A Chaperone Network Modulates the Homeostatic Regulation of the Unfolded Protein Response

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The unfolded protein response (UPR) is an intracellular signaling pathway that maintains proper function of the endoplasmic reticulum (ER), counteracting variable stresses that impair folding of proteins entering the secretory pathway. In that capacity, the UPR is at the center of many normal physiological responses and pathologies. In this study, we quantitatively interrogate the homeostatic capacity of the UPR. Moving between a predictive computational model and quantitative dynamic measurements, we establish how the ER chaperone BiP modulates the core ER stress sensor Ire1's activation and deactivation dynamics. Specifically, we demonstrate the ability of BiP binding to Ire1 and its dissociation in an ER stress-dependent manner to buffer the system against mild stresses. Furthermore, we show that BiP binding accelerates Ire1 deactivation when stress is removed. Therefore, BiP binding to Ire1 fine-tunes the dynamic behavior of the UPR by modulating its sensitivity and shutoff kinetics. The interaction between Ire1 and BiP to accomplish such intricate dynamic control may be a general paradigm for other systems in which proper signal sensing and amplification through oligomer formation and disassembly must be finely regulated.