Epigenetic control of *Streptomyces coelicolor* differentiation

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DNA cytosine methylation is one of the most important epigenetic modifications in eukaryotes regulating chromatin organization, genome maintenance and gene expression. The role of DNA cytosine methylation in prokaryotes has not been deeply investigated. In *Escherichia coli* cytosine methylation regulates gene expression during the stationary phase and cytosine hypermethylation leads to chromosomal DNA cleavage and cell death.

Streptomyces coelicolor is a mycelial soil microorganism, which exhibits a complex life cycle that includes three different cell types: unigenomic spores, a compartmentalized mycelium (MI) and a multinucleated mycelium (substrate and aerial mycelium, MII). The importance of DNA methylation was already described in Streptomycetes, but its biological role remained unknown. The main objectives of this study were to analyze the pattern of cytosine methylation in *Streptomyces coelicolor* and to investigate the relationship between DNA cytosine methylation and morphological/physiological differentiation.

Dot-blot analysis of genomic DNA using antibody anti-5-methylcytosine revealed that DNA methylation is modulated during hyphae differentiation. Specifically DNA cytosine methylation is higher at the MI stage than in the MII or spores. Cytosine methylome was investigated by bisulphite DNA sequencing showing that 30% of *S. coelicolor* genes contain a methylated motif in their upstream region. The biological effect of cytosine methylation was studied using 5-aza-2'-deoxycytidine (aza-dC), a hypomethylating agent. Phenotypic analyses of cultures treated with aza-dC demonstrated that they were impaired in germination, aerial mycelium formation and sporulation. In addition, they showed a strong reduction in antibiotic production.

Overall, our results suggest a role for DNA cytosine methylation in morphological and physiological differentiation of *S. coelicolor*. Further experiments are ongoing to characterize the molecular mechanisms and pathways behind the observed phenotypes.

POSTER ABSTRACT SUBMISSION

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