Endosome and Golgi-associated degradation (EGAD) of membrane proteins regulates sphingolipid metabolism

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Abstract

Cellular homeostasis requires the ubiquitin-dependent degradation of membrane proteins. This was assumed to be mediated exclusively either by endoplasmic reticulum associated degradation (ERAD) or by endosomal sorting complexes required for transport (ESCRT)-dependent lysosomal degradation. We identified in *Saccharomyces cerevisiae* an additional pathway that selectively extracts membrane proteins at Golgi and endosomes for degradation by cytosolic proteasomes [1]. One endogenous substrate of this endosome and Golgi-associated degradation pathway (EGAD) is the ER-resident membrane protein Orm2, a negative regulator of serine-palmitoyl transferase activity and hence sphingolipid biosynthesis. Orm2 degradation is initiated by phosphorylation via the target of repamycin complex 2 and its downstream kinases Ypk1/2, which triggers its ER export. Once on Golgi and endosomes, Orm2 is poly-ubiquitinated by the membrane-embedded 'Defective in SREBP cleavage' (Dsc) ubiquitin ligase complex. Cdc48/VCP then extracts ubiquitinated Orm2 from membranes, which is tightly coupled to its proteasomal degradation. Defective EGAD causes aberrant intracellular Orm2 accumulation, which disrupts sphingolipid homeostasis. Thus, the selective degradation of membrane proteins by EGAD maintains proteostasis and lipid homeostasis in eukaryotic cells.

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