High-resolution Phenomics to Decode Yeast Stress Physiology

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ABSTRACT

Once the DNA sequence of an organism is known, the next step is to identify genes and their function. A straightforward endeavor to reveal gene function is to delete genes and analyse the resulting phenotype. When this is performed on a genome-wide scale, the term phenomics is applicable. In this thesis I quantified and resolved the growth behavior of individually cultivated *Saccharomyces cerevisiae* gene deletion strains into the three physiologically relevant growth variables adaptation time (time to adapt to a new environment), growth rate (kinetics of growth) and efficiency of growth (cell density increase). Applying this high-resolution methodology, the majority of earlier known phenotypes were captured, and a multitude of new phenotypes and cellular processes of importance for yeast growth in stress were revealed. An unexpectedly high proportion of mutants, 17%, exhibited at least three phenotypes and were denoted pleiotropic. Combined with existing measures on protein evolutionary rate, our data suggested that pleiotropy does not restrict evolution, and that evolutionary unrelated proteins, rather than related proteins, play a more important role in genetic robustness against mutations. Further applying the microcultivation methodology, seven signalling pathways previously not recognized to be required for cell proliferation during oxidative stress were identified. One of them, the Oca pathway, was completely novel. All of its five components, Oca1-5p, exhibited a similar phenotypic profile in a multitude of conditions. Further characterizing them, I systematically constructed ~30,000 double gene deletion mutants and scrutinized the whole yeast genome for genes leading to an exaggerated growth defect when deleted in an *oca* deletion strain. I also analysed transcriptional changes after exposure to an oxidant in all *oca* single and double gene deletion mutants, investigating ~400,000 transcript abundances. Applying these two complementary genome-wide techniques, I found that the Oca proteins primarily are involved in three cellular processes: *i)* regulation of carbohydrate metabolism, notably processes required for the production of reducing power, such as the pentose phosphate cycle, *ii)* activation of general stress defense mechanisms, and *iii)* regulation of protein fate mechanisms. Thus, besides providing a comprehensive view on the ability of an organism to tolerate loss of every non-essential gene in the genome, the high-resolution phenomics methodology applied here also identified a novel protein complex.

Keywords: *phenotypic profiling, stress, pleiotropy, Saccharomyces cerevisiae, Oca1p, Siw14p.*

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