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Engineered *Saccharomyces cerevisiae* for *de novo* biosynthesis of curcumin

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Extensive research has been conducted on curcumin, a polyphenolic compound found in turmeric (*Curcuma longa*), due to its potential as a natural cancer-fighting drug. However, curcumin exhibits limited accumulation levels in the plant over an extended period, and its extraction is costly and ineffective. Curcumin biosynthesis involves the phenylpropanoid pathway, which converts aromatic amino acids into ferulic acid, its precursor. Subsequently, 4-coumarate-CoA ligase and type III polyketide synthases (PKSs) convert ferulic acid into curcumin using malonyl-CoA as an extender substrate. Here, we present the pioneering development of a genetically modified *Saccharomyces cerevisiae* strain able to produce curcumin from glucose. We used CRISPR-Cas9 to genome integrate the curcumin biosynthetic pathway. Initially, curcumin synthesis from supplemented ferulic acid was evaluated. We tested different enzyme combinations and the highest curcumin levels were obtained using a bacterial feruloyl-CoA synthetase and type III PKSs from *C. longa*. Subsequently, we employed *p*-coumaric acid-overproducing *S. cerevisiae* strain, enabling the expression of the enzymes responsible for the conversion of p-coumaric into ferulic acid. These enzymes included caffeic acid O-methyltransferase from *Arabidopsis thaliana* and two components of the bacterial enzyme 4-hydroxyphenylacetate 3-hydroxylase (HpaB/C). After confirming the successful biosynthesis of ferulic acid, the remaining part of the pathway required for curcumin synthesis was expressed in this strain. The resulting strain was able of produce curcumin from glucose. Next, to reduce *p*-coumaric acid accumulation, an additional copy of HpaB/C was integrated. As a result, the final strain exhibited a significant improvement, yielding a curcumin titer of 2.1 mg/L.