Evolutionary Diversification of Chaperonin Systems to Support Vectorial and Co-Translational Folding

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The GroEL/ES or Hsp60/10 chaperone system is essential and highly conserved for protein folding in all forms of life. In eukaryotes, the mitochondrial Hsp60/10 plays a crucial role in maintaining organellar proteostasis by assisting the folding of newly imported and synthesized proteins. Despite overall evolutionary conservation, different homologs show distinct substrate specificities and folding efficiencies. Using different multi-domain protein constructs, we show that the E. coli GroEL/ES folds two-domain proteins much less efficiently than single-domain proteins, both in vitro and in vivo.

In contrast, the human mitochondrial Hsp60/10 shows better folding efficiency for two-domain proteins in vivo, suggesting an enhanced capacity to assist complex substrates. Further, we demonstrate that the chaperone preferentially promotes folding when the slow-folding domain is positioned at the N-terminus, as opposed to the C-terminus, highlighting the importance of domain order in substrate recognition and folding. Ongoing investigations show the role of human Hsp60/10 in co-translational folding, where the chaperone may engage substrates as they emerge vectorially from the ribosome. Importantly, our previous findings suggested that the thermodynamic mechanism of substrate folding differs between the two systems, suggesting that the human mitochondrial Hsp60/10 may have evolved distinct folding strategies to meet the specialized demands of organellar proteostasis. These results provide important insights into how chaperone systems have evolved to cope with the increased complexity of eukaryotic proteomes, where multi-domain proteins are prevalent, contributing to the robustness of organellar protein homeostasis in higher eukaryotes.