Heterologous Expression of Tylosin Polyketide Synthase and Production of a Hybrid Bioactive Macrolide in *Streptomyces venezuelae*

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A mutant strain of *Streptomyces venezuelae* was engineered by deletion of the pikromycin polyketide synthase (PKS) and plasmid-based replacement with the entire tylosin (Tyl) PKS. Expression of Tyl PKS in the mutant strain resulted in a maximum level of 0.5mg/l production of 16-membered macrolactone, tylactone, after only 3-4 days culture. To improve the production level of tylactone, feeding of several precursors for ethylmalonyl-CoA[(1)] into the growing medium led to a considerable improvement in the production of tylactone, but switching promoter[(2)] has no observable effect, indicating that intracellular pool of ethylmalonyl-CoA seems to be the major limiting factor in the biosynthesis of tylactone in *S. venezuelae*. Small amount of desosamine-glycosylated tylactone was identified from extract of the resulting strains, revealing that the native glycosyltransferase DesVII probably glycosylated tylactone and had the relaxed specificity to 16-membered macrolactone. These results demonstrate a successful attempt of heterologous expression of entire Tyl PKS and generation of a hybrid macrolide in *S. venezuelae* as well as introduce *S. venezuelae* as a rapid and efficient heterologous expression system for production of secondary metabolites.

References

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