ABSTRACT

DISSERTATION/THESIS/RESEARCH PAPER/CREATIVE PROJECT: The Relationship between ER Stress and Protein Quality Control at the Translocon

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DATE: May 2020

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Endoplasmic reticulum (ER) stress arises when ER-resident proteins misfold and accumulate. Cells respond by activating multiple mechanisms which reduce ER stress, including the unfolded protein response (UPR), the ER surveillance (ERSU) pathway, the stress-induced homeostatically regulated protein degradation (SHRED) pathway, and the rapid ER stress-induced export (RESET) pathway. 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). Multiple diseases are associated with elevated levels of ER stress, including some forms of cancer, neurodegeneration, and heart disease. Previous work has indicated that ER stress caused by protein misfolding impairs ERAD of translocon-associated proteins (ERAD-T) in the model organism *Saccharomyces cerevisiae*. We compared the effects of ER stress caused by protein misfolding and 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 lipid perturbation. We also investigated the effects of different forms

of stress (oxidative stress, heat shock, and nutrient stress) on ERAD-T. We observed that general cellular stress did not impair ERAD-T. We tested whether known ER stress-sensing mechanisms (UPR, ERSU, SHRED, and RESET) are required for ERAD-T or its impairment during ER stress. We found that none of the characterized ER stress-sensing pathways tested were required for ERAD-T or its impairment by ER stress. These results suggest the existence of a novel ER stress-responsive mechanism that impairs ERAD-T. Finally, we determined if elevated abundance of an ERAD-T substrate itself induces ER stress, and found that it did. Understanding how the cell responds to ER stress may inform the treatment of such diseases associated with stress.