

2-Alkyl-4-hydroxymethylfuran-3-carboxylic acids, novel antibiotic production inducers in *Streptomyces*

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Many autoregulators of biosynthesis of secondary metabolites in *Streptomyces* species have been identified. Most of them belong to gamma-butyrolactone (GBLs) family. Mylenomycin (Mm) synthesis in *S. coelicolor* A3(2) is regulated by MmyR and MmfR, two DNA binding receptor proteins, which are homologous to A-factor like receptor. This suggested that Mm production might be regulated by a GBL. However, inducers of Mm production in organic extract were not inactivated by alkaline hydrolysis, which leads to a conclusion that these inducers are not GBLs. This study reports different family of autoregulator: Methylenomycin Furans (MMFs) which regulate the biosynthesis of Mm in *S. coelicolor* A3(2). MMFs were biosynthesized by *mmfLHP*. A cluster of three genes that is very similar to *mmfLHP* was also identified in *S. avermitilis* genome. This suggests that AHFCAs may be widespread in *Streptomyces*, where they are likely to function as a new general class of different signaling molecules.

紹介論文

2-Alkyl-4-hydroxymethylfuran-3-carboxylic acids, novel antibiotic production inducers in *Streptomyces coelicolor* genome mining

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要旨

All of the genetic elements necessary for the production of the antibiotic methylenomycin (Mm) and its regulation are contained within the 22-kb *mmy-mmf* gene cluster, which is located on the 356-kb linear plasmid SCP1 of *Streptomyces coelicolor* A3(s). A putative operon of 3 genes within this gene cluster, *mmfLHP*, was proposed to direct the biosynthesis of an A-factor-like signaling molecule, which could play a role in the regulation of Mm biosynthesis. The *mmfLHP* operon was expressed under the control of its native promoter in *S. coelicolor* M512, a host lacking the SCP1 plasmid, and the ability to produce prodiginine and actinorhodin antibiotics. Comparative metabolic profiling led to the identification and structure elucidation of a family of 5 new 2-alkyl-4-hydroxymethylfuran-3-carboxylic acids (AHFCAs), collectively termed Mm furans (MMFs), as the products of the *mmfLHP* genes. MMFs specifically induce the production of the Mm antibiotics in *S. coelicolor*. Comparative genomics analyses and searches of the natural product chemistry literature indicated that other streptomycetes may produce AHFCAs, suggesting that they could form a general class of antibiotic biosynthesis inducers in *Streptomyces* species, with analogous functions to the better known γ -butyrolactone regulatory molecules.

参考論文