Title:	A Genetic Screen To Identify Genes Influencing the Secondary Redox Couple NADPH/NADP+ in the Yeast Saccharomyces cerevisiae
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Abstract:	NADPH is an important cofactor in the cell. In addition to its role in the biosynthesis of critical metabolites, it plays crucial roles in the regeneration of the reduced forms of glutathione, thioredoxins and peroxiredoxins. The enzymes and pathways that regulate NADPH are thus extremely important to understand, and yet are only partially understood. We have been interested in understanding how NADPH fluxes are altered in the cell. We describe here both an assay and a genetic screen that allows one to discern changes in NADPH levels. The screen exploits the secondary redox property of NADPH. At low levels of glutathione we show that the redox contributions of NADPH become critical for growth, and we have used this to develop a genetic screen for genes affecting NADPH homeostasis. The screen was validated in pathways that both directly (pentose phosphate pathway) and indirectly (glycolytic pathway) affect NADPH levels, and was then exploited to identify mitochondrial genes that affect NADPH homeostasis. A total of 239 mitochondrial gene knockouts were assayed using this screen. Among these, several genes were predicted to play a role in NADPH homeostasis. This included several new genes of unknown function, and others of poorly defined function. We examined two of these genes, FMP40 which encodes a protein required during oxidative stress and GOR1, glyoxylate reductase. Our studies throw new light on these proteins that appear to be major consumers of NADPH in the cell. The genetic screen is thus predicted to be an exceedingly useful tool for investigating NADPH homeostasis.
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