

## INVITED LECTURE T4

### Protein quality control and ER stress tolerance

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The unfolded protein response (UPR) is an interorganellar signal transduction pathway that monitors endoplasmic reticulum (ER) homeostasis. Whole genome expression analysis in budding yeast has revealed nearly 400 genes regulated by the UPR. About half represent functions throughout the secretory pathway. The UPR target gene *KAR2* that encodes the ER chaperone BiP is particularly intriguing. BiP is a multi-functional protein whose activity is dictated through its recruitment to specific cofactors. Under stress, BiP mobilizes to misfolded proteins to maintain their solubility for ER-associated protein degradation (ERAD). BiP is also required for the translocation of newly synthesized proteins into the ER and their subsequent folding. BiP's essential functions of protein translocation and folding raise an interesting conundrum. Since half of UPR targets encode proteins that enter the secretory pathway, BiP is, in fact, an essential facilitator of the UPR at the stage of target protein synthesis. How then, do cells deploy the UPR when a key player is also immediately needed to deal with the misfolded products of stress? To address this question and to study the contribution of individual target genes to the ER stress response, we engineered a strain that specifically uncouples BiP regulation from the UPR without compromising the activation of other target genes. Under stress, BiP upregulation is essential for cell viability. We show that BiP upregulation is required to rid aberrant proteins through both the ERAD pathway and the ER-to-vacuolar overload pathway. Surprisingly, the essential functions of protein translocation and folding are unaffected when BiP levels becomes limiting under stress. This strategy allows cells to reduce its quality control functions to focus on the UPR until homeostasis is restored. The physiological importance of this "triage" mechanism was apparent because a temporary disruption of BiP essential functions is lethal. By contrast, cells can fully survive a temporary disruption of BiP's quality control functions.