The Relationship between ER Stress and Protein Quality Control at the Translocon

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Abstract

Multiple diseases are associated with elevated levels of endoplasmic reticulum (ER) stress, including some forms of cancer, neurodegeneration, and heart disease. ER stress arises when ER-resident proteins misfold and accumulate. Cells respond by activating multiple mechanisms which reduce ER stress. Our objective is to understand the relationship between ER stress and protein quality control at the endoplasmic reticulum, using Saccharomyces cerevisiae as a model organism. The ubiquitin-proteasome system (UPS) is responsible for the majority of degradation of misfolded and aberrant proteins at the ER (such as those arising during ER stress) through ER-associated protein degradation (ERAD). We have found ER stress differentially impairs ERAD pathways, including those mediated by the same ubiquitin ligase. For example, ER stress impairs degradation of translocon-associated proteins and of proteins with luminal degradation signals (ERAD-T and ERAD-L substrates, respectively). Degradation of these substrates is mediated by the Hrd1 ubiquitin ligase. In contrast, degradation of proteins with intramembrane degradation signals (ERAD-M substrates), which also requires Hrd1, was not impaired by ER stress. We compared the effects of ER stress caused by protein misfolding and of ER stress caused by disruption of lipid homeostasis on the degradation of ERAD-T substrates. We observed that ER stress caused by protein misfolding impaired ERAD-T. On the contrary, ERAD-T was unaffected by ER stress caused by disruption of lipid homeostasis. We then investigated the effects of different forms of stress on ERAD-T. We observed that oxidative stress and heat shock did not impair ERAD-T. We found that none of four characterized ER stress-sensing mechanisms were required for ERAD-T or its impairment by ER stress. Taken together, our results indicate that ER stress differentially impairs ER protein quality control mechanisms and suggest the existence of a novel ER stress-responsive mechanism that impairs ERAD-T. Understanding how the cell responds to ER stress may inform the treatment of diseases associated with stress.

The Unfolded Protein Response (UPR) & ER Surveillance (ERSU) pathways are not required for ERAD-T or its impairment by ER stress

The Stress-Induced Homeostatically Regulated Protein Degradation (SHRED) pathway is not required for ERAD-T or its impairment by ER stress

ERAD-L

ERAD-M

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Conclusions

- Characterized ER stress-sensing pathways are not required for ERAD-T or its impairment by ER stress.
- ERAD-T is specifically impaired by protein misfolding in the ER.
- A novel, uncharacterized ER stress response mechanism likely impairs ERAD-T.

Future Directions

- Identify other proteins that function in ERAD-T.
- Identify endogenous translocon-clogging proteins.
- Characterize novel ER stress response mechanism that impairs ERAD-T.