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Whole Genome DNA Methylation (Methylome) Analysis and Role of Dam DNA Methyltransferase in the Entomopathogenic Bacterium *Photorhabdus luminescens*.

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Background: DNA methylation is an epigenetic mechanism involved in the pathogenicity of several bacteria as in *Salmonella* or *E. coli*. It decreases the affinity of some transcriptional regulators to their binding site. Thus, two sub-populations can arise, one expressing the gene and the other not, depending on the DNA methylation state. Dam DNA Methyltransferase (MTase), widespread in *Gammaproteobacteria*, methylates the adenine of GATC sites. The role of Dam was investigated in *Photorhabdus luminescens*, an entomopathogenic bacterium in symbiosis with a soil nematode used in biocontrol against crop pests.

Methods: SMRT sequencing (PacBio), which allows identification of the DNA methylation of the whole genome, was performed in *P. luminescens*. Methylome, RNAseq and phenotypic analysis was also performed in a strain overexpressing Dam MTase.

Results: More than 99% of GATC sites of the *P. luminescens* genome are methylated. DNA methylation levels of the whole genome do not change during growth phase. However, the Dam-overexpressing strain displays more methylated GATC sites than the control and most of these sites are located in putative promoter regions. Dam overexpression leads to a decrease in motility and pathogenicity whereas it increases *Photorhabdus* biofilm formation. Symbiosis assays also revealed a decrease in symbiosis ability of Dam overexpressing strain. RNAseq analysis revealed that the observed phenotypes are related to differences at the transcriptional level.

Conclusions: The differentially methylated GATC sites found in promoter regions may be involved in the observed differences in phenotypes and gene expression. Combined analysis of phenotypes, transcriptome and methylome provides clues to understand the involvement of Dam DNA methylation in *P. luminescens* life cycle.

Key words: Epigenetics, DNA methylation ; Gene regulation