

Regulation of Endoplasmic Reticulum Stress Sensitivity by TORC1 Signalling in Yeast

Incorrect folding of secretory proteins in the endoplasmic reticulum (ER) results in an aberrant accumulation of misfolded proteins (ER stress) and activates a coping mechanism known as the unfolded protein response (UPR). While the mechanisms of UPR activation have been well established, how it integrates with other stress responses remains unclear.

Given that TORC1 is an important regulator of cell growth during protein misfolding stress, we sought to investigate how TORC1 signalling acts in parallel with the UPR to regulate ER stress sensitivity. Our studies employ the budding yeast, *Saccharomyces cerevisiae*, a biochemically traceable model organism that allows for extensive genetic manipulation.

Our results indicate that yeast cells carrying a hyperactive allele of *TORC1* (*TOR1^{L2134M}*) have increased sensitivity to canonical ER stressors and are inositol auxotrophs. Both phenotypes can be linked to a defective response to ER stress. Surprisingly, UPR activation and downregulation of ribosome biogenesis, two major consequences of ER stress, are equivalent between cells carrying a wild-type and hyperactive *TOR1* allele, suggesting that TORC1 controls other signalling events required to cope with secretory protein misfolding. Interestingly, ER stress tolerance in yeast depends on the activation of the cell wall integrity pathway, which is regulated by TORC1. Our results indicate that hyperactive *TOR1^{L2134M}* mutants are more sensitive to cell wall stressors and that the addition of sorbitol, a cell wall stabilizer, rescues ER stress sensitivity in hyperactive *TOR1^{L2134M}* mutants.

Overall, our studies in yeast may uncover new paradigms by which the response to protein misfolding is regulated.