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PROTEIN QUALITY CONTROL

Nuclear membrane proteins in check

The endoplasmic reticulum (ER)-associated degradation (ERAD) eliminates misfolded proteins in the membrane and lumen of the ER. Foresti *et al.* now reveal a specific ERAD branch for the quality control of inner nuclear membrane (INM) proteins in yeast. This branch involves the newly-characterized ubiquitin ligase Asi (Aminoacid Signalling Independent) complex, composed of Asi1, Asi2 and Asi3.

In *Saccharomyces cerevisiae*, the E2 enzyme Ubc7 was known to partner with two canonical ERAD ubiquitin ligases, Hrd1 or Doa10. Using a quantitative proteomics approach, the authors identified proteins that were unaffected by the absence of Hrd1 or Doa10, but that accumulated at higher levels in Ubc7-depleted cells compared with wild-type cells. Among these was Erg11, an enzyme involved in ergosterol biosynthesis. Erg11 degradation was also impaired in mutants lacking the Cdc48 ATPase, which is required for ERAD of all membrane-bound substrates, suggesting the existence of a non-canonical ERAD branch independent of Hrd1 and Doa10.

The paralogue proteins Asi1 and Asi3 constitute a ubiquitin ligase known to localize to the INM. Genetic and proteomic analyses revealed that Erg11 degradation was impaired in the absence of Asi1, Asi2 or Asi3. Therefore, these proteins define a novel ERAD branch that requires Ubc7 and Cdc48.

Immunoprecipitation experiments showed that the three Asi proteins assemble into a complex that binds to Erg11. Moreover, Asi1 depletion led to Erg11 accumulation specifically at the nuclear membrane, and Erg11 overexpression was toxic to cells lacking Asi1. This suggests that the Asi complex prevents accumulation of Erg11 at the INM thereby restricting sterol synthesis to specific ER subdomains.

> “the Asi complex mediates the ERAD of both misfolded proteins and functional sterol biosynthetic enzymes”

Given that the INM is not involved in protein biogenesis, does the Asi complex also have a role in protein quality control? To test this, the authors analysed the degradation of several misfolded proteins. They found that the degradation of a mutant translocon subunit, Sec61-2, depended on both Hrd1 and Asi complexes. However, if Sec61-2 was excluded from the INM, its degradation relied mostly on Hrd1, whereas the dependence on the Asi complex was reduced, indicating that Asi can function in protein quality control at the INM. Thus, like other ERAD branches, the Asi complex mediates the ERAD of both misfolded proteins and functional sterol biosynthetic enzymes, but it is spatially restricted to the INM.

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ORIGINAL RESEARCH PAPER Foresti, O. *et al.* Quality control of inner nuclear membrane proteins by the Asi complex. *Science* http://dx.doi.org/10.1126/science.1255638 (2014)