

ZOMES III: the interface between signalling and proteolysis

Meeting on The COP9 Signalosome, Proteasome and eIF3

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The ZOMES III meeting was organized by W. Dubiel, M. Naumann, D. Chamovitz and M. Glickman, and was held in Berlin, Germany, between 9 and 12 May, 2004.

The meeting title refers to the fact that two of the protein complexes discussed, namely the COP9 signalosome and the 26S proteasome, end with the suffix '-some'

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(Glickman *et al*, 1998), the eukaryotic translation initiation factor 3 (eIF3) complex is essential for initiating messenger RNA (mRNA) translation (Asano *et al*, 1997) and the COP9 signalosome (CSN) was first shown to control photomorphogenesis in *Arabidopsis* (Chamovitz *et al*, 1996; Kwok *et al*, 1996) but has since been found to be central to many other signalling events (see below). At first glance, these three complexes do not seem to have anything in common; however, many of their subunits contain either a Proteasome–COP9–Initiation factor (PCI) or an Mpr1–Pad1–amino (N)-terminus (MPN) domain. The presence of similar domains in complexes with apparently divergent functions challenges us to think more critically and creatively about their role in the cell, and about what advantages there might be to recruiting the same protein domain into functionally distinct protein machineries. For example, could similar molecular mechanisms govern fundamentally different cellular functions? Or could the related domains allow interaction with the same molecular targets, thereby facilitating the assembly of similar subunits into a complex?

For the third time since 1999, around 100 scientists from all over the world gathered at the ZOMES III meeting to discuss our present understanding of the biochemical and biological functions of these three protein complexes. A hallmark of these meetings has been the unique and exciting interaction of researchers from diverse fields working on distinct biological systems.

PCI and MPN domain proteins in each complex

The presence of both PCI and MPN domains in the lid of the proteasome, the CSN and the eIF3 complex was first reported in 1998 (Aravind & Ponting, 1998; Hofmann & Bucher, 1998). Initially, the domains were found in only a handful of proteins that were known to be subunits of these three complexes. At ZOMES III, K. Hofmann (Cologne, Germany) combined his bioinformatic analyses with biochemical data from other laboratories to update the list of subunits that are known to contain PCI and MPN domains. He showed that the proteasome lid and CSN are markedly similar in their subunit composition (Table 1; Fig 1). In higher eukaryotes, both of these complexes contain six subunits with the PCI domain and two subunits with the MPN domain; this is referred to hereafter as the '6 + 2'

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Introduction

It is generally assumed that evolutionarily conserved protein domains participate in similar biochemical processes. Frequently, however, similar protein domains are found in the subunits of protein complexes that, at first glance, have no functions in common. For example, the 'lid' of the 26S proteasome regulates the degradation of proteins that are marked for proteolysis by polyubiquitylation

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Table 1 | PCI and MPN proteins in the proteasome lid and the COP9 signalosome

| Protein domain | Proteasome lid | COP9 signalosome | COP9 signalosome subunits in various species* | | | | |
|----------------|----------------|------------------|---|----|--------------------|-------|----|
| | | | Hs | Sp | Sc | Ca | Cm |
| PCI | Rpn7 | Csn1 | + | + | Csn11 [†] | Csn11 | + |
| PCI | Rpn6 | Csn2 | + | + | Csn10 | + | + |
| PCI | Rpn3 | Csn3 | + | + | Csn12 | Csn12 | + |
| PCI | Rpn5 | Csn4 | + | + | - | - | - |
| PCI | Rpn9 | Csn7 | + | + | Csn9 | Csn9 | + |
| PCI | Rpn12 | Csn8 | + | - | - | - | - |
| MPN | Rpn11 | Csn5 | + | + | + | + | + |
| MPN | Rpn8 | Csn6 | + | - | - | - | - |

*Ca, *Candida albicans*; Cm, *Cyanidioschyzon merolae*; eIF3, eukaryotic translation initiation factor 3; Hs, *Homo sapiens*; Sc, *Saccharomyces cerevisiae*; Sp, *Schizosaccharomyces pombe*. CSNs in *Drosophila*, *Arabidopsis* and *Caenorhabditis*, similar to those in humans, have all of the canonical subunits. [†]CSNs are missing or diverted from the canonical structures in some lower eukaryotes. For example, Csn11, -10, -12 and -9 seem to have been diverted from Csn1, -2, -3 and -7, respectively.

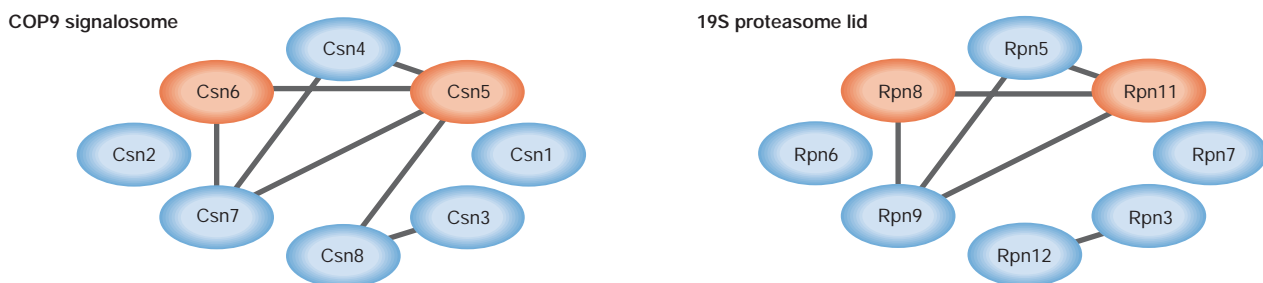


Fig 1 | Similarities in subunit compositions and pairwise interactions between the COP9 signalosome and the proteasome lid. Synonymous subunits are plotted at identical positions. MPN domain proteins are depicted in orange, and PCI domain proteins are shown in blue. Strong pairwise binding between synonymous subunits was detected using the yeast two-hybrid system (Fu *et al.*, 2001).

configuration. The eIF3 complex was initially reported to have a 3 + 2 configuration, but Hofmann has now confirmed the presence of PCI domains in the human subunits, eIF3j and eIF3l, as predicted by other authors (Morris-Desbois *et al.*, 2001; Valasek *et al.*, 2001), along with a previously overlooked PCI domain in eIF3k (Mayeur *et al.*, 2003). It therefore seems that all three complexes in humans display the 6 + 2 configuration.

Although the 6 + 2 configuration of the proteasome lid is conserved in all multicellular model organisms, Hofmann noted that some subunits of the CSN and the eIF3 complex are apparently missing in more simple organisms (Table 1). For example, in some unicellular eukaryotes, including *Saccharomyces cerevisiae*, only five (in some cases, poorly conserved) CSN subunits have been identified, which represent a 4 + 1 configuration. Taken together, these observations support the hypothesis that a minimal CSN is composed of four PCI proteins (Csn1, -2, -3 and -7, or their derivatives) plus one MPN protein (Csn5, which is also known as Jab1). As the *S. cerevisiae* eIF3 seems to contain only three PCI domain proteins (Table 2), the minimal structure for this complex might not contain an MPN domain protein.

Diverse functions involving the COP9 signalosome

Many subunits of the CSN were identified initially from studies of *Arabidopsis* constitutive photomorphogenic (*cop*) mutants, which mimic the development of light-grown seedlings when transferred to the dark. Work from several laboratories was presented at ZOMES III

to showcase the remarkably diverse biological functions that require the CSN. These include: the regulation of auxin responses and photomorphogenesis in *Arabidopsis* (C. Schwechheimer and E. Dohmann, Tübingen, Germany); the light-dependent execution of circadian rhythms in *Drosophila* (A. Knowles from the laboratory of J. Blau, New York, NY, USA); sexual development in *Aspergillus nidulans* (G. Braus, Göttingen, Germany); a proposed role in the nuclear factor (NF)-κB pathway in mammalian and *Drosophila* immunity (J. Schmid, Vienna, Austria; M. Naumann, Magdeburg, Germany; and D. Chamovitz, Tel Aviv, Israel); cell cycle and checkpoint regulation in *Schizosaccharomyces pombe* (T. Carr, Brighton, UK); and the DNA damage-response pathway in mammalian cells (Y. Shiloh, Tel Aviv, Israel, and H. Zhang, New Haven, CT, USA).

The importance of CSN function for mammalian development was highlighted by studies with knockout mice for *Csn2* (N. Wei, New Haven, CT, USA) and *Csn5* (J. Kato, Nara, Japan). Knockout mice for either subunit are defective in early embryogenesis, and contain elevated levels of the cell-cycle regulators p27^{Kip1}, p53 and cyclin E. As a result, cell proliferation is impaired and apoptosis is accelerated.

COP9-signalosome-dependent deneddylation

As the CSN and the proteasome lid share structural similarity (Fig 1), the CSN has long been regarded as a candidate proteolysis regulator. Indeed, it has now been established that an important function of the CSN is to regulate proteolysis by interacting with

the Skp1–Cullin (Cul)–F-box (SCF)-type E3 ubiquitin (Ub) ligases, which selectively mark proteins for degradation by promoting polyubiquitylation.

The Cul subunits of the SCF-type E3s are modified by the conjugation of the Ub-like protein Nedd8, which can be removed by a deneddylating enzyme. It is thought that Csn5 is chiefly responsible for this activity, as it carries an MPN domain with a predicted metalloprotease activity. An MPN domain protein from *Archaeoglobus fulgidus* was analysed using X-ray crystallography by J. Tran from the laboratory of M. Bycroft (Cambridge, UK). She reported that this domain resembles cytidine deaminase, which is a member of the metal hydrolase superfamily (Tran *et al*, 2003). This result supports the hypothesis that the MPN domain is enzymatically responsible for the cleavage and indicates that it might function in a manner similar to that of metal hydrolases.

Several presentations questioned whether Csn5 is essential for CSN-dependent deneddylation. Carr reported that the *S. pombe* CSN has a role in promoting entry into the S-phase by inducing S-phase delaying protein 1 (Spd1) degradation, which is a process that is dependent on a Cul4 homologue (Pcu4). Intriguingly, however, whereas Cul4, similar to Cul1 and Cul3, is neddylated, its deneddylation requires Csn1 and Csn2, but not Csn5 (Liu *et al*, 2003). Similarly, O. Harari-Steinberg from the laboratory of Chamovitz, reported that Cactus, which is the *Drosophila* homologue of the NF- κ B inhibitor (I κ B), is efficiently degraded in *Drosophila csn5* mutants. These results raise the possibility that there is another CSN-associated deneddylation enzyme besides Csn5, or that Cactus degradation is independent of CSN or CSN-mediated deneddylation.

Is there any evidence that several CSN complexes in the cell affect the proteolysis of distinct sets of proteins? The Kato laboratory observed that *Csn5* deletion in mice creates a haploinsufficiency, as heterozygous *Csn5*^{+/−} mice are smaller than their wild-type littermates. When they examined *Csn5*^{+/−} mouse embryonic fibroblasts, they found that the loss of a single copy of *Csn5* does not significantly affect the integrity of the canonical CSN complex, although the level of a second Csn5-containing complex, which is known as the Jab1-containing subcomplex (JACS), is reduced. As the level of p27^{Kip1}, but not p53 and cyclin E, is elevated in these cells, this abnormality seems to correlate with selective proteolysis.

Cycling of neddylation and SCF regulation

The CSN evidently mediates deneddylation of the Cul subunits in the SCF, but is the deneddylated SCF active? Genetic data from a wide range of model organisms indicate that the CSN is required to activate the SCF. However, *in vitro* studies presented at ZOMES II indicated that the CSN might, in fact, inhibit SCF function. This controversy was addressed at ZOMES III by D. Wolf (Cambridge, MA, USA). His group showed that CSNs that are purified from red blood cells and *S. pombe* also contain the deubiquitylating enzyme Ubp12 (Zhou *et al*, 2003). Therefore, it is possible that the previously observed *in vitro* SCF 'inactivation' by the CSN might be caused by Ubp12-dependent deubiquitylation, which counteracts the effects of SCF on ubiquitylation.

How might the CSN activate the SCF? Wolf found that the F-box protein Pop1 in the *S. pombe* SCF is degraded rapidly if either Ubp12 or Csn5 is absent. Moreover, *ubp12Δ* and *csn5Δ* both intensify defects that are caused by *skp1* mutations. These results are consistent with the theory that the deneddylation of Cul by the

Table 2 | PCI and MPN proteins in eIF3 complexes

| Protein domain | eIF3 subunits in humans | eIF3 subunits in various species | | | |
|----------------|-------------------------|----------------------------------|----|----|----|
| | | Sp | Sc | Ca | Cm |
| PCI | eIF3a/p170 | + | + | + | + |
| | eIF3b/p116 | + | + | + | + |
| PCI | eIF3c/p110 | + | + | + | + |
| | eIF3d/Moe1/p66 | + | − | − | + |
| PCI | eIF3e/Int6/p48 | + | − | − | + |
| MPN | eIF3f/p47 | + | − | − | + |
| | eIF3g/p40 | + | + | + | + |
| MPN | eIF3h/p36 | + | − | + | + |
| | eIF3i/p36 | + | + | + | + |
| PCI | eIF3j/p35 | + | + | + | + |
| PCI | eIF3k/p28 | − | − | − | + |
| PCI | eIF3l/p69 | − | − | − | + |

Ca, *Candida albicans*; Cm, *Cyanidioschyzon merolae*; eIF3, eukaryotic translation initiation factor 3; Sc, *Saccharomyces cerevisiae*; Sp, *Schizosaccharomyces pombe*.

CSN, and the efficient deubiquitylation of accidentally ubiquitylated F-box proteins by Ubp12, can cooperatively stabilize the SCF. Consistent with these findings, J.-T. Wu from the laboratory of C.-T. Chien (Taipei, Taiwan) reported that neddylated *Drosophila* Cul1, which accumulates as a result of *csn5* mutations, is unstable. They also showed that neddylated Cul1 is selectively degraded by the lysosome, but not by the proteasome. Whether neddylated Cul1 is selectively degraded by the lysosome warrants further investigation in other systems.

Covalent modification of the CSN in response to signals

The CSN is thought to relay signals to the proteolytic machinery. Two presentations described the covalent modifications of the CSN in response to signalling. Regulation of the DNA damage response is an important function that is coordinated by the CSN, as illustrated by studies of human and *S. pombe* cells. The ataxia-telangiectasia mutated (ATM) kinase pathway has a central role in mobilizing the cellular response to DNA damage in mammalian cells. Shiloh and Y. Galanty (Rehovot, Israel) described a direct physical association between the CSN and ATM. Furthermore, one of the CSN subunits was phosphorylated in an ATM-dependent manner after DNA damage. In relation to signalling, Schmid also found that tumour necrosis factor- α (TNF- α) induces CSN5 ubiquitylation and degradation. Whether covalent modification of the CSN is a method by which these signals regulate cell functions remains to be established.

Deubiquitylation and substrate recognition in proteolysis

Although the 20S catalytic core of the proteasome is able to degrade short peptides, it cannot break down polyubiquitylated proteins without the base and the lid of the 19S regulatory complex. One important function of the lid was discovered through the study of the proteasome subunit Rpn11, which, similar to Csn5, contains an MPN domain. Rpn11 cleaves the polyubiquitin chain from the proteasome substrates, thereby facilitating the entry of protein substrates into the catalytic chamber of the 20S core. M. Glickman (Haifa, Israel) presented his mutagenesis analysis of

Rpn11 and reported that proteasomes purified from mutants in the catalytic MPN domain retain deubiquitylation activity. He also found that mutations in the non-MPN carboxy-terminal region of Rpn11 disrupt mitochondrial functions. He therefore proposed that this region might have a role in directing the proteasome to the mitochondria. The proteasome base contains another deubiquitylation component, Ubp6, the activity of which is sensitive to cysteine-protease inhibitors. Although these inhibitors block the deubiquitylation of polyubiquitylated substrates, they unexpectedly promote the degradation of monoubiquitylated substrates. Glickman therefore raised the interesting possibility that Ubp6-dependent deubiquitylation might also prevent poorly ubiquitylated substrates from being degraded.

Another area of intense discussion at ZOMES III centred on how substrate specificity is achieved by the 26S proteasome. R. Verma from the laboratory of R. Deshaies (Pasadena, CA, USA) presented evidence for the presence of several polyubiquitin chain 'receptors' in *S. cerevisiae*, each of which link a specific group of protein substrates to the proteasome for degradation (Verma *et al*, 2004). Rpn10 and Rad23 are two such receptors: the former preferentially targets substrate/subunit inhibitor of cyclin-dependent kinase 1 (Sic1), G2/mitotic-specific cyclin 2 (Cib2) and GTPase-interacting component 2 (Gic2) for degradation, whereas the latter selectively mediates degradation of the cyclin-dependent kinase inhibitor factor arrest 1 (Far1). To underscore further the importance of binding between receptor proteins and the ubiquitylated substrates, Verma screened chemical libraries and identified a new class of compounds, ubistatins, which block proteolysis by inhibiting binding between the receptor and the substrate. The *S. pombe* Ub-conjugating enzymes Ubx2 and Ubx3 contain a UBX domain. C. Gordon (Edinburgh, UK) reported that this domain binds cell-division-control protein 48 (Cdc48), which is an AAA-ATPase and a potential polyubiquitin chain receptor (Hartmann-Petersen *et al*, 2004). This indicates that extra adaptors and/or scaffolds, such as Ubx2 and Ubx3, might further diversify the mechanisms by which proteasomes select specific proteins for degradation. The presence of several proteasome-associated proteins that bind polyubiquitylated proteins, together with the large range of Ub ligases, establishes several layers of selectivity in the proteolytic pathway, thereby ensuring that the correct protein is subject to irreversible proteolytic inactivation. Finally, C. Gorbea from the laboratory of M. Rechsteiner (Salt Lake City, UT, USA) reported that proteasomes are present in various cell compartments in association with extracellular mutant 29 (Ecm29), which indicates that proteolysis selectivity can be further modulated by proteasome compartmentalization, possibly through this protein.

Proteolysis without the proteasome regulatory complex

For every rule there is an exception. Most proteasome studies have focused on the 19S regulatory complex. However, at ZOMES III, two talks showed that the 20S catalytic core can act without this complex in many biological processes. Y. Shaul (Rehovot, Israel) showed that the degradation of several short-lived proteins, including p53 and the related p73, does not require the 19S cap, but does involve NADPH:quinone oxidoreductase (NQO1). NQO1 inhibits proteolysis when it is bound to both the 20S core and the substrate, whereas the dissociation of NQO1 accelerates proteolysis. P. Kloetzel (Berlin, Germany) presented evidence supporting a three-step model for antigen presentation through the major histocompatibility

complex (MHC) class I pathway. Antigens are thought to be cleaved initially by the 26S proteasome. The resulting large peptide fragments are then trimmed further by tripeptidyl peptidase II and the products are processed by the 20S core before they are suitable for recognition by the MHC class I complex.

Int6/eIF3e: a regulator of translation or proteolysis?

Int6, which contains a PCI domain, was first identified from an insertional mutagenesis screen as an important component that influences breast tumorigenesis (Gallahan & Callahan, 1987). It was also found to associate physically with the eIF3 complex and so was independently named eIF3e (Asano *et al*, 1997). Int6 has since been shown to interact with the proteasome and the CSN (Yahalom *et al*, 2001). This PCI-domain protein therefore associates with all three complexes—determining why this happens is of great interest.

E. Chang (Houston, TX, USA) described the recent findings from his group concerning an Int6 homologue in *S. pombe*, which is known as Yin6 (Yen *et al*, 2003). He presented evidence that although Yin6 is not essential for viability and translation initiation, it influences a wide range of functions, including chromosome segregation and mitotic exit. Chromosome and mitotic defects were also observed by P. Jalinot (Lyon, France) in Int6-deficient HeLa cells. The cause of these mitotic defects was investigated in *S. pombe*, and Chang showed that Yin6 associates with and regulates the proteasome. In the *yin6*-null mutant, the proteasome is improperly assembled, and securin and cyclin levels increase; these defects can be rescued by human *INT6*.

Wolf investigated whether Yin6 might influence the synthesis of a specific group of mRNAs. His group performed pull-down experiments that identified approximately 100 mRNA clones that associated specifically with this protein. Further studies will determine whether such differential associations with mRNA molecules lead to specialized protein synthesis. Evidence for differential translation mediated by another eIF3 component was presented by A. von Arnim (Knoxville, TN, USA). He showed that the *Arabidopsis* eIF3h influences the translation initiation of a subset of mRNAs, which, when defective, leads to a range of developmental phenotypes, including sugar-signalling defects and decreased fertility.

Interactions between subunits from different complexes

Csn2 is a PCI protein that is structurally similar to Rpn6 in the proteasome lid (Table 1). The marked similarity between the lid and the CSN raises the question of whether the subunits in these complexes might be functionally interchangeable. W. Dubiel (Berlin, Germany) overexpressed *Csn2* and performed pull-down experiments in B8 fibroblasts to show that Csn2 is integrated with the proteasome base, similar to Rpn6, which indicates a substitution of the lid by the CSN. Furthermore, *Csn2* overexpression was accompanied by enhanced p53 degradation. As both the CSN and the proteasome can influence p53 degradation, further experiments are needed to determine whether the CSN-substituted proteasome is biologically functional.

An interaction between the eIF3 and CSN subunits was presented by von Arnim, who reported that a synthetic interaction between the *Arabidopsis eif3h* and *csn8* mutations affects embryogenesis. This observation complements previous data that has shown a physical interaction between the *Arabidopsis* CSN and eIF3 (Yahalom *et al*, 2001).

Outlook

The CSN and the proteasome lid are not only structurally but also functionally related, in that they both act to remove Ub-like molecules from proteins. Although ubiquitylation allows protein substrates to bind to the proteasome, deubiquitylation, as mediated by the MPN domain protein Rpn11, promotes the entry of these substrates into the catalytic site. For the CSN, Csn5-mediated deneddylation can similarly influence the protein-protein interactions that are necessary for the assembly of a functional E3, as well as specifying whether its components should be rapidly degraded. The association of eIF3 components with the CSN and the proteasome is puzzling. Protein synthesis and degradation need to be tightly coordinated as a quality-control mechanism to prevent the release of abnormal proteins into the cell. The observed binding between the three complexes might therefore facilitate such organization.

The ZOMES meetings undoubtedly provide an open forum that promotes the exchange of ideas across many fields. These events have taken further tangible steps to facilitate communication. For example, at ZOMES I, the importance of unifying the nomenclature of various components in the complexes was stressed (Deng *et al*, 2000). During ZOMES III, it was proposed that a database should be established to assemble information on, for example, mutant phenotypes and protein-protein interactions. This would allow ideas to be continually shared in a cybernetic virtual domain before the next ZOMES meeting, which will be held in 2006.

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