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Abstract

Life requires the presence of proteins. These proteins can perform a variety of functions within the cell, from various aspects of cell regulation to DNA synthesis. Protein synthesis is essential, but just as important is the process of protein degradation. When a protein is no longer needed in the cell, is damaged, or behaves aberrantly, it must be degraded to prevent organismal harm. One way a protein can behave aberrantly is by persistently engaging with, or clogging, the translocon. The translocon is a protein channel that allows proteins to cross the membrane of the endoplasmic reticulum. A protein known to clog translocons in humans is a component of low-density lipoproteins (or “bad cholesterol”). In yeast, a ubiquitin ligase known as Hrd1 polyubiquitylates a translocon-clogging protein, tagging it for degradation. The proteasome detects polyubiquitylation and degrades tagged proteins, breaking them into short amino-acid chains. Ubiquitin ligases rarely function alone; they operate with accessory proteins called cofactors. Additionally, yeast lacking Hrd1 still exhibit residual degradation of translocon-clogging proteins, suggesting the existence of at least one alternative degradation pathway. A previous master’s student performed a genome-wide screen to identify genes that may play a role in degradation of translocon-clogging proteins. With over 150 genes identified in the screen, small-scale reporter assays were performed, confirming potential roles for 42 genes in protein degradation. These confirmed genes are being biochemically validated by cycloheximide chase to visualize protein degradation over time. The goal of this study is to validate genes that either work as cofactors to Hrd1 or in a parallel pathway. One gene identified in the screen is a transcription factor. The gene product is one subunit of a heterodimeric complex. In the work described here, roles for the genes encoding both components of the complex in degradation of translocon-associated proteins were confirmed. With the process of protein degradation being conserved in both yeast and humans, the gene may represent therapeutic targets for patients with elevated levels of cholesterol.

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