Reprogramming nonribosomal peptide synthetases for "clickable" amino acids

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Abstract

Nonribosomal peptide synthetases (NRPSs) are multifunctional enzymes that produce a wide array of bioactive peptides. Here we show that a single tryptophan-to-serine mutation in phenylalanine-specific NRPS adenylation domains enables the efficient activation of non-natural aromatic amino acids functionalized with azide and alkyne groups. The resulting 10(5)-fold switch in substrate specificity was achieved without appreciable loss of catalytic efficiency. Moreover, the effective communication of the modified A domains with downstream modules in dipeptide synthetases permitted incorporation of O-propargyl-L-tyrosine into diketopiperazines both in vitro and in vivo, even in the presence of competing phenylalanine. Because azides and alkynes readily undergo bioorthogonal click reactions, reprogramming NRPSs to accept non-natural amino acids that contain these groups provides a potentially powerful means of isolating, labeling, and modifying biologically active peptides.

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