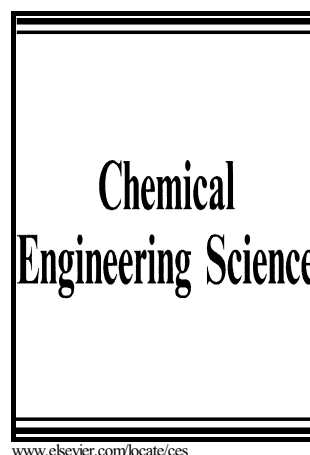


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Engineering of the Terpenoid Pathway in *Saccharomyces cerevisiae* Co-overproduces Squalene and the Non-terpenoid Compound Oleic acid

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Abstract

The balanced and optimal expression of genes in an engineered pathway is a prerequisite for the overproduction of a natural compound in a customized strain. Hence, 13 new constitutive promoters were characterized and optimized for overexpressing genes in the squalene biosynthetic pathway (SB) and squalene overproduction in *S. cerevisiae*. Subsequently, these newly characterized promoters were employed for overexpressing genes in the mevalonate pathway; as a result, 29.41-fold (100 mg/L) more squalene was produced in the engineered strain (FOH-0) than in the wild-type strain (WS). Afterward, the entire squalene biosynthetic pathway was upregulated with the newly characterized promoters to engineer the FOH-2 strain, and it resulted in the production of 304.16 mg/L of squalene after inhibition of squalene monooxygenase with terbinafine. The FOH-2 strain also overproduced 154.94 mg/L oleic acid, and this was perhaps because of an indirect upregulation of the oleic acid biosynthetic pathway by an unknown regulatory mechanism. The production of ergosterol and biomass in the FOH-2 strain was also increased by up to 34 mg/L and 13.5 g DW/L, respectively, compared to the WS strain. Consequently, the overexpression of genes in the SB pathway increased the production of squalene, oleic acid, ergosterol and biomass by 89.46-, 4.66-, 3.37- and 2.25-fold, respectively, in the FOH-2 strain compared to the WS strain. The growth rate of the FOH-2 strain was also 1.3-fold higher than the WS strain.

Finally, our study reports the enhanced coproduction of squalene, ergosterol, oleic acid and biomass in yeast due to the overexpression of genes in the SB pathway by newly characterized constitutive promoters. It also shows that ergosterol overproduction indirectly upregulates its complementary pathway.

Keywords: *Saccharomyces cerevisiae*, promoters, squalene biosynthetic pathway, squalene, oleic acid, terpenoid.

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