Molecular analysis of the benastatin biosynthetic pathway and genetic engineering of altered fatty acid-polyketide hybrids.

Xu Z, Schenk A, Hertweck C (2007) Molecular analysis of the benastatin biosynthetic pathway and genetic engineering of altered fatty acid-polyketide hybrids. *J Am Chem Soc* 129(18), 6022-6030.

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Abstract

The entire gene locus encoding the biosynthesis of the potent glutathione-S-transferase inhibitors and apoptosis inducers benastatin A and B has been cloned and sequenced. The cluster identity was unequivocally proven by deletion of flanking regions and heterologous expression in S. albus and S. lividans. Inactivation and complementation experiments revealed that a KSIII component (BenQ) similar to FabH is crucial for providing and selecting the rare hexanoate PKS starter unit. In the absence of BenQ, several novel penta- and hexacyclic benastatin derivatives with antiproliferative activities are formed. In total, five new compounds were isolated and fully characterized, and the chemical analysis was confirmed by derivatization. The most intriguing observation is that the ben PKS can utilize typical straight and branched fatty acid synthase primers. If shorter straight-chain starters are utilized, the length of the polyketide backbone is increased, resulting in the formation of an extended, hexacyclic ring system reminiscent of proposed intermediates in the griseorhodin and fredericamycin pathways. Analysis and

manipulation of the hybrid fatty acid polyketide pathway provides strong support for the hypothesis that the number of chain elongations is dependent on the total size of the polyketide chain that is accommodated in the PKS enzyme cavity. Our results also further substantiate the potential of metabolic engineering toward polyphenols with altered substituents and ring systems.

Beteiligte Forschungseinheiten

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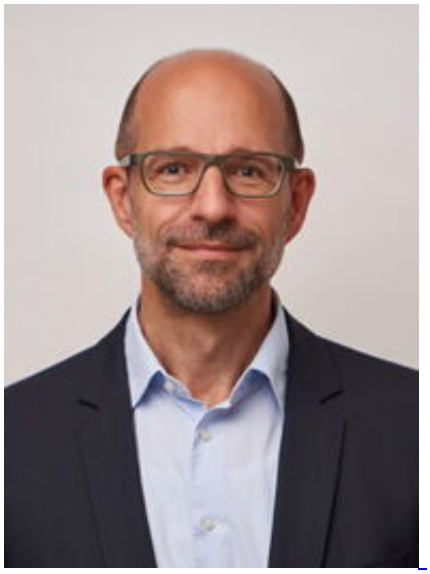

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Identifier

PMID: 17439117