

2 EDEM2 initiates mammalian glycoprotein ERAD by catalyzing the first mannose trimming step.

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Endoplasmic reticulum-associated degradation (ERAD) of glycoproteins depends on trimming of the N-glycan(s) attached to the misfolded protein. In yeast, mannosidase 1 performs the first step (Man9 to Man8), followed by Htm1 (Man8 to Man7). The situation in mammalian cells has been more confusing, with three Htm1 homologues (EDEM1-3) with different reported levels of mannosidase activity and a single mannosidase 1 homologue, but with a reported Golgi localization. In this paper, Ninagawa and colleagues knock out the EDEM and mannosidase I genes individually in human and chicken cell lines and analyze the structure of N-glycans accumulating in the cells. They find that in contrast to yeast, where all N-glycans are rapidly processed to Man8 by mannosidase 1, mammalian glycoprotein ERAD has two limiting glycan-processing steps, from Man9 to Man8, and from Man8 to Man7. In vertebrates, EDEM2, not mannosidase 1, is responsible for the first processing step and EDEM3 (with some help from EDEM1) for the second. So, perhaps mammalian mannosidase 1 in the Golgi serves only as a back-up for the processing of glycoproteins that have escaped EDEM2 in the ER. The paper illustrates that ERAD in mammals is more carefully controlled than in yeast, perhaps owing to the more complex proteins or the higher volume of traffic through the mammalian secretory pathway.

Disclosures

None declared

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Abstract:

ABSTRACT

Glycoproteins misfolded in the endoplasmic reticulum (ER) are subjected to ER-associated glycoprotein degradation (gpERAD) in which Htm1-mediated mannose trimming from the oligosaccharide Man8GlcNAc2 to Man7GlcNAc2 is the rate-limiting step in yeast. In contrast, the roles of the three Htm1 homologues (EDEM1/2/3) in mammalian gpERAD have remained elusive, with a key controversy being whether EDEMs function as mannosidases or as lectins. We therefore conducted transcription activator-like effector nuclease-mediated gene knockout analysis in human cell line and found that all endogenous EDEMs possess mannosidase activity. Mannose trimming from Man8GlcNAc2 to Man7GlcNAc2 is performed mainly by EDEM3 and to a lesser extent by EDEM1. Most surprisingly, the upstream mannose trimming from Man9GlcNAc2 to Man8GlcNAc2 is conducted mainly by EDEM2, which was previously considered to lack enzymatic activity. Based on the presence of two rate-limiting steps in mammalian gpERAD, we propose that mammalian cells double check gpERAD substrates before destruction by evolving EDEM2, a novel-type Htm1 homologue that catalyzes the first mannose trimming step from Man9GlcNAc2.

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