Reprogramming Yeast Metabolism from Alcoholic Fermentation to Lipogenesis

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Engineering microorganisms for production of fuels and chemicals often requires major re-programming of metabolism to ensure high flux toward the product of interest [1]. This is challenging, as millions of years of evolution have resulted in establishment of tight regulation of metabolism for optimal growth in the organism's natural habitat.

Here, we show through metabolic engineering that it is possible to alter the metabolism of Saccharomyces cerevisiae from traditional ethanol fermentation to a pure lipogenesis metabolism, resulting in high-level production of free fatty acids [2]. Through metabolic engineering and process design, we altered subcellular metabolic trafficking, fine-tuned NADPH and ATP supply, and decreased carbon flux to biomass, enabling production of 33.4 g/L extracellular free fatty acids. We further demonstrate that lipogenesis metabolism can replace ethanol fermentation by deletion of pyruvate decarboxylase enzymes followed by adaptive laboratory evolution. Genome sequencing of evolved strains showed that pyruvate kinase mutations were essential for this phenotype.

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[2] Yu T*, Zhou Y .J.J*, Huang M, Liu Q, Pereira R, David F, Nielsen J: **Reprogramming Yeast Metabolism from Alcoholic Fermentation to Lipogenesis**. Cell 2018, **174**:1549-1558 e1514. (*co-first author)