires CSN in addition to SCF^{TIR1}. Taken together, these data strongly suggested that the CSN interaction positively regulates E3-mediated protein degradation. Since these initial discoveries, CSN function has been shown to be essential for the degradation of a range of proteolysis substrates. Interestingly, these proteins are known to be targeted for degradation by different E3 complexes that include all known types of cullin-containing E3 ubiquitin ligase complexes (Fig. 1) [15,33–40].

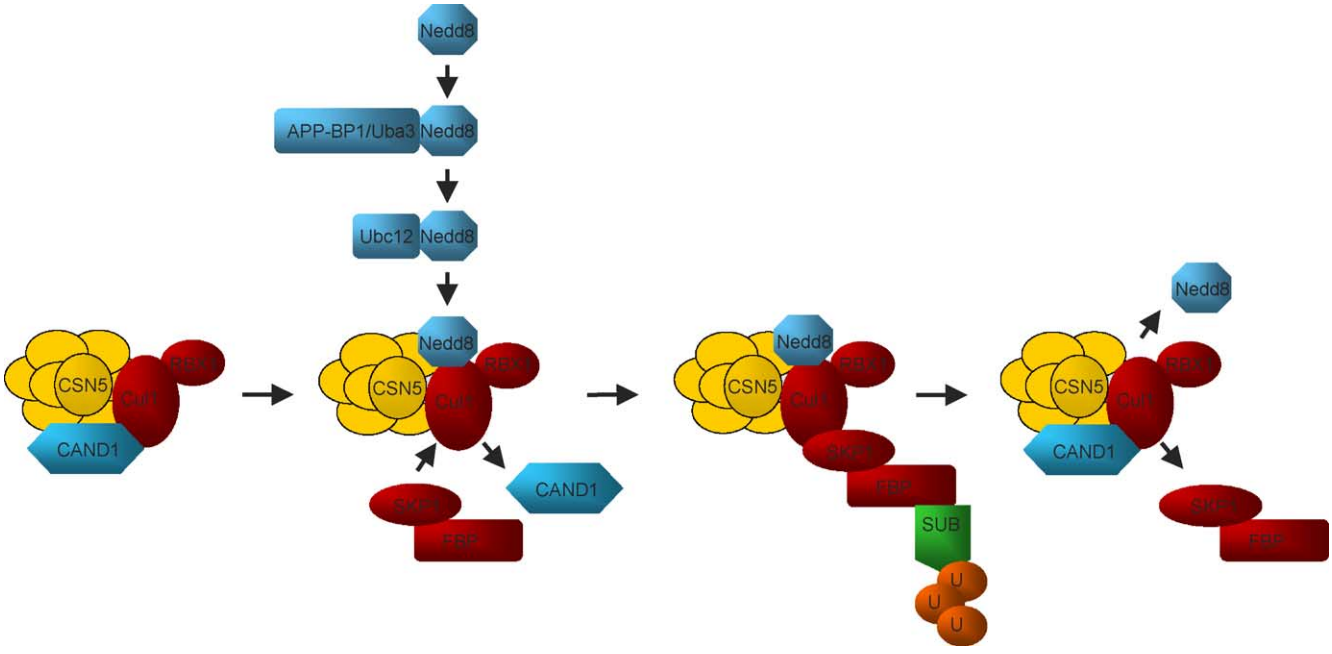

Fig. 2. Model for the regulation of SCF-complex assembly by CAND1 and CSN. The recently described CAND1 protein associates specifically with unneddylated cullins. Upon neddylation, CAND1 dissociates from the cullin-RBX1 heterodimer, thus allowing the association of the SKP1/F-box protein heterodimer. Substrate (Sub) ubiquitylation by the functional SCF complex may be stopped when CSN subunit CSN5 mediates cullin deneddylation followed by the dissociation of the SKP1/F-box protein and de novo association of CAND1.

2.3. Deneddylation is catalyzed by the JAMM/MPN$^+$ motif of CSN5

Cullins are the core complex subunits of a number of distinct E3 ubiquitin ligases (Fig. 1). All cullins are known to be modified by the ubiquitin-related protein Nedd8 (or RUB1) [41,42]. Typically, neddylated as well as un- or deneddylated cullins are detectable in wild-type protein extracts. However, CSN mutants accumulate exclusively neddylated cullins [31,32]. Furthermore, purified CSN can deneddylate cullins in vitro suggesting that CSN or an associated protein has the isopeptidase activity required for deneddylation [31]. The protein with this isopeptidase activity was found to be subunit CSN5 of the complex [27,43]. CSN5 has a conserved signature motif in its MPN domain for metal-dependent isopeptidases, designated JAMM (*JA*B1/*M*PN/*M*OV34) or MPN$^+$. Protein variants with mutations in the JAMM/MPN$^+$ domain were unable to restore deneddylation deficiency and to rescue the mutant phenotypes of CSN5 loss-of-function mutants from *S. pombe*, *S. cerevisiae*, and *Drosophila* [27]. The structure of the JAMM domain has been solved and additional amino acids outside of the JAMM/MPN$^+$ domain have been reported to be essential for the deneddylation reaction [44,45]. Interestingly, recombinant CSN5 monomer or monomeric CSN5 as found in *Arabidopsis* CSN mutants is unable to catalyze the deneddylation reaction [27,32]. Therefore, it has been postulated that CSN5 deneddylation function requires the association of CSN5 with the CSN complex.

2.4. CAND1 specifically recognizes unneddylated cullins

While neddylation and deneddylation had been observed as cullin modifications for many years, the biological role of neddylation and deneddylation in the context of E3 ubiquitin ligase activity or proteolysis had, for a long time, remained obscure. Recently, however, a number of laboratories have reported on the 120 kDa CAND1 protein (*c*ullin-*a*ssociated *n*eddylation *d*issociated)[46–48]. CAND1 specifically interacts with the unneddylated cullin/RBX1 core complex. Upon cullin neddylation, CAND1 dissociates from the complex thus allowing the F-box protein/SKP1 substrate receptor subcomplex to interact. It may be that CAND1 regulates SCF complex assembly by regulating the interaction of cullin with F-box protein/SKP1 (Fig. 2). In the context of these processes, CSN, which is believed to interact with unneddylated and neddylated cullins, could control

Table 2
Identity and function of CSN-interacting proteins that are not directly involved in proteolysis

Protein	Function	Interacting CSN subunit	Connection to protein degradation	Reference
Bcl-3	modulator of NF-κB activity	CSN5		[85]
Casein kinase 2	protein kinase	CSN2, CSN3, CSN7	phosphorylates p53, c-JUN	[53]
c-JUN, JUN-D	transcription factor	CSN5	sumoylated degraded by 26S proteasome	[75,86,87]
ID3	inhibitor of DNA binding	CSN5	degraded by 26S proteasome	[88]
Inositol 1,3,4-triphosphoate 5/6 kinase	protein kinase	CSN1, CSN5	phosphorylates	[52]
Interferon consensus sequence binding protein	transcription factor	CSN2		[89]
p53	transcription factor, cell cycle regulator	CSN5	sumoylated nucleocytoplasmic partitioning degraded by 26S proteasome	[86] [90] [49,50]
Progesterone receptor	hormone receptor	CSN5	sumoylated?	[91,92]
Protein kinase D	protein kinase	CSN2, CSN3, CSN5, CSN7	phosphorylates p53, c-JUN	[47]
Retinoic acid receptor	hormone-dependent transcription factor	CSN2	degraded by 26S proteasome	[93,94]
Steroid receptor coactivator	transcriptional coactivator	CSN5		[91]
Thyroid hormone receptor	hormone-dependent transcription factor	CSN2	degraded by 26S proteasome	[95]
p27^{KIP1}	cell-cycle inhibitor	CSN5	nucleocytoplasmic partitioning degraded by 26S proteasome	[81,82,96]
Macrophage migration inhibitory factor	cytokine	CSN5		[77]
Integrin LFA-1	cell adhesion receptor	CSN5	nucleocytoplasmic partitioning LFA-1 engagement linked to c-JUN activation	[79]
Lutropin/choriogonadotropin receptor (precursor)	hormone receptor	CSN5	CSN5 promotes the degradation of the precursor in the endocytoplasmic reticulum	[97]
HIV-1 Vpr		CSN6	nuclear import	[98]

the dissociation of the F-box protein/SKP1 heterodimer by deneddylation. Although this is a very attractive model for the biological role of the hitherto rather enigmatic neddylation process, the signals that control cullin neddylation and deneddylation remain to be identified.

2.5. Protein kinases and de-ubiquitylating enzymes are associated with CSN

Already the first purification of human CSN reported co-purification of protein kinases that phosphorylate c-JUN, IκBα, and p53 [10]. p53 phosphorylation by the CSN-associated kinases triggers p53 destabilization [49]. An E3 complex, $DCX^{hDET1-hCOP1}$, that mediates c-JUN and p53 degradation has recently been identified [34,50]. Inositol 1,3,4-trisphosphate 5/6 kinase physically interacts with CSN subunits CSN1 and CSN5 and has several features of the originally described CSN-associated kinase, e.g. it phosphorylates IκBα, c-Jun, as well as p53 and its activity is inhibited by curcumin [10,51,52]. Therefore, phosphorylation by inositol 1,3,4-trisphosphate 5/6-kinase may target c-JUN and p53 for degradation by the CSN-associated E3 $DCX^{hDET1-hCOP1}$.

In addition to inositol 1,3,4-trisphosphate 5/6-kinase, to other kinases, CK2 and protein kinase D, were also found to physically interact with individual CSN subunits [53]. Both kinases phosphorylate c-JUN and p53 as well as individual CSN subunits (Table 2). Interestingly, CK2 phosphorylates p53 at a site known to be essential for p53 stability. On the contrary, CK2 phosphorylation does not affect c-JUN stability. It was hypothesized that this phosphorylation event may prevent c-JUN from binding to its cognate E3.

Several in vitro studies reported that the ubiquitylation activity of E3 ubiquitin ligases is severely compromised in the presence of CSN [31,38,54]. In one of these studies it was observed that purified E3 complexes did not possess poly-ubiquitylation activity unless the E3 complexes were purified free of CSN [38]. However, various in vivo data clearly indicated that CSN positively regulates E3 ubiquitin ligase activity [27,32,33]. This obvious contradiction has now seemingly been solved by the finding that CSN-associated de-ubiquitylating enzymes co-purify with CSN [38,54]. Two different de-ubiquitylating activities could be attributed to CSN, de-ubiquitylation of a mono-ubiquitylated cullin 4 and de-ubiquitylation of poly-ubiquitin chains [38]. Experiments conducted in fission yeast then lead to the isolation of the de-ubiquitylating enzyme Ubp12 as a candidate for this de-ubiquitylation activity [54]. While E3s purified from wild-type cells were inactive in ubiquitylation assays, E3s purified from CSN and Ubp12 mutants were active. Based on these findings, it was suggested that degradation substrate de-ubiquitylation may represent an additional level of proteolysis control at the CSN.

3. The CSN in eukaryotic development

3.1. The role of CSN in plant development

CSN was initially identified from *Arabidopsis* as a repressor of photomorphogenic seedling development. To date, a mutant locus for each of the six PCI domain-containing CSN subunits has been identified in *Arabidopsis* [1,4–9]. All of these mutations seem to affect CSN complex integrity as CSN could no longer be detected in mutants of individual CSN subunits. *Arabidopsis* CSN mutants are seedling-lethal and this fact had for long obscured the developmental roles of CSN besides photomorphogenesis. However, using weaker antisense and co-suppression lines, it has been possible to assign a role to CSN in auxin and jasmonate responses, seedling, root, and floral development, as well as pathogen response [8,32,33,55,56]. At least some aspects of auxin and jasmonate response and specific defects in floral development can be attributed to the physical interactions observed between CSN and the E3 complexes SCF^{TIR1}, SCF^{COI1}, and SCF^{UFO} [32,33,57,58]. Interestingly, although CSN appears to be absent from these transgenic plants at the specific developmental stages examined, the reduction of individual CSN subunits brings about partially overlapping but also clearly distinct phenotypes, e.g. while a partial reduction of CSN5 function by antisense and co-suppression lines results in plants with normal flowers, plants with reduced CSN1, CSN3, and CSN6 function have abnormal flower phenotypes [8,32,33,55,57]. This is a surprising finding as all of these CSN subunits are believed to act as one biochemical entity. Hence, these results can only be explained if specific biological functions can be attributed to individual CSN subunits.

Genetic evidence from *Arabidopsis cop1* and *det1* mutants had strongly suggested that COP1 and DET1 are required for CSN function in controlling photomorphogenesis [59,60]. The phenotypes of *cop1* and *det1* mutants are almost indistinguishable from the CSN complex mutants. In *Arabidopsis*, COP1 functions as an E3 ubiquitin ligase in vitro and in vivo. COP1 mediates the degradation of the transcription factors HY5, HY5-homologue, LAF1, as well as that of the far-red light receptor phytochrome A [61–66]. DET1 does not contain any recognizable functional domains and therefore DET1's role in these processes had for long remained obscure. However, the recent identification of a CSN-dependent human E3 ubiquitin ligase complex containing the human COP1 and DET1 orthologues strongly suggests that an orthologous $DCX^{DET1-COP1}$ E3 complex also exists in plants [34,38].

A very intriguing feature of COP1 is the fact that all known degradation substrates co-localize with COP1 in intra-nuclear structures designated "speckles" [62,63,65,67]. The function of these "speckles" remains to be elucidated. As many of COP1's targets are transcription factors and as

COP1 itself is involved in their proteolysis, it has been speculated that "speckles" represent active sites of transcription or protein degradation, two processes that may not necessarily be mutually exclusive [68].

3.2. CSN in Drosophila and Caenorhabditis development

Several recent studies have significantly contributed to the understanding of the role of CSN in animal development. *Drosophila* CSN has now been implicated in oogenesis, embryogenesis, and neuronal development [13,69,70]. Mutations in *Drosophila* CSN4 and CSN5 cause lethality at the larval stage. A molecular basis for the larval lethality of these mutants has been provided through the analysis of a range of markers. These studies indicate that these mutants have defects in dorsoventral and anteroposterior patterning, defects that have been attributed to a failure to produce the Gurken protein [13,70,71].

CSN4 and CSN5 loss-of-function mutants have common but also distinct developmental phenotypes. CSN4 but not CSN5 mutants display a range of molting defects, while CSN5 but not CSN4 mutant larvae develop melanotic capsules [70]. As proposed for the *Arabidopsis* CSN subunits, these observations suggest that *Drosophila* mutants may, in addition to their role in CSN, also have subunit-specific functions. *Drosophila* CSN4, CSN5 and CSN7 exist as CSN subunits as well as CSN-independent forms [70]. Another interesting observation is the fact that *Drosophila* CSN5 mutants still contain an intact CSN complex indicating that CSN5 is an associated subunit of the complex and is not required for its integrity.

Taking into account that CSN is important for proper SCF-complex function and that SCF-complex activities play a major role in cell cycle regulation, it is surprising that *Drosophila* (and *Arabidopsis*) CSN mutants are not blocked in their first cell divisions. At least in *Drosophila*, this can now be explained by the finding that CSN subunits are maternally transmitted [70]. (Maternally transmitted) CSN can be detected in mutant embryos but is not detectable when mutant phenotypes become apparent. To understand the role of CSN during earlier developmental stages, CSN4 and CSN5 germline mutants were established. These studies indicated that CSN activity is already required for proper oocyte development [70]. Through genetic interaction studies, it could be shown that cyclin E, a degradation target of the SCF-complex containing the F-box protein Argonaute, may be the major target of CSN during oogenesis (Fig. 1) [71].

CSN also has an important function in the development of the nematode *Caenorhabditis elegans* [15,72]. At present, orthologues for six of the eight CSN subunits have been identified [15]. RNAi-mediated suppression of CSN subunits resulted in aberrant mitotic spindle formation and orientation. These defects have been attributed to a failure to degrade MEI-1/katanin, a target of a cullin 3 containing E3 complex [15]. MEI-1/katanin degradation seems to be the major CSN target at this stage, as the observed phenotypes could be rescued by the concomitant reduction of MEI-1/katanin (RNAi) function.

3.3. CSN in mammalian development and signal transduction

CSN subunits have been identified as interactors of a diverse set of mammalian signaling proteins such as the transcription factor c-JUN and p53, the cell cycle regulator $p27^{Kip1}$, hormone receptors, the macrophage migration inhibitory factor (MIF1), and the integrin LFA-1 (Table 2). The picture that emerges from these interactions is difficult to interpret and may simply reflect the multitude of signaling processes that require CSN function. However, it is noteworthy that many of the interacting proteins have been reported to be targeted for degradation by the 26S proteasome (Table 2). Furthermore, several of these interactors, notably p53, c-Jun, HIF-α, have been linked to CSN via their cognate E3 ubiquitin ligases (Fig. 1). It is at present not understood why these proteins seemingly interact directly with CSN and at the same time with CSN-interacting E3 ubiquitin ligases.

Consistent with the apparent important role of CSN in a diverse set of signaling processes, knock-out mice of CSN2 and CSN3 die during early embryo stages [73,74]. Consistent with the expectation that proteolysis substrates may not be properly degraded in these mutant mice, the unstable cell cycle regulators p53 and cyclin E were found to accumulate in CSN2 mutants [74].

The bZIP transcription factor c-JUN and the cell cycle regulator $p27^{KIP1}$ have attracted most attention in cell culture studies on mammalian CSN. c-JUN had been reported early on as an interactor of CSN5, hence its original name *J*un *a*ctivation domain *b*inding protein-1 (JAB1) [75]. In these studies, CSN5 was found to enhance the transcriptional activation potential of c-Jun in transient expression assays by stabilizing the interaction between c-JUN and its cognate promoter. Several other reports have since then linked the function of CSN5 and its interactors to c-JUN controlled transcription processes [76–80]. In the light of the new findings that c-JUN degradation is mediated by the CSN-dependent cullin 4a-containing E3 complex $DCX^{hDEt1–hCOP1}$, it can be envisioned that many of these studies interfered in one way or another with the role of CSN and/or CSN/CSN5-mediated deneddylation of $DCX^{hDEt1–hCOP1}$ and c-JUN proteolysis [34].

The cyclin-dependent kinase inhibitor $p27^{KIP1}$ was also identified as a CSN5 interactor [81]. $p27^{KIP1}$ is targeted for degradation by the E3 SCF^{SKP2}. In vitro, CSN blocks the degradation of $p27^{KIP1}$ [36]. This may be explained by a CSN-induced dissociation of the SCF^{SKP2} complex as a consequence of the deneddylation of its cullin subunit. Interestingly, CSN5 and also other CSN subunits are required for the nuclear export of $p27^{KIP1}$, a prerequisite

of $p27^{KIP1}$ degradation [82]. Furthermore, nuclear localization of CSN5 and phosphorylation of $p27^{Kip1}$ are required for CSN5-mediated nuclear export. CSN5 cannot mediate these processes if CSN5/JAB1 is constitutively cytoplasmic or if $p27^{Kip1}$ has a mutation in a conserved phosphorylation site. In these studies, CSN5 was reported to be present in a smaller, predominantly cytoplasmic CSN-related protein complex that also contains subunits CSN4, CSN6, CSN7 and CSN8 [82]. The relationship between this CSN-related complex and bona fide CSN remains to be established.

3.4. CSN in yeasts and fungi

CSN and CSN-related complexes have been identified from the fission yeast *S. pombe*, the budding yeast *S. cerevisiae* and the filamentous fungus *Aspergillus nidulans* [14,16,17]. The CSN1 orthologue of the fission yeast *S. pombe* was identified from a CSN1 loss-of-function mutant with delayed S phase [14]. Fission yeast orthologues of a total of seven CSN subunits have been found to date [35,39,83]. Deletion mutants in CSN1 and CSN2 are delayed in S phase and are sensitive to UV light and ionizing radiation. However, mutants of CSN3, CSN4, and CSN5 display neither the phenotypes observed with CSN1 and CSN2 mutant strains nor any other obvious phenotypes, indicating that distinct CSN subunits may have distinct developmental roles in fission yeast [83]. The replication inhibitor protein Spd1 has recently been identified as a protein degradation substrate that requires the activities of the fission yeast homologues of cullin 4 and DDB1 as well as CSN [39,84]. Taken together, these data suggest that Spd1 may be degraded by a protein complex related to the cullin 4-containing E3 ubiquitin ligase from humans (Fig. 1).

All fission yeast subunits examined to date, CSN1 through CSN5, cofractionate in a CSN complex while one report also identified CSN5 in a smaller complex that does not contain CSN1, CSN3, or CSN4 [35,83]. However, while all deletion strains of individual CSN subunits lose deneddylation activity, smaller CSN-related complexes that vary in size and subunit distribution could still be detected in these deletion strains [31,35,83].

Besides an obvious orthologue of CSN5, the budding yeast *S. cerevisiae* does not contain any easily recognizable CSN subunits [31]. However, a CSN-related complex could be identified by the systematic analysis of CSN5 interactors reported in large-scale analyses of yeast protein complexes [17,18]. The fact that deletion mutants for each of the proposed subunits are deneddylation deficient was taken as an indication that these proteins form a CSN-related complex in vivo. Although none of these proposed proteins has obvious homology to any of the previously identified CSN subunits, four of them contain a PCI domain, thus a domain characteristic for CSN subunits (Table 1). The evolutionary relationship between CSN and the 26S proteasome is underlined by the fact that the CSN-related complex from budding yeast also seems to contain the proteasome lid subunit RPN5 (Table 1). RPN5 mutant strains are lethal; however, mutants for all other proposed CSN subunits are viable and have increased mating efficiencies due to increased pheromone responses [17,18]. Furthermore, CSN5 deletion mutants in combination with temperature-sensitive mutants of SCF complex subunits are delayed in growth, a phenotype that can be attributed to the stabilization of the cell cycle inhibitor Sic1p [27]. Taken together, this may indicate that the CSN-related complex from budding yeast has retained its function as a deneddylating isopeptidase that is required for the regulation of SCF complexes.

4. Perspectives

Recent advances in CSN research have attributed a biochemical activity to CSN and have linked this complex to numerous biological processes that require E3 ubiquitin ligase function. Now, this knowledge opens the way to address a number of important questions on CSN function such as: (1) What is the relationship between CSN and the 26S proteasome? CSN and the lid of the 19S proteasome clearly have a common evolutionary origin and this invites the hypothesis that CSN may function in the context of a proteasome. In fact, several reports have already suggested that CSN associates with the 26S proteasome. However, clear biochemical and functional evidence in support of these findings is still absent. In the same context, it needs to be resolved why numerous E3 ubiquitin ligases are found to interact with CSN while the number of E3s that interact with the 26S proteasome is still rather small. This could indicate that CSN may have a function in assembling SCF complexes rather than mediating fast degradation by bridging between E3s and the 26S proteasome as had been proposed earlier. (2) What are the biochemical and biological functions of individual CSN subunits and CSN-related complexes? It has been observed in studies conducted in *Arabidopsis*, *Drosophila* and fission yeast, that loss of distinct CSN subunits results in distinct phenotypes. This strongly suggests that individual CSN subunits have specific roles within CSN as a biochemical entity or independent of CSN. Future research should try to identify these functions and their mechanisms to contribute to a better understanding of CSN.

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