Engineered Production of Short-Chain Acyl-Coenzyme A Esters in Saccharomyces cerevisiae

Short-chain acyl-coenzyme A esters serve as intermediate compounds in fatty acid biosynthesis, and the production of polyketides, biopolymers and other value-added chemicals. S. cerevisiae is a model organism that has been utilized for the biosynthesis of such biologically and economically valuable compounds. However, its limited repertoire of short-chain acyl-CoAs effectively prevents its application as a production host for a plethora of natural products. Therefore, we introduced biosynthetic metabolic pathways to five different acyl-CoA esters into S. cerevisiae. Our engineered strains provide the following acyl-CoAs: propionyl-CoA, methylmalonyl-CoA, n-butyryl-CoA, isovaleryl-CoA and n-hexanoyl-CoA. We established a yeast-specific metabolite extraction protocol to determine the intracellular acyl-CoA concentrations in the engineered strains. Propionyl-CoA was produced at 4-9 μM; methylmalonyl-CoA at 0.5 μM; and isovaleryl-CoA, n-butyryl-CoA, and n-hexanoyl-CoA at 6 μM each. The acyl-CoAs produced in this study are common building blocks of secondary metabolites and will enable the engineered production of a variety of natural products in S. cerevisiae. By providing this toolbox of acyl-CoA producing strains, we have laid the foundation to explore S. cerevisiae as a heterologous production host for novel secondary metabolites.

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