Thermosensitivity of growth is determined by chaperone-mediated proteome reallocation - DTU Orbit (15/01/2019)

Thermosensitivity of growth is determined by chaperone-mediated proteome reallocation

Maintenance of a properly folded proteome is critical for bacterial survival at notably different growth temperatures. Understanding the molecular basis of thermostability has progressed in two main directions, the sequence and structural basis of protein thermostability and the mechanistic principles of protein quality control assisted by chaperones. Yet we do not fully understand how structural integrity of the entire proteome is maintained under stress and how it affects cellular fitness. To address this challenge, we reconstruct a genome-scale protein-folding network for Escherichia coli and formulate a computational model, FoldME, that provides statistical descriptions of multiscale cellular response consistent with many datasets. FoldME simulations show (i) that the chaperones act as a system when they respond to unfolding stress rather than achieving efficient folding of any single component of the proteome, (ii) how the proteome is globally balanced between chaperones for folding and the complex machinery synthesizing the proteins in response to perturbation, (iii) how this balancing determines growth rate dependence on temperature and is achieved through nonspecific regulation, and (iv) how thermal instability of the individual protein affects the overall functional state of the proteome. Overall, these results expand our view of cellular regulation, from targeted specific control mechanisms to global regulation through a web of nonspecific competing interactions that modulate the optimal reallocation of cellular resources. The methodology developed in this study enables genome-scale integration of environment-dependent protein properties and a proteome-wide study of cellular stress responses.

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