

A ketosynthase homolog uses malonyl units to form esters in cervimycin biosynthesis.

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Abstract

Ketosynthases produce the carbon backbones of a vast number of biologically active polyketides by catalyzing Claisen condensations of activated acyl and malonyl building blocks. Here we report that a ketosynthase homolog from *Streptomyces tendae*, CerJ, unexpectedly forms malonyl esters during the biosynthesis of cervimycin, a glycoside antibiotic against methicillin-resistant *Staphylococcus aureus* (MRSA). Deletion of *cerJ* yielded a substantially more active cervimycin variant lacking the malonyl side chain, and in vitro biotransformations revealed that CerJ is capable of transferring malonyl, methylmalonyl and dimethylmalonyl units onto the glycoside. According to phylogenetic analyses and elucidation of the crystal structure, CerJ is functionally and structurally positioned between the ketosynthase catalyzing Claisen condensations and acyl-ACP shuttles, and it features a noncanonical catalytic triad. Site-directed mutagenesis and structures of CerJ in complex with substrates not only allowed us to establish a model for the reaction mechanism but also provided insights into the evolution of this important subclass of the thiolase superfamily.

Beteiligte Forschungseinheiten

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