Rational design of flavonoid production routes using combinatorial and precursor-directed biosynthesis.

Kufs JE, Hoefgen S, Rautschek J, Bissell AU, Graf C, Fiedler J, Braga D, Regestein L, Rosenbaum MA, Thiele J, Valiante V (2020) Rational design of flavonoid production routes using combinatorial and precursor-directed biosynthesis. *ACS Synth Biol* 9(7), 1823-1832.

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PubMed
OPEN ACCESS
PAPER

Abstract

Combinatorial biosynthesis has great potential for designing synthetic circuits and amplifying the production of new active compounds. Studies on multienzyme cascades are extremely useful for improving our knowledge on enzymatic catalysis. In particular, the elucidation of enzyme substrate promiscuity can be potentially used for bioretrosynthetic approaches, leading to the design of alternative and more convenient routes to produce relevant molecules. In this perspective, plant-derived polyketides are extremely adaptable to those synthetic biological applications. Here, we present a combination of an in vitro CoA ligase activity assay coupled with a bacterial multigene expression system that leads to precursor-directed biosynthesis of 21 flavonoid derivatives. When the vast knowledge from protein databases is exploited, the herein presented procedure can be easily repeated with additional plant-derived polyketides. Lastly, we report an efficient in vivo

expression system that can be further exploited to heterologously express pathways not necessarily related to plant polyketide synthases.

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Identifier

doi: 10.1021/acssynbio.0c00172

PMID: 32525654