URLs

PROTEIN DEGRADATION

A new chapter for ERAD?

To ensure that non-native glycoproteins are eliminated from the ER, misfolded proteins are recognized and then exported to the cytosol to be ubiquitylated and degraded through a process known as ERAD — endoplasmic reticulum (ER)-associated degradation. ERAD is known to require substrate glycosylation in many cases, but how exactly this process works remains a mystery. This is now closer to being solved thanks to the efforts of three groups who have characterized the functions of the *Saccharomyces cerevisiae* lectin-like protein Yos9 in this process.

Bhamidipati *et al.* looked at the directionality of ERAD by fusing a highly stable protein domain to a purposefully misfolded, known ERAD substrate. The stably folded domains impeded protein retrotranslocation and first had to be released into the ER lumen. A genetic screen for yeast mutants that were unable to clip off the stable domain led to the identification of Yos9, which forms a complex with ERAD substrates that are subsequently degraded. Yos9 also has a sugar-binding pocket that is essential for its function in ERAD, although, in this study, substrate recognition by Yos9 was not prevented by either mutation of this site or by a lack of glycosylation of the substrate.

The results of Szathmary *et al.* differ from those of Bhamidipati *et al.* in that Yos9 was found to bind only to ERAD substrates that were glycosylated. This was probably due to a more stringent experimental protocol that failed to pick up weaker interactions. However, Szathmary *et al.* believe that these data are complimentary, and that their results do not preclude the possibility that Yos9 interactions with unglycosylated substrates might be involved in the ERAD pathway. They also found that Yos9 is likely to function in the same pathway as the 'degradation lectin' Htm1.

The results of Kim *et al.* extend these observations as they indicate that, although Yos9 and Htm1 are sometimes required together, they can also function in the absence of one another within the same pathway. Along with Szathmary *et al.*, by looking at the overall processing of ERAD substrates, Kim *et al.* show that Yos9 is not required for the biosynthesis or transport of glycosylphosphatidylinositol-anchored proteins, as had been previously suggested. In agreement with Bhamidipati *et al.*, they also show that Yos9 specifically functions in the ERAD-L (lumenal) pathway, which only processes proteins for which the substrate lesion is located in the ER lumen (as opposed to the cytosol).

Altogether, these studies indicate that Yos9 has an important role in identifying misfolded proteins and removing them from the pool of correctly folding intermediates — effectively acting as a quality-control receptor for ERAD. Many further questions have been raised by these studies, and the next installment of the Yos9 story is eagerly awaited.

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References and links

ORIGINAL RESEARCH PAPERS Bhamidipati, A. *et al*. Exploration of the topological requirements of ERAD identifies Yos9p as a lectin sensor of misfolded glycoproteins in the ER lumen. *Mol. Cell* **19**, 741–751 (2005) | Kim, W. *et al*. Yos9p detects and targets misfolded glycoproteins for ER-associated degradation. *Mol. Cell* **19**, 753–764 (2005) | Szathmary, R. *et al.* Yos9 protein is essential for degradation of misfolded glycoproteins and may function as lectin in ERAD. *Mol. Cell* **19**, 765–775 (2005)

WEB SITE

Davis Ng's lab: http://www.tll.org.sg/res/davis.asp