Engineering Saccharomyces cerevisiae for biosynthesis of antioxidants

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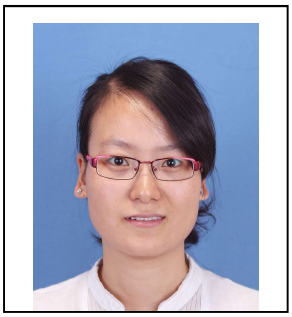

Abstract

Natural antioxidants are facing a fast growing global market. As an important chasiss organism, *S. cerevisiae* has been engineered to develop a variety of cell factories, delivering a vast range of valuable products. We have constructed *S. cerevisiae* strains for biosynthesis of tocotrienols, an important form of the essential nutrient and common antioxidant vitamin E, and astaxanthin, the most potent natural antioxidant found so far, by means of gene mining, protein engineering and metabolic engineering.

Biosynthesis of the bioactive 3S, 3'S-astaxanthin was made possible by introduction of the algal β-carotene ketolase and hydroxylase genes into a β-carotene-hyperproducing *S. cerevisiae* strain. Elevation of precursor supply and accelerated conversion of β-carotene to astaxanthin by directed evolution of the key enzymes further improved the astaxanthin yield. Finally, employment of a temperature-responsive dynamic regulation system facilitated high-density fermentation of astaxanthin, achieving the highest ever astaxanthin titer by engineered yeasts.

Although biosynthesis of δ-tocotrienol in *E. coli* had been reported in 2008, the low yields and biosafety concerns discourage its further application in biotechnological production. Considering the GRAS (generally regarded as safe) nature of *S. cerevisiae* and its outstanding performance in heterologous production of terpenoids and aromatic compounds, we attempted to construct a tocotrienols biosynthetic pathway by introducing the key genes cloned from photosynthetic organisms, resulting in detection of γ-tocotrienol and α-tocotrienol in recombinant yeast strains. Subsequent identification and elimination of rate-limiting steps in addition to strengthening of precursor supply led to improved yields of tocotrienols. This is for the first time biosynthesis of these tocotrienols is made possible in nonphotosynthetic hosts.

Brief Biography

Dr. Lidan Ye received her Bachelor and Master degree from Zhejiang University in 2004 and 2006, respectively, and got her PhD in 2010 from Friedrich-Schiller University of Jena in Germany. After that, she worked in National University of Singapore and Institute of Chemical Engineering and Sciences (A*STAR) as a postdoctoral research fellow. Since 2013, she has been a faculty member as a Lecturer (2013-2014) and Associate Professor (2015-now) in Zhejiang University. Her research interest lies in metabolic engineering of microorganisms for biosynthesis of terpenes and other valuable natural products. She has published 55 peer-reviewed papers in journals including *Metabolic Engineering*, *Biotechnology and Bioengineering*, *ACS Synthetic Biology,* etc.

Brief CV

Lidan Ye, Ph.D.

Colledge of Chemical and Biological Engineering, Zhejiang University

Education:

B.S Biological Sciences, Zhejiang University, China, 2004

M.S Microbiology, Zhejiang University, China, 2006

Ph.D. Biology, Friedrich-Schiller University of Jena, Germany, 2010

Professional Career:

2010.8-2013.2: National University of Singapore, Singapore, Research Fellow.

2013.3-2013.8:Institute of Chemical Engineering and Sciences, A*STAR, Singapore, Scientist.

2013.8-2014.12: Zhejiang University, China, Lecturer.

2015.1-present: Zhejiang University, China, Associate Professor.

Research Interests:

1. Protein Engineering
2. Development of Metabolic Regulation Strategies
3. Biosynthesis of Terpernes and Derivatives

Selected publications

1. Zhou, P. et al. ***J. Agric. Food Chem.***, 2019, 67 (4), 1072–1080.
2. Zhou, P. et al. ***Biotechnol. Bioeng.***, 2018, 115(5):1321-1330.
3. Ye, L. et al. ***Metab. Eng.***, 2016, 38:125-138.
4. Wang, F. et al. ***Metab. Eng.***, 2017, 39:257-266.
5. Lv, X. et al. ***Biotechnol. Bioeng.***, 2016, 113(12):2661-2669.
6. Yao, Z. et al. ***ACS Synth. Biol.***, 2018, 7(9):2308-2316.
7. Ye, L. et al. ***Appl. Microbiol. Biotechnol.***, 2018, 102(2):559-567.
8. Lv, X. et al. ***J. Biotechnol.***, 2014, 186: 128–136.
9. Zhou, P. et al. ***Enzyme Microb.Technol.***, 2017, 100: 28-36.
10. Jiang, L. et al. ***Proc. Biochem.*** 2014, 49(7):1135–1138.