A non-canonical peptide synthetase adenylates 3-methyl-2-oxovaleric acid for auriculamide biosynthesis.

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Projects

Investigation of polyketide biosynthesis in agaricomycetes
Details

Abstract

Auriculamide is the first natural product known from the predatory bacterium Herpetosiphon aurantiacus. It is composed of three unusual building blocks, including the non-proteinogenic amino acid 3-chloro-L-tyrosine, the α-hydroxy acid L-isoleucic acid, and a methylmalonyl-CoA-derived ethane unit. A candidate genetic locus for auriculamide biosynthesis was identified and encodes four enzymes. Among them, the non-canonical 199 kDa four-domain nonribosomal peptide synthetase, AulA, is extraordinary in that it features two consecutive adenylation domains. Here, we describe the functional characterization of the recombinantly produced AulA. The observed activation of 3-methyl-2-oxovaleric acid by the enzyme supports the hypothesis that it participates in the biosynthesis of auriculamide. An artificially truncated version of AulA that lacks the first adenylation domain activated this substrate like the full-length enzyme which shows that the first adenylation domain is dispensable. Additionally, we provide evidence that the enzyme tolerates structural variation of the substrate. α-Carbon substituents significantly affected the substrate turnover. While all tested aliphatic α-keto acids were accepted by the enzyme and minor differences in chain size and branches did not interfere with the enzymatic activity, molecules with methylene α-carbons led to low turnover. Such enzymatic plasticity is an important attribute to help in the perpetual search for novel molecules and to access a greater structural diversity by mutasynthesis.

Identifier

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