Genetic robustness during environmental stress

Jonas Warringer

Department of Cell and Molecular Biology, Microbiology, Göteborg University
Medicinaregatan 9c, Box 462, SE-40530, Göteborg, Sweden

Abstract

Defining the cellular roles of proteins and how they functionally cooperate constitutes a central aim in biology. An important clue as to the function of proteins is how well an organism can grow and reproduce in different environments when particular proteins are missing, i.e. the ability of an organism to tolerate loss of these proteins. In this thesis, I describe a high-throughput methodology for the large-scale characterization of the consequences of loss of proteins in the yeast *Saccharomyces cerevisiae*. I demonstrate that the methodology, encompassing the cultivation of isogenic cultures of cells in a micro-scale format, may be applied on a genome-wide scale to precisely quantify the adaptation time, rate- and efficiency of growth of a complete collection of deletion strains. I find that the results obtained are reliable and coherent with earlier known phenotypic data; for example, quantifying the genetic robustness during saline stress on a genome-wide scale, ~80% of earlier known saline phenotypes were captured. In addition to verifying earlier reported data, profiling of the genetic robustness during conditions of saline, oxidative and reductive stress applying this approach, revealed many phenotypes previously not known, thus providing clues as to the function of hundreds of unclassified proteins. One example of previously functionally uncharacterized proteins that here are assigned functions on the basis of phenotypic data are five proteins, termed the Oca proteins, that were found to form a novel phosphatase complex vital for the proliferation during oxidative stress. Many of the previously unknown phenotypes were supported by data from other genome-wide approaches. In particular, I report on a high degree of overlap between gene dispensability data and data on physical interactions between proteins. Specifically, I find that protein complexes tend to be homogeneous with regards to the importance of its components, indicating that evolution favor modularization of essentially linear processes. The data reported here provide a coherent view of the ability of an organism to tolerate individual loss of each an every gene in a genome during environmental stress, allowing the deduction of fundamental design principles of life.

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