

Loss of single domain function in modular assembly line alters size and shape of complex polyketide.

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Abstract

The structural wealth of complex polyketide metabolites produced by bacteria results from intricate, highly evolved biosynthetic programs of modular assembly lines, in which the number of modules defines the size of the backbone, and the domain composition controls the degree of functionalization. We report a remarkable case where polyketide chain length and scaffold depend on the function of a single b-keto processing domain: A ketoreductase domain represents a switch between diverging biosynthetic pathways leading either to the antifungal aureothin or to the nematocidal luteoreticulins. By a combination of heterologous expression, mutagenesis, metabolite analyses, and in vitro biotransformation we elucidate the factors governing non-colinear polyketide assembly involving module skipping and demonstrate that a simple point mutation in type I polyketide synthase (PKS) can have a dramatic effect on the metabolic profile. This finding sheds new light on possible evolutionary scenarios and may inspire future synthetic biology approaches.

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