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Genome-minimized *Streptomyces* host for the heterologous expression of secondary metabolism

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Heterologous expression system has been used for exploitation of biosynthetic gene clusters and combinatorial biosynthesis of natural products. Despite recent interest in the development of a bacterial strain for efficient heterologous production of secondary metabolites, there has been not much progress. *S. avermitilis* is an attractive host for heterologous expression as this organism is already producing secondary metabolites at industrial level and has enough supply of primary metabolites. The authors report the development of a versatile host by genetic engineering of *S. avermitilis*. The authors could validate their system by the production of aminoglycoside, nonribosomal peptide, polyketide and plant terpene from engineered *S. avermilitis.*

紹介論文

Genome-minimized *Streptomyces* host for the heterologous expression of secondary metabolism
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要旨

To construct a versatile model host for heterologous expression of genes encoding secondary metabolite biosynthesis, the genome of the industrial microorganism *Streptomyces avermitilis* was systematically deleted to remove nonessential genes. A region of more than 1.4 Mb was deleted stepwise from the 9.02-Mb *S. avermitilis* linear chromosome to generate a series of defined deletion mutants, corresponding to 83.12–81.46% of the wild-type chromosome, that did not produce any of the major endogenous secondary metabolites found in the parent strain. The suitability of the mutants as hosts for efficient production of foreign metabolites was shown by heterologous expression of three different exogenous biosynthetic gene clusters encoding the biosynthesis of streptomycin (from *S. griseus* Institute for Fermentation, Osaka [IFO] 13350), cephamycin C (from *S. clavuligerus* American type culture collection (ATCC) 27064), and pladienolide (from *S. platensis* Mer-11107). Both streptomycin and cephamycin C were efficiently produced by individual transformants at levels higher than those of the native-producing species. Although pladienolide was not produced by a deletion mutant transformed with the corresponding intact biosynthetic gene cluster, production of the macrolide was enabled by introduction of an extra copy of the regulatory gene *pldR* expressed under control of an alternative promoter. Another mutant optimized for terpenoid production efficiently produced the plant terpenoid intermediate, amorpha-4,11-diene, by introduction of a synthetic gene optimized for *Streptomyces* codon usage. These findings highlight the strength and flexibility of engineered *S. avermitilis* as a model host for heterologous gene expression, resulting in the production of exogenous natural and unnatural metabolites.

参考論文

Ikeda H, Ishikawa J, Hanamoto A, Shinose M, Kikuchi H, Shiba T, Sakaki Y, Hattori M, Omura S. Complete genome sequence and comparative analysis of the industrial microorganism *Streptomyces avermitilis. Nat Biotechnol. 2003;21:526-31.*