Engineering DNA-Templated Nonribosomal Peptide Synthesis.

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Projects

Combinatorial biosynthesis of nonribosomal peptide antibiotics
Details

Abstract

Diffusive escape of intermediates limits the rate enhancement that nanocontainers or macromolecular scaffolds can provide for artificial biocatalytic cascades. Nonribosomal peptide synthetases (NRPSs) naturally form gigantic assembly lines and prevent escape by covalently tethering intermediates. Here, we have built DNA-templated NRPS (DT-NRPS) by adding zinc-finger tags to split NRPS modules. The zinc fingers direct the NRPS modules to 9-bp binding sites on a DNA strand, where they form a catalytically active enzyme cascade. Geometric constraints of the DT-NRPSs were investigated using the template DNA as a molecular ruler. Up to four DT-NRPS modules were assembled on DNA to synthesize peptides. DT-NRPSs outperform previously reported DNA-templated enzyme cascades in terms of DNA acceleration, which demonstrates that covalent intermediate channeling is possible along the DNA template. Attachment of assembly line enzymes to a DNA scaffold is a promising catalytic strategy for the sequence-controlled biosynthesis of nonribosomal peptides and other polymers.

Identifier

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