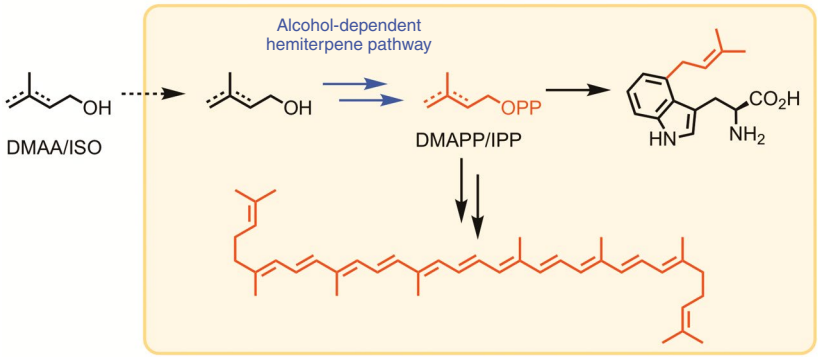
ISOPRENOIDS

Shortcut for isoprenoid biosynthesis

ACS Synth. Biol. http://doi.org/cz3c (2019)



Credit: American Chemical Society 2019

Isoprenoids are a diverse class of natural products which find application in many industries, for example as drugs and fragrances. Their biosynthesis involves the use of dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) as central building blocks. For the biosynthesis of DMAPP and IPP, nature employs two alternative hemiterpene biosynthetic pathways that are lengthy and highly substrate specific. Therefore, these pathways are difficult to engineer to accept non-natural analogues for the biosynthesis of artificial isoprenoids from simple precursors. In addition, direct feeding of DMAPP and IPP analogues to cells has generally not proven successful due to the negative charge of the pyrophosphate group which lowers the cell permeability of these compounds.

Now, a team led by Gavin J Williams at North Carolina State University reports the in vivo synthesis of DMAPP and IPP via an artificial alcohol-dependent hemiterpene biosynthesis pathway. First, they cloned the enzymes IPK and PhoN from *Thermoplasma acidophilum* and *Shigella flexneri*, respectively. Then, the compounds isopentenol (ISO) and dimethylallyl alcohol (DMAA) were added to the culture medium and efficiently taken up by the *Escherichia coli* cells. Via a stepwise phosphorylation of the alcohol moiety by IPK and PhoN, the required diphosphates (DMAPP, IPP) were produced in vivo. The researchers showcased the functionality of this system by the production of lycopene and a prenylated tryptophan in *E. coli*. Remarkably, this simplified artificial pathway revealed to be equally productive as its natural counterparts.

Further experiments are required to explore the promiscuity of this artificial pathway for the production of unnatural DMAPP and IPP analogues by supplementation of derivative alcohols of ISO and DMAA. Certainly, it appears easier to engineer such promiscuity into this short artificial pathway compared to the natural ones, which involve significantly more enzymes. Then, with the in vivo produced analogues of DMAPP and IPP, the promiscuity and plasticity of the downstream isoprenoid biosynthesis can be tested for the production of complex, unnatural isoprenoids.

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Published online: 13 February 2019
https://doi.org/10.1038/s41929-019-0240-8