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Impact of heterologous production of carotenoids on *S. cerevisiae* metabolism

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Heterologous production of high value chemicals like carotenoids has been performed in several yeasts species and recent advances in synthetic biology and biotechnology allowed spectacular yield improvements. Up to 18 mg / g dry cell weight β -carotene have been recently reported in *S. cerevisiae* (1) and even 90 mg / g dry cell weight in the lipophilic yeast *Y. lipolytica* (2), thus rendering these organisms economically viable sources of carotenoids for the cosmetic or pharmaceutical industry. But even though product yields have been improved dramatically, still little is known about the impact of this pathway introduction on yeast overall metabolism. Intermediary metabolites of a designated pathway can have different fates in the cell e.g. accumulation (leading to a pathway bottleneck), degradation (leading to a final product yield decrease) or toxicity (leading to a cell growth defect). To better understand how *S. cerevisiae* is affected by the heterologous production of carotenoids we constructed several strains producing different levels of geranylgeranyl diphosphate and phytoene, respectively the precursor and the first product of the carotenoids synthesis pathway. By then performing a transcriptomic analysis on these strains, we were able to detect the host metabolic response to different levels of carotenoids production. From the analysis of up- and down-regulated genes, we highlight the central role of acetyl-coA for the cell, as genes responsible for its utilization or liberation are overrepresented. Acetyl-coA is situated at the crossroad of many metabolic routes like the glucose metabolism, the lipid biosynthesis or the cellular respiration and this is also the first brick leading to carotenoid production. To go more into detail, we show that the production of high amounts of phytoene has a main effect on lipid beta-oxidation, protein acylation and pyruvate decarboxylation, all biological processes which are involved in acetyl-coA production and utilization. We are now constructing mutant strains to better understand to which extent modifying these biological processes has an impact on the availability of acetyl-coA and on the carotenoids production yield. Even though this work is restricted to a very specific heterologous pathway in one yeast specie, we believe that this innovative approach can be successfully applied to other pathways and hosts, thus giving researchers new tools to improve heterologous compound production in microorganisms.

- (1) Reyes LH, Gomez JM, Kao KC. 2014. Improving carotenoids production in yeast via adaptive laboratory evolution. *Metabolic engineering* 21:26-33
- (2) Larroude M, Celinska E, Back A, Thomas S, Nicaud JM, Ledesma-Amaro A. 2018. A synthetic biology approach to transform *Yarrowia lipolytica* into a competitive biotechnological producer of β -carotene. *Biotechnology and Bioengineering* 2:464-72

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