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# Characterization and Exploitation of the SCO1731 DNA Methyltransferase of Streptomyces Coelicolor M145 A(3)2 Strain

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Streptomycetes are multicellular, Gram-positive bacteria with a GC-rich genome and are characterized by complex morphological and physiological differentiation. They are among the most important strains for biotechnological applications due to their ability to produce a wide range of clinically useful antibiotics, as well as other industrially significant secondary metabolites, including antitumor agents and immunosuppressants.

*Streptomyces coelicolor* M145 A(3)2 is widely used as a model organism to study the complex morpho-physiological differentiation of the *Streptomyces* genus. Antibiotic production in these bacteria is tightly regulated by a hierarchy of multi-level regulators, including global, pleiotropic, and cluster-situated regulators, the latter often referred to as pathway-specific regulators. Recently, we demonstrated that 5-methylcytosine plays a role in the differentiation of *Streptomyces coelicolor* A(3)2 M145. Furthermore, we identified the SCO1731 DNA methyltransferase as the key enzyme responsible for cytosine methylation (Pisciotta et al., 2018; Pisciotta et al., 2023). However, the target genes regulated by SCO1731 and the effects of its activity on transcription remain unknown.

5-methylcytosine is one of the most widespread epigenetic modifications found in the DNA of both prokaryotic and eukaryotic genomes. However, its role in regulating gene expression in bacteria has been less extensively investigated compared to eukaryotic systems.

The main objectives of this study were the identification of the target genes regulated by SCO1731-mediated methylation and the evaluation of the role of SCO1731 in modulating antibiotic production yields in other industrially relevant strains.

The challenge was to elucidate the molecular mechanism by which DNA methylation controls antibiotic biosynthesis, thereby enhancing our understanding of these fascinating bacteria and increasing the yields of well-known antibiotics. To address this,

we performed methylome and transcriptome analyses of the ΔSCO1731 mutant strain and compared the results to those of the wild-type strain. A SCO1731 overexpression plasmid was constructed and introduced into *Streptomyces* strains, where 5-methylcytosine levels and antibiotic yields were subsequently quantified.

Our findings demonstrate that cytosine methylation significantly influences morphological differentiation and antibiotic production in *S. coelicolor*. These results enhance our understanding of this model bacterial system and present new opportunities to exploit this genetic tool in other bacterial systems.