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Engineering Escherichia coli for Production of Short Chain Fatty Acid by Exploiting Fatty Acid Metabolic Pathway

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Abstract : Worldwide demand of natural and sustainable fuels and chemicals have encouraged researchers to develop microbial platform for synthesis of short chain fatty acids as they are useful precursors to replace petroleum-based fuels and chemicals. In this study, we evaluated the role of fatty acid synthesis and β-oxidation cycle of Escherichia coli to produce butyric acid, a 4-carbon short chain fatty acid, with the help of three thioesterases, i.e., TesAT from Anaerococcus tetradius, TesBF from Bryantella formatexigens and TesBT from Bacteroides thetaiotaomicron. We found that E. coli strain transformed with gene for TesBT and grown in presence of 8 g/L glucose produced maximum butyric acid titer at 1.46 g/L, followed by that of TesBF at 0.85 g/L and TesAT at 0.12 g/L, indicating that these thioesterases were efficiently converting short chain fatty acyl-ACP intermediate of fatty acid synthesis pathway into the corresponding acid. The titer of butyric acid varied significantly depending upon the plasmid copy number and strain genotype. Deletion of genes for fatty acyl-CoA synthetase and acyl-CoA dehydrogenase, which are involved in initiating the fatty acid degradation cycle, and overexpression of FadR, which is a dual transcriptional regulator and exerts negative control over fatty acid degradation pathway, reduced up to 30% of butyric acid titer. This observation suggested that β-oxidation pathway is working synergistically with fatty acid synthesis pathway in production of butyric acid. Moreover, accelerating the fatty acid elongation cycle by overexpressing acetyl-CoA carboxyltransferase (Acc) and 3-hydroxy-acyl-ACP dehydratase (FabZ) or by deleting FabR, the transcription suppressor of elongation, did not improve the butyric acid titer, rather favored the long chain fatty acid production. Finally, a balance between cell growth and butyric acid production was achieved with the use of phosphorous limited growth medium and 14.3 g/L butyric acid, and 17.5 g/L total free fatty acids (FFAs) titer was achieved during fed-batch cultivation. We have engineered an E. coli strain which utilizes the intermediate of both fatty acid synthesis and degradation pathway, i.e. butyryl-ACP and -CoA, to produce butyric acid from glucose. The strategy used in this study resulted in highest reported titers of butyric acid and FFAs in engineered E. coli.

Keywords : butenoic acid, butyric acid, Escherichia coli, fed-batch fermentation, short chain fatty acids, thioesterase
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