

Emulating evolutionary processes to morph aureothin-type modular polyketide synthases and associated oxygenases.

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Abstract

Polyketides produced by modular type I polyketide synthases (PKSs) play eminent roles in the development of medicines. Yet, the production of structural analogs by genetic engineering poses a major challenge. We report an evolution-guided morphing of modular PKSs inspired by recombination processes that lead to structural diversity in nature. By deletion and insertion of PKS modules we interconvert the assembly lines for related antibiotic and antifungal agents, aureothin (aur) and neo-aureothin (nor) (aka spectinabilin), in both directions. Mutational and functional analyses of the polyketide-tailoring cytochrome P450 monooxygenases, and PKS phylogenies give contradictory clues on potential evolutionary scenarios (generalist-to-specialist enzyme evolution vs. most parsimonious ancestor). The KS-AT linker proves to be well suited as

fusion site for both excision and insertion of modules, which supports a model for alternative module boundaries in some PKS systems. This study teaches important lessons on the evolution of PKSs, which may guide future engineering approaches.

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