

Leucine Biosynthesis is Involved in Regulating High Lipid Accumulation in *Yarrowia lipolytica*

Eduard J. Kerkhoven*¹ (eduardk@chalmers.se), Young-Mo Kim², Siwei Wei², Carrie D. Nicora², Thomas L. Fillmore², Samuel O. Purvine², Bobbie-Jo Webb-Robertson³, Richard D. Smith², Scott E. Baker², Thomas O. Metz², **Jens Nielsen**¹

¹ Chalmers University of Technology, Gothenburg, Sweden; ² Earth and Biological Sciences Directorate, Pacific Northwest National Laboratory, Richland, WA; ³ National Security Directorate, Pacific Northwest National Laboratory, Richland, WA

Project Goals: Our goal is to elucidate the regulation of lipid metabolism in *Yarrowia lipolytica* to identify new targets to improve the TAG yield.

The yeast *Yarrowia lipolytica* is a potent accumulator of lipids and lipogenesis in this organism can be influenced by a variety of factors, such as genetics and environmental conditions. We have previously identified the involvement of the regulation of amino-acid metabolism to redirect flux to lipid accumulation [1]. We have followed up on this using a multifactorial study, thereby elucidating the effects of both genetic and environmental factors on regulation of lipogenesis in *Y. lipolytica* and identifying how two opposite regulatory states both result in lipid accumulation.

The study involved the comparison of a strain overexpressing diacylglycerol acyltransferase (*DGAI*) with a control strain grown under either nitrogen or carbon limited conditions. A strong correlation was observed between the responses on the levels of transcript and protein. Combination of *DGAI* overexpression with nitrogen limitation resulted in high-level of lipid accumulation accompanied by downregulation of various amino acid biosynthetic pathways, with leucine in particular, and these changes were further correlated with a decrease in metabolic fluxes.

The downregulation in leucine biosynthetic pathway genes was supported by a measured decrease in the level of 2-isopropylmalate, an intermediate of leucine biosynthesis. Combining the multi-omics data with putative transcription factor binding motifs uncovered a contradictory role for TORC1 in controlling lipid accumulation, likely mediated through 2-isopropylmalate and a Leu3-like transcription factor.

References

1. Kerkhoven EJ, Pomraning KR, Baker SE and Nielsen J. (2016) Regulation of amino-acid metabolism controls flux to lipid accumulation in *Yarrowia lipolytica*. npj Syst Biol App. doi:10.1038/npjbsa.2016.5

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