Artificial reconstruction of two cryptic angucycline antibiotic biosynthetic pathways.

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Abstract

Genome-sequencing projects have revealed that Streptomyces bacteria have the genetic potential to produce considerably larger numbers of natural products than can be observed under standard laboratory conditions. Cryptic angucycline-type aromatic polyketide gene clusters are particularly abundant. Sequencing of two such clusters from Streptomyces sp. PGA64 and H021 revealed the presence of several open reading frames that could be involved in processing the basic angucyclic carbon skeleton. The pga gene cluster contains one putative FAD-dependant monooxygenase (pgaE) and a putatively bifunctional monooxygenase/short chain alcohol reductase (pgaM), whereas the cab cluster contains two similar monooxygenases (cabE and cabM) and an independent reductase (cabV). In this study we have reconstructed the biosynthetic pathways for aglycone synthesis by cloning and sequentially expressing the angucycline tailoring genes with genes required for the synthesis of the unmodified angucycline metabolite-UWM6-in Streptomyces lividans TK24. The expression studies unequivocally showed that, after the production of UWM6, the pathways proceed through the action of the similar monooxygenases PgaE and CabE, followed by reactions catalysed by PgaM and CabMV. Analysis of the metabolites produced revealed that

addition of pgaE and cabE genes directs both pathways to a known shunt product, rabelomycin, whereas expression of all genes from a given pathway results in the production of the novel angucycline metabolites gaudimycin A and B. However, one of the end products is most probably further modified by endogenous S. lividans TK24 enzymes. These experiments demonstrate that genes that are either inactive or cryptic in their native host can be used as biosynthetic tools to generate new compounds.

Beteiligte Forschungseinheiten

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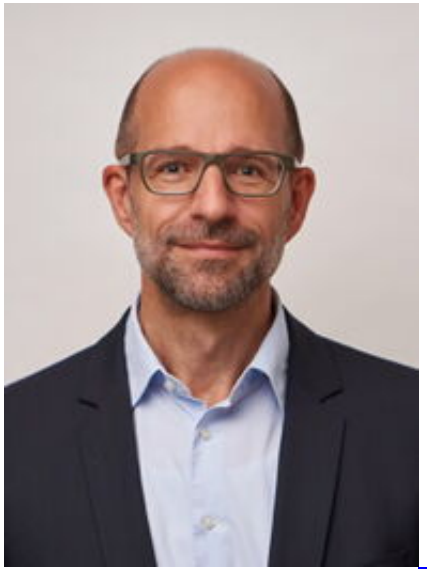

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