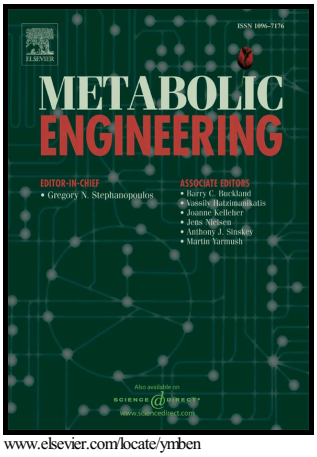

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Engineering *Saccharomyces cerevisiae* for production of simvastatin

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Abstract

Simvastatin is a semisynthetic cholesterol-lowering medication and one of the top-selling statins in the world. Currently, industrial production of simvastatin acid (SVA) is a multistep process starting from the natural product lovastatin. For this reason, there is significant interest in direct production of simvastatin from a microbial host. In this study, six heterologous biosynthetic genes were introduced into *Saccharomyces cerevisiae* and the acyl-donor dimethylbutyryl-*S*-methyl mercaptopropionate (DMB-SMMP) was added, resulting in initial production of 0.5 mg/L SVA. Switching the yeast strain from JHY686 to BJ5464-NpgA increased total polyketide production to over 60 mg/L and conversion from dihydromonacolin L acid to monacolin J acid (MJA) was increased from 60 to 90% by tuning the copy number of the P450 *lovA*. Increasing the media pH to 8.7 led to a further 10-fold increase in SVA production. Optimized chemical lysis of the cell walls *in situ* after maximum MJA production led to 55 mg/L SVA titer, representing nearly complete conversion from MJA and a 110-fold increase in titer from the initial SVA production strain. The yeast strains developed in this work can be used as an alternative production method for SVA, and the strategies employed can be broadly