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Introduction:

Microbial biosynthesis of isoprene provides an attractive and potentially alternative route to the sustainable development of isoprene-related industries. In addition to the common advantages of using microbial systems for production of natural products, such as the ease of pathway engineering and the ability for large-scale fermentation, the use of microbial platforms for isoprene production can also simplify downstream processes due to the volatile and hydrophobic nature of isoprene, which can be easily condensed from the gas phase in bioreactors, with no need for additional purification. In nature, there are two distinct biochemical pathways involved for production of isoprenoids, the mevalonate (MVA) pathway and methylerythritol phosphate (MEP) pathway. With some exceptions, the MVA pathway is typically found in eukaryotes, whereas the MEP pathway is present in most bacteria and green algae. Although no ISPS gene (encoding isoprene synthase) has been elucidated in any microorganism, overexpression of ISPS gene from plants can effectively endow microorganisms with the capability of isoprene production using their own metabolic pathways. In yeast, acetyl-CoA is produced and consumed in different compartments, especially the cytoplasm and mitochondria. Recently, much of the work on enhancing isoprenoid production has been targeted to improve acetyl-CoA supply and utilization; however, all of these studies focused on cytoplasmic engineering on the account of the MVA pathway being located in cytoplasm. In contrast, engineering of mitochondrial acetyl-CoA metabolism has largely been ignored.

In the present work, the authors have explored the potential capacity of *S. cerevisiae* in isoprene biosynthesis by dual regulation of cytoplasmic and mitochondrial acetyl-CoA utilization.

Dual regulation of cytoplasmic and mitochondrial acetyl-CoA utilization for improved isoprene production in *Saccharomyces cerevisiae.*

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Abstract:

Microbial production of isoprene from renewable feedstock is a promising alternative to traditional petroleum-based processes. Currently, efforts to improve isoprenoid production in *Saccharomyces cerevisiae* mainly focus on cytoplasmic engineering, whereas comprehensive engineering of multiple subcellular compartments is rarely reported. Here, we propose dual metabolic engineering of cytoplasmic and mitochondrial acetyl-CoA utilization to boost isoprene synthesis in *S. cerevisiae*. This strategy increases isoprene production by 2.1-fold and 1.6-fold relative to the recombinant strains with solely mitochondrial or cytoplasmic engineering, respectively. By combining a modified reiterative recombination system for rapid pathway assembly, a two-phase culture process for dynamic metabolic regulation, and aerobic fed-batch fermentation for sufficient supply of acetyl-coA and carbon, we achieve 2527 mg/L of isoprene, which is the highest ever reported in engineered eukaryotes. We propose this strategy as an efficient approach to enhancing isoprene production in yeast, which might open new possibilities for bio-production of other value-added chemicals