Systematically redesigning and optimizing the expression of D-lactate dehydrogenase efficiently produces high-optical-purity D-lactic acid in Saccharomyces cerevisiae - DTU Orbit (02/08/2019)

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D-lactic acid (D-LA) is gaining increased attention as it can improve the thermostability of poly lactic acid. Acid-tolerant Saccharomyces cerevisiae is a good host for D-LA fermentation. High catalytic efficiency of D-lactate dehydrogenase (D-LDH, EC 1.1.1.28) is crucial for the production of D-LA in yeast. Here, a synthetic biology approach was used to construct high-producing D-LA strains by redesigning and optimization of D-LDH expression by a combination of different promoters, terminators and D-LDHs. The pyruvate decarboxylase-deficient mutant strain TAMH was used as host strain for optimizing the 40 D-LDH expression cassettes. The TCSt strain harboring the pTCSt plasmid with the TEF1 promoter, E. coli D-LDH and Synth25 synthetic short terminator produced 5.8 g/L D-LA with an optical purity of 99.9%. The production of D-LA was further improved by integrating this high expression cassette into the Ty1 transposable element of the YIP-01 strain with deleted Pdc1 and Pdc6. The resulting strain YIP-pTCSt-301 (CGMCC2.5726) was screened by a double enzyme-coupled system. Genomes sequencing of the strain revealed three copies of the D-LDH expression cassette. This strain was further improved by deleting the Jen1, Cyb2, Dld1, and Adh1 genes and the resulting strain YIP-J-C-D-A1 (CGMCC2.5783) produced 80.0 g/L D-LA with a yield of 0.6 g/g glucose and a volumetric productivity of 1.1 g/L/h in fed-batch fermentation under non-neutralization conditions.

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