Leucine Biosynthesis Is Involved in Regulating High Lipid Accumulation in Yarrowia lipolytica

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. Using a multifactorial study, we elucidated the effects of both genetic and environmental factors on regulation of lipogenesis in Y. lipolytica and identified how two opposite regulatory states both result in lipid accumulation. This study involved comparison of a strain overexpressing diacylglycerol acyltransferase (DGA1) with a control strain grown under either nitrogen or carbon limitation conditions. A strong correlation was observed between the responses on the transcript and protein levels. Combination of DGA1 overexpression with nitrogen limitation resulted in a high level of lipid accumulation accompanied by downregulation of several amino acid biosynthetic pathways, including that of leucine in particular, and these changes were further correlated with a decrease in metabolic fluxes. This downregulation was supported by the 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. IMPORTANCE The ubiquitous metabolism of lipids involves refined regulation, and an enriched understanding of this regulation would have wide implications. Various factors can influence lipid metabolism, including the environment and genetics. We demonstrated, using a multi-omics and multifactorial experimental setup, that multiple factors affect lipid accumulation in the yeast Yarrowia lipolytica. Using integrative analysis, we identified novel interactions between nutrient restriction and genetic factors involving regulators that are highly conserved among eukaryotes. Given that lipid metabolism is involved in many diseases but is also vital to the development of microbial cell factories that can provide us with sustainable fuels and oleochemicals, we envision that our report introduces foundational work to further unravel the regulation of lipid accumulation in eukaryal cells.

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