CHEMICAL BIOLOGY

A bacterial treasure trove

A newly identified bacterial biosynthetic pathway enables the production of nonstandard amino acids.

Terminal alkyne amino acids can be used for Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions, which makes them of interest for protein-labeling applications. The soil bacterium *Streptomyces cattleya* synthesizes the two related terminal alkyne amino acids β -ethynylserine (β es) and L-propargylglycine (Pra), which differ in the hydroxylation of the β -carbon.

Michelle Chang at the University of California, Berkeley, and her colleagues used a comparative genomic approach to identify the genes of the β es biosynthetic pathway. They found one cluster encoding BesABCDE in *S. cattleya*, which is not present in *Streptomyces* species that do not produce β es. The authors generated *S. cattleya* strains in which these genes were deleted and then used comparative

metabolomics experiments to identify the precursors and intermediates of the β es pathway. In the first step, the halogenase BesD chlorinates the substrate lysine to 4-Cl-lysine. BesC catalyzes the oxidative C–C cleavage of 4-Cl-lysine, yielding the alkene intermediate 4-Cl-allylglycine, which is converted to Pra by BesB. β es is not formed directly by hydroxylation of Pra. Instead, BesA catalyzes the reaction of glutamate with Pra, and the γ -Glu-Pra intermediate is formed. γ -Glu-Pra is hydroxylated by BesE, forming γ -Glu- β es, and yet unknown cellular hydrolases then release β es.

The researchers reconstituted γ -Glu- β es biosynthesis in vitro. Pra and the pathway intermediates can be produced in *Escherichia coli* by coexpression of the β es cluster genes. The authors demonstrated

that Pra was incorporated into the *E. coli* proteome when they used an engineered Pra-specific aminoacyl-tRNA synthase and labeled Pra-containing protein extracts with a fluorescent dye via the CuAAC reaction.

The β es pathway enzymes enable the synthesis of halo, terminal alkene, and alkyne amino acids in cells, and these nonstandard amino acids could be incorporated into proteins by genetic code expansion for a variety of applications.

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Research papers

Marchand, J. A. et al. Discovery of a pathway for terminal-alkyne amino acid biosynthesis. *Nature* **567**, 420–424 (2019).

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