Metabolic impact of redox cofactor perturbations in Saccharomyces cerevisiae

Redox cofactors play a pivotal role in coupling catabolism with anabolism and energy generation during metabolism. Therefore, cofactors are emerging to be attractive targets to induce widespread changes in metabolism. We present a detailed analysis of the impact of perturbations in redox cofactors in the cytosol or mitochondria on glucose and energy metabolism in Saccharomyces cerevisiae to aid metabolic engineering decisions that involve cofactor engineering. We enhanced NADH oxidation by introducing NADH oxidase or alternative oxidase, its ATP-mediated conversion to NADPH using NADH kinase as well as the interconversion of NADH and NADPH independent of ATP by the soluble, non-proton-translocating bacterial transhydrogenase. Decreasing cytosolic NADH level lowered glycerol production, while decreasing mitochondrial NADH lowered ethanol production. However, when these reactions were coupled with NADPH production, the metabolic changes were more moderated. The direct consequence of these perturbations could be seen in the shift of the intracellular concentrations of the cofactors. The changes in product profile and intracellular metabolite levels were closely linked to the ATP requirement for biomass synthesis and the efficiency of oxidative phosphorylation, as estimated from a simple stoichiometric model. The results presented here will provide valuable insights for a quantitative understanding and prediction of cellular response to redox-based perturbations for metabolic engineering applications.

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