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# ZOMES: expanding roles of the PCI complexes from protein metabolism to drug discovery

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The XII-ZOMES Conference (Shenzhen, 2024) showcased advances in PCI complexes—proteasome, COP9 signalosome, and eIF3—which regulate cellular proteostasis through conserved architectures. Presentations covered translation initiation, proteasome assembly, ubiquitin and ubiquitin-like modification regulation, protein quality control mechanisms, and emerging therapeutic technologies including PROTACs and molecular glues for targeted protein degradation.

In 1999, a group of scientists convened in Israel for the inaugural ZOMES meeting to discuss the emerging properties of PCI complexes, which comprise the 26S Proteasome Lid (P), the COP9 Signalosome (CSN, C), and eukaryotic translation initiation factor 3 (eIF3, I)-collectively termed "ZOMES" complexes. These molecular machineries share similar subunit architecture and assembly mechanisms and play essential roles in maintaining cellular proteostasis. Since then, the ZOMES conference has convened every 2–3 years to discuss the latest advancements and future directions in this field[1–5].

From October 31 to November 3, 2024, the XII-ZOMES Conference was held in Shenzhen (China), co-organized by Feng Rao, Hai Rao, Xing Wang Deng, Brenda Schulman, Ning Zheng, Dieter Wolf, Ning Wei, Qi Xie, Dimitris Xirodimas, and Elah Pick. Centered on PCI complexes and related assemblies, the conference explored recent advances in understanding how these multi-protein complexes mediate cellular signaling, metabolism, and other physiological processes through proteostasis regulation. The participants presented discoveries spanning structure biology, fundamental mechanisms, signaling pathways, novel functions, model organism studies, human disease connections, and innovative targeted protein degradation technologies. The dynamic interactions fostered during this conference catalyzed new ideas and established foundations for future collaborations.

## ZOMES possess conserved PCI domains

ZOMEs, also known as PCI complexes, play essential roles in cellular homeostasis through distinct but interconnected regulation of protein metabolism[1–5]. eIF3, the largest eukaryotic initiation factor, ensures accurate translation and facilitates proper folding of nascent proteins. CSN functions as a deneddylase, removing NEDD8 modifications from Cullin proteins, which serve as the scaffold of the largest family of E3 ligases, Cullin-RING E3 ubiquitin ligases (CRL). CRL-catalyzed substrate ubiquitination often acts as signals for recognition by the 19S Regulatory Particle and ultimately for degradation by the 20S proteasome core. What eIF3, CSN, and 19S share in common is a conserved PCI/MPN octamer core structure, comprising six PCI domain subunits with scaffolding subunits and two Mpr1-Pad1 N-terminal (MPN) metalloprotease domain subunits that are either catalytically active or inactive. For example, the eIF3f/h subunits of eIF3, the RPN8/11 subunits of the 19S regulatory particle, and the CSN5/6 subunits of the COP9 Signalosome all contain MPN domains, while other known subunits perform main scaffolding functions or are involved in protein-protein interactions (Figs. 1–3).

The structure of PCI complexes is like the Chinese "Burr puzzle". Each subunit appears similar but has subtle differences, allowing them to assemble correctly and orderly without the need for additional molecular glue. **Hsueh-Chi Sherry Yen** discovered that subunits of these PCI complexes exhibit cooperative stabilization during assembly, with unassembled or oligomeric subunits being degraded[6]. This finding provides new insights into the quality control mechanisms governing PCI complex assembly and reveals common principles underlying their biogenesis.

## eIF3 ensures proper translation and folding of nascent peptides

eIF3 is a conserved, essential complex that orchestrates translation initiation in eukaryotes. eIF3 facilitates the recognition of mature mRNA bearing a 5' cap structure, promotes mRNA binding to the 40S ribosomal small subunit, and maintains the stability of the initiation complex. EIF3 comprises 13 subunits, eight of which contain PCI/MPN domains that form the structural core of the complex (Fig. 1). **Baochun Han & Dieter A. Wolf** demonstrated that eIF3's function extends beyond translation initiation to include participation in early elongation, where it interacts with 80S ribosomes to recruit quality control factors. Their work revealed that eIF3 binding to 5'-UTRs is critical for ensuring proper co-translational protein folding[7]. **Yaser Hashem** resolved the cryo-EM structure of eIF3 within the DHX29-bound 43S complex, achieving approximately 6 Å resolution for the PCI/MPN core. This structural analysis elucidated key mRNA interactions with eIF3 and other eukaryotic initiation factors, as well as with 40S ribosomal proteins, providing insights into their impact on late-stage 48S initiation complexes[8].

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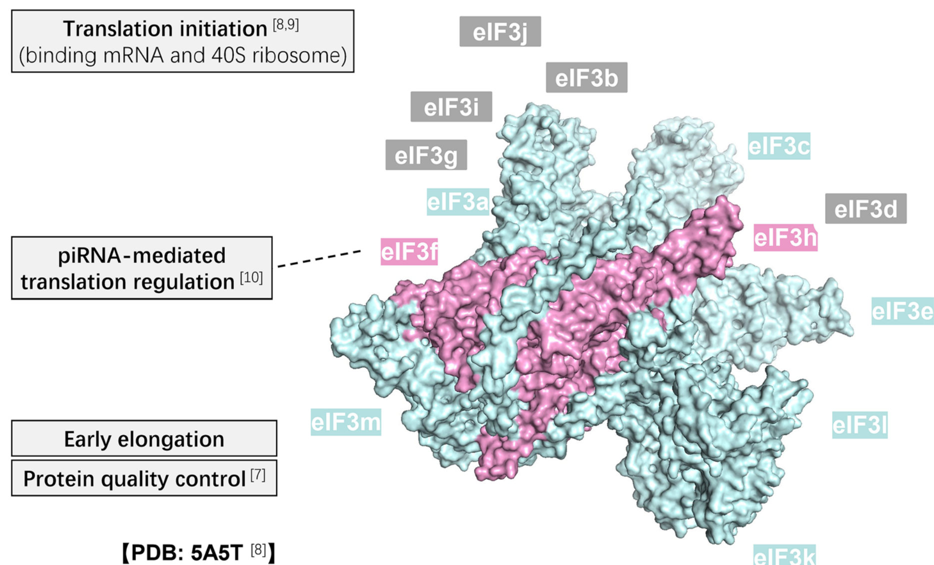


**Fig. 1 |** The structure of PCI/MPN subunits in eIF3 and related research progress reported in ZOMES-XII.

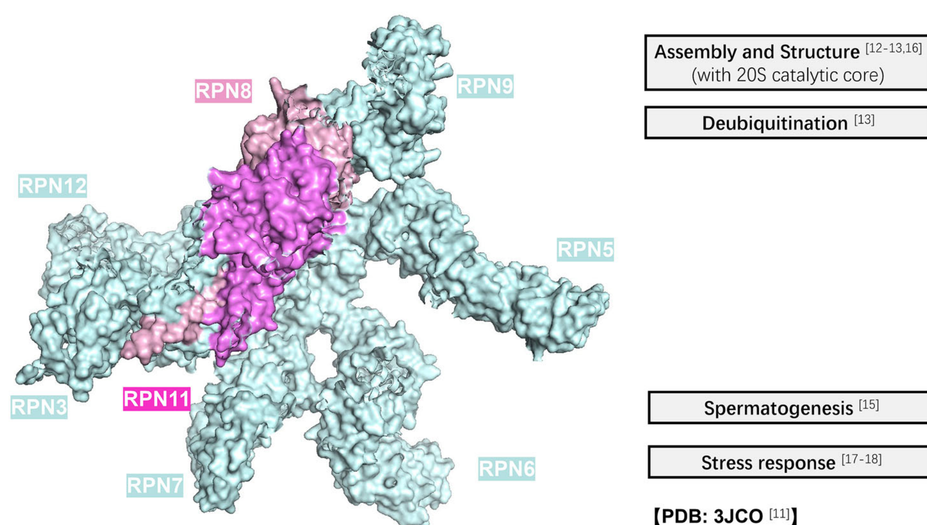


**Fig. 2 |** The structure of PCI/MPN subunits in 19S regulatory particle and related research progress are reported in ZOMES-XII.

**Ayala Shiber** reported the use of Selective Ribosome Profiling (SeRP) to capture dynamic interactions between ribosomes and nascent polypeptide chains. This approach led to the proposal of mRNA co-localization mechanisms that facilitate co-translational assembly of partner subunits in the complex[9]. **Mo-Fang Liu** identified eIF3f, one of the MPN-domain subunits, as essential for MIWI/piRNA-mediated translational regulation in spermatids, functioning beyond its role in promoting mRNA degradation, expanding our understanding of eIF3's diverse cellular functions[10].

## Proteasome clears misfolded and redundant ubiquitinated proteins

The 26S proteasome, comprising the 19S regulatory particle (a PCI/MPN complex) and 20S catalytic core, is responsible for degrading the majority of cellular proteins through the ubiquitin-proteasome system. Despite its fundamental importance, the molecular mechanisms underlying proteasome assembly, regulation, and substrate degradation remain incompletely understood[11] (Fig. 2). **Brenda Schulman** elucidated key aspects of 20S core particle biogenesis and assembly[12], as well as in-cellulo, stress-regulated assembly dynamics of the yeast 26S proteasome, while **Kai Liu** uncovered the molecular mechanisms governing the stepwise assembly of 20S[13]. Building on the established identification of three major proteasome-associated deubiquitinating enzymes (DUBs)[14], **Michael Glickman** identified a fourth putative deubiquitinating enzyme (DUB) functionally associated with the proteasome to disassemble primarily short ubiquitin chains. **Wei Li** demonstrated essential roles of 19S and 20S proteasomes in spermatogenesis, with 20S in sperm and 19S in oocytes preventing polyspermy[15]. **Xing Guo** identified N-myristoylation of the Rpt2 subunit as critical for the proteasome-membrane interactions, demonstrating how lipid-anchored proteasomes influence both developmental processes and cancer progression[16]. Under cellular stress conditions, **Min Jae Lee** described how inactive 26S proteasomes undergo stress-induced aggregation into insoluble condensates that are subsequently cleared through lysosomal pathways[17]. **Kefeng Lu** investigated immune-proteasome clearance during inflammatory responses[18] and discovered that 5-iodotuberculin can reduce proteotoxic stress. Both clearance processes involve SQSTM1/p62-mediated selective autophagy mechanisms. **Ruixi Li** revealed that AP-3β specifically recruits 19S regulatory particles to stress granules, facilitating their disassembly during heat stress responses[19].

## CSN regulates ubiquitination via deneddylation

The CSN complex, also containing PCI scaffolding and MPN subunits, removes NEDD8 from CRLs to enhance ubiquitination. However,

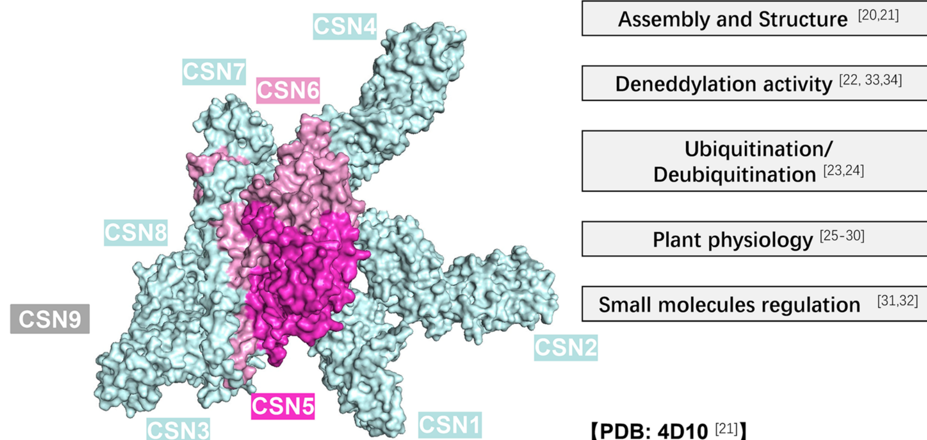


**Fig. 3 |** The structure of PCI/MPN subunits in COP9 signalosome and the latest research progress reported at ZOMES-XII.

substantial uncertainties remain regarding the assembly of CSN holocomplex and functional mechanisms of dynamic CRL-CSN complex formation (Fig. 3). **Gerhard H. Braus** resolved step-wise CSN assembly in *Aspergillus nidulans*: CSN2 bridges two trimers (CSN1-CSN3-CSN8 and CSN4-CSN6-CSN7) into a heptameric precursor, which binds CSN5 to form the active complex[20]. **Lan Huang** used cross-linking mass spectrometry (XL-MS) to probe the structural dynamics of the CSN complex, revealing a CSN9-dependent conformation that facilitates CSN-CRL interactions and underlies CSN function[21]. **Dawadschargal Dubiel** reported that the mammalian CSN is degraded by autophagy during serum starvation. These recent insights enrich our understanding on CSN assembly and disassembly.

Significant progress has been made with regard to CSN participation in physiology and pathology. **Wolfgang Dubiel** identified CSN7A and CSN7B variants regulating CRL3 and CRL4 neddylation, respectively, with different roles in adipogenesis[22]. **Mong-Hong Lee** showed CSN6 stabilizes HMGCS1 by inhibiting SPOP ubiquitin ligase, activating YAP1, and promoting hepatocellular carcinoma[23]. **Michael Naumann** demonstrated that the CSN and the deubiquitinase USP48 cooperatively stabilize NF-κB/RelA in the context of gastric pathology, particularly in response to the lipopolysaccharide metabolite ADP-heptose[24].

With regard to plant CSN, **Ning Wei** demonstrated that deneddylated CUL1 exhibits enhanced binding to its substrate recognition receptor EBF1, but CUL1 displays ubiquitin ligase activity only when neddylated[25], providing new insights into the function of Cullin neddylation-deneddylation cycle. **Giovanna Serino** studied CSN-mediated CRL regulation under biotic/abiotic stress[26], and revealed that high-salt stress specifically induces CUL1 neddylation in Arabidopsis seedlings. **Vicente Rubio** demonstrated that the phytohormone abscisic acid (ABA) prevents ubiquitination of its receptor PYL8 by inhibiting the assembly of the CRL4-CDDD-CSN complex[27]. COP1 acts as an E3 ubiquitin ligase that competes with CSN for CRL complex binding, with both regulators exhibiting functionally intertwined relationships. **Xing Wang Deng** identified the plant-specific spliceosome component DCS1 as a novel COP1 substrate[28], while **Hongtao Liu** and **Li Yang** independently characterized novel immune-related functions of the upstream COP1 receptor CRY1 in plants[29,30].

The role of small molecules in CRL-CSN dynamics is gaining increasing attention. **Feng Rao** identified the glue-like function of inositol phosphate in mediating CSN-CRL complexation in animals, and further demonstrated that this process is subjected to nutrient regulation, with important implications in tumor initiation[31]. **Saikat Bhattacharjee** systemically examined the role of inositol phosphate kinases in regulating CSN-mediated CRL deneddylation, and how it interplays with plant phosphate homeostasis[32]. **Yi Sun** demonstrated that enhanced neddylation of CUL5 promotes the growth of KRAS-mutant pancreatic cancer[33], and is currently screening small-molecule drugs to inhibit CUL5 neddylation through targeted mechanisms. **Jürgen Bernhagen** utilized the CSN-5i inhibitor to reveal a protective role for CSN in cardiovascular and neurovascular diseases, contrasting with its tumorigenic functions[34]. These findings showcased the potential of CRL neddylation/deneddylation as therapeutic targets.

## Ubiquitin and non-ubiquitin protein quality control

Protein quality control (PQC) maintains cellular homeostasis through two primary mechanisms: refolding misfolded proteins via molecular chaperones, or eliminating them through degradation pathways, including the ubiquitin-proteasome system (UPS) and non-UPS routes such as autophagy. **Yingying Lin** showed that the folding chaperonin CCT7 exists in monomeric form and colocalizes with ALS-related proteins to promote their autophagic clearance[35]. **Dimitris Xirodimas i**dentified a specialized nuclear protein quality control system where cellular stress triggers the formation of nucleolus-associated protein inclusions, which are subsequently cleared through the coordinated action of the E1 ubiquitin-activating enzyme UBA1 and nuclear proteasomes once stress conditions resolve[36]. During cellular stress, translation arrest leads to the formation of stress granules (SGs)—dynamic, membrane-less ribonucleoprotein assemblies. **Yanfen Liu** demonstrated that SGs contain multiple quality control factors, notably the E3 ubiquitin ligase TRIM21, which regulates SG dynamics by ubiquitinating and promoting degradation of the core scaffolding protein G3BP1[37].

Organelle quality control also relies on PQC. For example, mitochondrial quality control centers on mitophagy to selectively degrade damaged mitochondria. **Han-Ming Shen** demonstrated that the PINK1-Parkin (an E3 ligase) pathway creates amplifying positive feedback loops that enhance mitophagic efficiency, and SMAD3 can participate in this process by regulating the transcription of PINK1[38]. The process through which ER misfolded or incompletely assembled secretory proteins are recognized, transported to the cytoplasm, and degraded via the ubiquitin-proteasome system is known as ER-associated protein degradation (ERAD). **Yihong Ye** elucidated key ERAD mechanisms, including ribosome UFMylation and NEMF-mediated CATylation, which facilitate the clearance of proteins stalled during translocation[39]. Dysfunction of peroxisomes leads to various diseases, and, distinct from that of other organelles, the maintenance of protein homeostasis within them relies on a unique transport process mediated by a series of PEX gene-encoded proteins. **Tom A. Rapoport**[40] revealed how PEX5 continuously shuttles cytosolic cargo into peroxisomes through cyclic mono-ubiquitination and deubiquitination at its N-terminus, highlighting a non-proteolytic regulatory function of ubiquitin modification. Building on this understanding. **Min Zhuang** characterized how the E3 ubiquitin ligase MARCH5 controls both the formation and segregation of mitochondrial-derived peroxisomal precursor vesicles by ubiquitinating PEX3[41].

## Ubiquitin-mediated physiological processes as potential therapeutic targets

Beyond organellar quality control, the ubiquitin system regulates diverse cellular and developmental processes through tissue-specific and context-dependent mechanisms. **Daniel Finley** has been working on proteasome regulation[42]. He reported that the YPEL5-dependent CTLH E3 ubiquitin ligase complex targets myriad mRNA-binding proteins, as revealed through quantitative global proteomics, thereby orchestrating erythroid differentiation and development. **Zhouhua Li** describes how JAK/STAT downstream target, the E3 ligase UBR5, degrades another JAK/STAT target, Drumstick, a member of the Odd-skipped family of zinc finger proteins, to maintain niche homeostasis and prevent cell fate conversion[43].

Disease mechanisms frequently involve disrupted ubiquitin signaling, exemplified by **Xu Tan**'s findings that deletion mutations in the ubiquitin ligase KLHL24 in epidermolysis bullosa patients impair its auto-ubiquitination, resulting in enhanced degradation of the substrate keratin 14 (KRT14)[44]. In oncology contexts, **Ceshi Chen** established that the E3 ubiquitin ligase Hectd3 functions as a tumor suppressor by ubiquitinating STAT1[45]. **Xinhua Feng** revealed crosstalk between E3 ligases, demonstrating that HERC3 binds to SCFβ-TrCP and blocks its recruitment of YAP/TAZ substrates, consequently promoting mammary tumorigenesis[46]. **Jianping Jin** identified dual pathways for IκBα degradation involving not only the canonical SCFβ-TrCP complex but also BRAP-mediated ubiquitination, thereby modulating downstream inflammatory gene expression[47]. Post-translational modifications beyond ubiquitin also contribute to protein regulation, as **Xingzhi Xu** showed that PARP1 UFMylation enhances its enzymatic activity to maintain genome stability[48].

Finally, **Ziqing Yu** showed that a peptide segment inserted into hypoxia-inducible factor HIF2A (EPAS1) during high-altitude adaptation prevents its binding to the E3 ligase pVHL, thereby blocking subsequent ubiquitination[49], exemplifying the role of ubiquitin-mediated regulation in environmental adaptation.

## Emerging targeted protein degradation technologies

The therapeutic potential of protein degradation systems has driven innovative drug development strategies. **Hai Rao, Xiaobo Qiu**, and **Chao Xu** advanced PROTAC (PROteolysis TArgeting Chimera) technology through multiple breakthroughs: development of single amino acid-based Mini-PROTACs for enhanced efficiency[50], creation of NuTACs that exploit non-ubiquitin-dependent protein degradation pathways[51], and engineering of PROTACs utilizing the $CRL2^{FEM1B}$-recognized Arg/C-degron system[52]. These innovations collectively expand the therapeutic landscape of targeted protein degradation.

Beyond traditional PROTACs, **Ning Zheng** introduced the molecular glue UM171, which promotes the interaction between HDAC1/2 and KBTBD4, the substrate receptor of CRL3, thereby driving degradation of LSD1-HDAC1-CoREST transcriptional corepressors[53]. Complementing these therapeutic approaches, **Lei Liu** developed advanced chemical protein synthesis methodologies specifically designed for ubiquitin research applications, enabling precise targeting of pathological ubiquitin E3 ligases and deubiquitinating enzymes[54].

## Conclusion and prospects

Despite its grassroots origins, the ZOMES meeting series has sustained momentum for over three decades, establishing itself as a distinguished forum for informal yet rigorous scientific discourse. The success of this approach was exemplified by the robust attendance and stimulating presentations at ZOMES-XII. The symposium's emphasis on face-to-face interactions has fostered numerous collaborative partnerships throughout its history, with similar outcomes anticipated from the current meeting. Advances in structural biology methods, combined with physiological studies across different species, tissues, and environments, have provided new insights into the similarities and differences in PCI complex assembly, as well as their crucial roles in protein metabolism and function.

Looking ahead, with the development of emerging technologies such as artificial intelligence, PROTACs, and molecular glues, along with the deepening of pathological research, we anticipate more exciting progress in the precise targeting and regulation of PCI complexes. The scientific community eagerly awaits continued dialogue at ZOMES-XIII in Montpellier, South France, where further advances in refining our understanding of protein quality control mechanisms are expected to emerge.

## Data availability

No datasets were generated or analysed during the current study.

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## Author contributions

F.R., L.Z., and C.D. wrote the main manuscript text, and L.Z. prepared Figs. 1–3. All authors reviewed the manuscript.

## Competing interests

The authors declare no conflict of interest as defined by Nature Portfolio, or other interests that might be perceived to influence the results and/or discussion reported in this paper. Note that F.R. is an associate editor of npj Metabolic Health and Disease.

## Additional information

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