

## ABSTRACT

**THESIS:** CHARACTERIZING THE ROLE OF PHOSPHOLIPID SYNTHESIS IN PROTEIN QUALITY CONTROL

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Protein quality control (PQC) is an essential function for all living organisms, ensuring proper protein synthesis, folding, and clearance of potentially toxic, aberrant proteins in the cell. Impaired PQC is linked to human diseases such as Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and type 2 diabetes, underscoring its importance. The role of phospholipid synthesis in maintaining efficient PQC is incompletely characterized. Previous work shows that impaired phospholipid synthesis via *INO4* deletion stabilizes the translocon-clogging Hrd1 substrate *Deg1*\*-Sec62 in *Saccharomyces cerevisiae*. *INO4* is required for the synthesis of several phospholipids. It is unknown if selective disruption of phosphatidylcholine (PC) synthesis (whose synthesis is regulated by the Ino2/Ino4 master transcriptional regulator) results in similar stabilization of model ER-associated degradation (ERAD) substrates. I showed that impaired PC synthesis partially stabilizes *Deg1*\*-Sec62. The mechanism by which impaired phospholipid synthesis impairs ERAD is unknown. Prior research suggests that impaired phospholipid synthesis might globally impair

translocation into the ER. I determined that *INO4* deletion does not globally impair translocation, but partially impairs *Deg1*\*-Sec62 glycosylation. The breadth of the impact of impaired phospholipid synthesis on protein degradation is unclear. I showed that *INO4* deletion does not stabilize the soluble nucleoplasmic degradation substrate,  $\alpha 2$ \*-UH. I also showed that *INO4* deletion does not destabilize ER proteins Cue1 and Sbh1. Together, these results enhance our understanding of the impact phospholipid synthesis has on cellular physiology, potentially identifying unaccounted for features of human disorders associated with disrupted phospholipid synthesis.