Effects of acetoacetyl-CoA synthase expression on production of farnesene in Saccharomyces cerevisiae

Efficient production of sesquiterpenes in Saccharomyces cerevisiae requires a high flux through the mevalonate pathway. To achieve this, the supply of acetyl-CoA plays a crucial role, partially because nine moles of acetyl-CoA are necessary to produce one mole of farnesyl diphosphate, but also to overcome the thermodynamic constraint imposed on the first reaction, in which acetoacetyl-CoA is produced from two moles of acetyl-CoA by acetoacetyl-CoA thiolase. Recently, a novel acetoacetyl-CoA synthase (nphT7) has been identified from Streptomyces sp. strain CL190, which catalyzes the irreversible condensation of malonyl-CoA and acetyl-CoA to acetoacetyl-CoA and, therefore, represents a potential target to increase the flux through the mevalonate pathway. This study investigates the effect of acetoacetyl-CoA synthase on growth as well as the production of farnesene and compares different homologs regarding their efficiency. While plasmid-based expression of nphT7 did not improve final farnesene titers, the construction of an alternative pathway, which exclusively relies on the malonyl-CoA bypass, was detrimental for growth and farnesene production. The presented results indicate that the overall functionality of the bypass was limited by the efficiency of acetoacetyl-CoA synthase (nphT7). Besides modulation of the expression level, which could be used as a means to partially restore the phenotype, nphT7 from Streptomyces glaucescens showed clearly higher efficiency compared to Streptomyces sp. strain CL190.