Molecular analysis of the kirromycin biosynthetic gene cluster revealed beta-alanine as precursor of the pyridone moiety - DTU Orbit (17/01/2019)

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Kirromycin is a complex linear polyketide that acts as a protein biosynthesis inhibitor by binding to the bacterial elongation factor Tu. The kirromycin biosynthetic gene cluster was isolated from the producer, Streptomyces collinus Tu 365, and confirmed by targeted disruption of essential biosynthesis genes. Kirromycin is synthesized by a large hybrid polyketide synthase (PKS)/nonribosomal peptide synthetase (NRPS) encoded by the genes kirAI-kirAVI. This complex involves some very unusual features, including the absence of internal acyltransferase (AT) domains in KirAI-KirAV, multiple split-ups of PKS modules on separate genes, and swapping in the domain organization. Interestingly, one PKS enzyme, KirAVI, contains internal AT domains. Based on in silico analysis, a route to pyridone formation involving PKS and NRPS steps was postulated. This hypothesis was experimentally proven by feeding studies with [U-13C3(15)N]beta-alanine and NMR and MS analyses of the isolated pure kirromycin.

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