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Multiscale analysis of regulatory adaptive mutations

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Organisms living in natural changing environments require mechanisms to ensure survival in non-optimal conditions Adaptive evolution is a tool that enables the understanding of growth optimality principles. Through genome sequencing the genetic changes that lead to a new phenotype can be easily discovered[1]. However, their system wide effects are rarely understood. Mutations in regulatory genes are frequent in experimental evolution, nevertheless effects of these mutations in molecular phenotype have been detailed but the mechanisms that underlie the network reprogramming have not been decoded [2,3]. A convergence of recent technological developments allows for addressing this fundamental issue. Adaptive laboratory evolutions followed by whole-genome sequencing can be used to identify mutational hot-spots that alter the expression of bet-hedging functions. Genome engineering technologies can be used to generate many variants of the identified hot-spots for phenotypic characterization. High-throughput phenotypic assays and gene expression profiling elucidate the molecular and physiological consequences of the mutations. Finally, these data types can be integrated with a comprehensive genome-scale model[4] to quantify the proteomic and energetic requirements of bet-hedging maintenance functions. Here, we show that these capabilities together provide clear answers about the identity, proteomic and energetic resource requirements (maintenance coefficient can be reduced by 40%), and regulatory mechanisms of maintenance functions. We show that the expression of these functions comes at a cost of lower fitness in constant (i.e., steady-state) environments, but their expression can be perturbed by single amino acid changes in a regulatory protein. Structural and regulatory insights of mechanism of global network reprogramming are presented and their physiological implications for metabolic engineering highlighted.

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