Lipid engineering combined with systematic metabolic engineering of Saccharomyces cerevisiae for high-yield production of lycopene

Saccharomyces cerevisiae is an efficient host for natural-compound production and preferentially employed in academic studies and bioindustries. However, S. cerevisiae exhibits limited production capacity for lipophilic natural products, especially compounds that accumulate intracellularly, such as polyketides and carotenoids, with some engineered compounds displaying cytotoxicity. In this study, we used a nature-inspired strategy to establish an effective platform to improve lipid oil-triacylglycerol (TAG) metabolism and enable increased lycopene accumulation. Through systematic traditional engineering methods, we achieved relatively high-level production at 56.2mg lycopene/g cell dry weight (cdw). To focus on TAG metabolism in order to increase lycopene accumulation, we overexpressed key genes associated with fatty acid synthesis and TAG production, followed by modulation of TAG fatty acyl composition by overexpressing a fatty acid desaturase (OLE1) and deletion of Seipin (FLD1), which regulates lipid-droplet size. Results showed that the engineered strain produced 70.5mg lycopene/g cdw, a 25% increase relative to the original high-yield strain, with lycopene production reaching 2.37g/L and 73.3mg/g cdw in fed-batch fermentation and representing the highest lycopene yield in S. cerevisiae reported to date. These findings offer an effective strategy for extended systematic metabolic engineering through lipid engineering.

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Contributors: Ma, T., Shi, B., Ye, Z., Li, X., Liu, M., Chen, Y., Xia, J., Nielsen, J., Deng, Z., Liu, T.
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