Ketosynthase III as a gateway to engineering the biosynthesis of antitumoral benastatin derivatives.

Xu Z, Metsä-Ketelä M, Hertweck C (2009) Ketosynthase III as a gateway to engineering the biosynthesis of antitumoral benastatin derivatives. *J Biotechnol* 140(1-2), 107-113.

Abstract

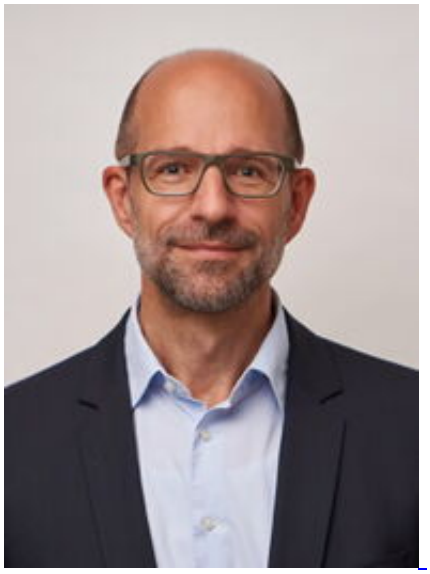
Benastatins are aromatic polyketides from Streptomyces spp. that efficiently inhibit glutathione-S-transferases and induce apoptosis. Their biosynthesis involves a type II polyketide synthase, and a ketoacyl synthase (KAS) III component (BenQ) similar to FabH that is crucial for providing and selecting the rare hexanoate PKS starter unit. The function of BenQ as a KAS III was experimentally proven by point mutation of the active site cysteine. In the mutant several novel short chain fatty acid derived penta- and hexacyclic benastatin derivatives with antiprolieferative activities are formed. Strategies for engineering benastatin biosynthesis were attempted. Synthetic starter units surrogates were not incorporated by block mutants, which suggests that the primer needs to be enzyme-bound. Thus, on the basis of KAS III crystal structures the three-dimensional structure of BenQ was modeled and the predicted substrate-binding tunnel was altered by individual mutations of potential gatekeeping residues (H95A and M99A). However, no significant changes in substrate specificity were observed, indicating that there are other or additional gatekeeping amino acid residues in BenQ or secondary factors including likely protein-protein interactions between BenQ and the PKS complex, and possible conformational changes in BenQ.

Finally, a benQ null mutant was complemented with butyrate starter unit biosynthesis genes from the alnumycin biosynthesis gene cluster, which resulted in a great (10x) enhancement in the production of butyrate-primed hexacyclic benastatin derivatives. The successful generation of an alnumycin-benastatin FAS-PKS hybrid pathway highlights the potential of metabolic pathways, which may lead to novel potential therapeutics and increased yields of desired natural products.

Beteiligte Forschungseinheiten

Biomolekulare Chemie Christian Hertweck Mehr erfahren

Leibniz-HKI-Autor*innen



Christian Hertweck

Details

Identifier

doi: 10.1016/j.jbiotec.2008.10.013

PMID: 19047004