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Interplay between chaperones and protein disorder promotes the evolution of protein networks.

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Abstract

Evolution is driven by mutations, which lead to new protein functions but come at a cost to protein stability. Non-conservative substitutions are of interest in this regard because they may most profoundly affect both function and stability. Accordingly, organisms must balance the benefit of accepting advantageous substitutions with the possible cost of deleterious effects on protein folding and stability. We here examine factors that systematically promote non-conservative mutations at the proteome level. Intrinsically disordered regions in proteins play pivotal roles in protein interactions, but many questions regarding their evolution remain unanswered. Similarly, whether and how molecular chaperones, which have been shown to buffer destabilizing mutations in individual proteins, generally provide robustness during proteome evolution remains unclear. To this end, we introduce an evolutionary parameter λ that directly estimates the rate of non-conservative substitutions. Our analysis of λ in Escherichia coli, Saccharomyces cerevisiae, and Homo sapiens sequences reveals how co- and post-translationally acting chaperones differentially promote non-conservative substitutions in their substrates, likely through buffering of their destabilizing effects. We further find that λ serves well to quantify the evolution of intrinsically disordered proteins even though the unstructured, thus generally variable regions in proteins are often flanked by very conserved sequences. Crucially, we show that both intrinsically disordered proteins and highly re-wired proteins in protein interaction networks, which have evolved new interactions and functions, exhibit a higher λ at the expense of enhanced chaperone assistance. Our findings thus highlight an intricate interplay of molecular chaperones and protein disorder in the evolvability of protein networks. Our results illuminate the role of chaperones in enabling protein evolution, and underline the importance of the cellular context and integrated approaches for understanding proteome evolution. We feel that the development of λ may be a valuable addition to the toolbox applied to understand the molecular basis of evolution.

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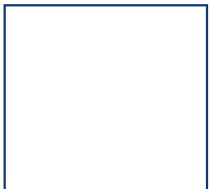

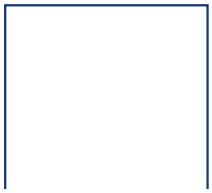

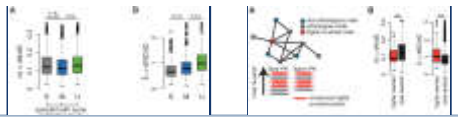

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