Enhancement of Farnesyl Diphosphate Pool as Direct Precursor of Sesquiterpenes Through Metabolic Engineering of the Mevalonate Pathway in Saccharomyces cerevisiae - DTU Orbit (01/03/2019)

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The mevalonate pathway in the yeast Saccharomyces cerevisiae was deregulated in order to enhance the intracellular pool of farnesyl diphosphate (FPP), the direct precursor for the biosynthesis of sesquiterpenes. Overexpression of the catalytic domain of HMG1, both from the genome and plasmid, resulted in higher production of cubebol, a plant originating sesquiterpene, and increased squalene accumulation. Down-regulation of ERG9 by replacing its native promoter with the regulatable MET3 promoter, enhanced cubebol titers but simultaneous overexpression of tHMG1 and repression of ERG9 did not further improve cubebol production. Furthermore, the concentrations of squalene and ergosterol were measured in the engineered strains. Unexpectedly, significant accumulation of squalene and restoring the ergosterol biosynthesis were observed in the ERG9 repressed strains transformed with the plasmids harboring cubebol synthase gene. This could be explained by a toxicity effect of cubebol, possibly resulting in higher transcription levels for the genes under control of MET3 promoter, which could lead to accumulation of squalene and ergosterol. Biotechnol. Bioeng. 2010;106: 86-96.