Marked for Destruction: MANNOSIDASE4 and 5 Process N-Linked Glycans into ER-Associated Degradation Tags

Elaborate chaperone systems in the endoplasmic reticulum (ER) fold nascent polypeptides and refold misfolded proteins, but if those systems fail or get overwhelmed, the resulting aberrant proteins can be harmful and even toxic to the cell. ER quality control is therefore a critical area of cell biology. Among the quality control mechanisms ensuring that only properly folded proteins are allowed to continue through the secretory system is ER-associated degradation (ERAD), in which terminally misfolded proteins (i.e., proteins that are no longer candidates for refolding) are removed from the ER and degraded by the proteasome (reviewed in Vembar and Brodsky, 2008). Most of what we know about ERAD comes from yeast and mammals, but the identification of plant homologs of ERAD machinery has opened the door to studying this process in plants.

One of the central questions in ERAD is how terminally misfolded proteins (which should be degraded) are distinguished from nascent proteins and folding intermediates (which should theoretically be protected from degradation). Many proteins that go through the secretory system have N-linked glycan structures (glycans linked to the side chain of certain Asn residues) that function in both folding and quality control. In yeast, removal of terminal mannose residues of an N-glycan by α-mannosidases creates a tag that targets the glycoprotein for degradation; in plants, only a few ERAD substrates are known, but there is evidence that a similar mechanism might target some of them for degradation (reviewed in Hüttner and Strasser, 2012).

New work from Hüttner et al. (pages 1712–1728) beautifully combines genetic and biochemical approaches to demonstrate that two α-mannosidases from Arabidopsis thaliana generate a tag marking glycoproteins for degradation.

Arabidopsis has five related mannosidases (MNS1 to MNS5); MNS1 to MNS3 function in N-glycan processing and maturation in the ER and Golgi (see figure). In their current work, Hüttner et al. characterized MNS4 and MNS5, finding that both proteins were targeted to the ER, and not to the Golgi. Single and double mutants of MNS4 and MNS5 had no phenotypes under normal conditions, and the quintuple mutant of all five MNS genes resembled the mns1 mns2 mns3 triple mutant. Consistent with this, N-glycan processing was normal in the mns4 and mns5 single and double mutants. Together, these findings support the idea that MNS1 to MNS3 have roles in processing correctly folded glycoproteins, whereas MNS4 and MNS5 do not.

The mns4 mns5 double mutant showed signs of ER stress, suggestive of accumulation of misfolded proteins. Combinatorial analysis of the mns4 and mns5 mutants with two brassinosteroid insensitive1 (bri1) mutants, both of which produce variants of the brassinosteroid receptor, revealed that MNS4 and MNS5 are required for ERAD of the aberrant BR1 proteins. Hüttner et al. went on to demonstrate that both MNS4 and MNS5 have α-mannosidase activity that is necessary for their role in ERAD of the BR1 variants.

This work provides strong evidence that MNS4 and MNS5 (at least partially redundantly) remove a mannose residue from the C-branch of N-glycans, thereby generating a terminal α1,6-mannose residue and creating the ERAD tag that marks misfolded glycoproteins for proteasomal degradation. As such, it represents important progress in understanding ER quality control in plants.

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REFERENCES


