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Cellular Resilience and Fragility in Response to Environmental and Gene Expression Perturbations

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ABSTRACT

Cells are constantly subjected to perturbations. Whether these are extracellular or intracellular, they can be detrimental to cellular fitness. The cell has evolved elaborate systems and mechanisms that allow it to remain functional in the face of disturbances.

Cellular signal transduction can be summarised as the processes by which environmental stimuli is integrated with information on cellular status through the transmission of intracellular signals. This information is carried by specific proteins that operate jointly in signalling networks, or pathways. An important output of these pathways is to establish cellular responses to perturbations. To remain functional the signalling network must be robust to fluctuations in both environmental stimuli and levels of signalling components.

In this thesis it is investigated to what extent cellular fitness is affected by gene overexpression of signalling components. A high degree of fragility to increases in gene dosage was observed. This stands in stark contrast to overall system resilience to deletions of the same components. Fragile nodes were also dispersed over different classes of signalling components as well as throughout the signalling networks. The observed fragility patterns were further demonstrated to be largely independent of environmental and genotypic fluctuations suggesting fragility to be a product of local network architecture.

Cellular responses to the rare but toxic metalloid tellurite, in terms of gene-by-environment interactions, are also investigated. To genetically elucidate mechanisms of sensitivity and resistance to this compound a genome-wide collection of gene deletion mutants was screened in presence of tellurite. A metabolic pathway, the sulfate assimilation pathway, was found to be central to tellurite toxicity. Chemically related compounds were also shown to share a common toxicity mechanism.

Quantitative biology is central to this thesis and high-throughput high-resolution measurement regimes for microbial growth have been applied to all studies included herein. Phenomics is introduced and the different types of phenotyping strategies applied to studies in this thesis are elaborated on.

Keywords: *Saccharomyces cerevisiae*, phenomics, liquid microcultivation, tellurite, gene overexpression, gToW, cellular signalling, HOG, protein phosphatase

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