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The Role Of Edem1 In The Quality Control And Degradation Of Misfolded Glycoproteins

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Abstract
Immature or incompletely assembled proteins that do not fold correctly are retained in the endoplasmic reticulum (ER) by quality control factors. Terminally misfolded glycoproteins are eventually sorted for dislocation out of the ER and ubiquitinated, leading to degradation by the 26S proteasome in a process termed ER-associated degradation (ERAD).

Mannose-trimming of glycans has been proposed to act as a sorting mechanism for the degradation of misfolded glycoproteins. EDEM1 (ER degradation-enhancing α-mannosidase-like 1) is hypothesized to extract misfolded proteins out of the calnexin cycle and sort them for degradation by recognizing a mannose-trimmed glycan. This extraction is proposed to be assisted by a direct interaction between the transmembrane domain of calnexin and a putative transmembrane domain of EDEM1. To investigate the role of EDEM1 in the quality control and degradation of misfolded glycoproteins, initially, the fundamental properties of EDEM1 were characterized. We observed that endogenous EDEM1 matures to a soluble protein that is heterogeneously glycosylated. This predominantly soluble phenotype was in disagreement with the proposed mechanism for EDEM1 extraction of misfolded glycoproteins from the calnexin binding cycle.

EDEM1 binding to misfolded proteins has been proposed to be mediated through the presence of a mannose-trimmed glycan on the misfolded substrate. After establishing an EDEM1 binding assay, we found that EDEM1 bound transiently associated with misfolded glycoproteins in a glycan-independent manner. EDEM1 was also found to bind SEL1L, an ERAD dislocation and ubiquitination complex adapter glycoprotein. Inhibition of mannose trimming with kifunensine or disruption of the EDEM1 mannosidase-like domain by mutation had no effect on EDEM1 substrate binding, but diminished its association with the SEL1L. Therefore, we propose a model where EDEM1 binds to misfolded glycoproteins in a glycan-independent manner and delivers the non-native cargo to the ERAD dislocation and ubiquitination complex using its mannosidase-like domain, which associates with SEL1L. This investigation presents an alternative hypothesis of the function of EDEM1 in the degradation of misfolded glycoproteins while also emphasizing the importance of glycans in the degradation of misfolded glycoproteins.