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EPIGENETICS

Bacterial DNA methylation gets SMRT

> “methylation of adenines may have broad roles in gene regulation”

DNA methylation in bacteria is typically associated with pairs of sequence-specific methyltransferases and restriction endonucleases that protect host sequences through methylation while lysing the same sequences in unmethylated foreign DNA. A new study has applied a kinetics-based DNA-sequencing technique to suggest that methylation of adenines may have broad roles in gene regulation and DNA replication in bacteria.

Most high-throughput sequencing methodologies for DNA methylation profiling can reliably identify only 5-methylcytosine (5mC). By contrast, single-molecule real-time DNA sequencing (SMRT) detects the kinetic effect of methylated bases on DNA polymerization and can thus potentially detect any methylated nucleotide. Fang *et al.* used SMRT to characterize the methylome of a pathogenic strain of *Escherichia coli*, and they identified 49,311 putative 6-methyladenine (6mA) residues in addition to 1,407 putative 5mC residues.

Genome analysis of this strain identified nine known or predicted adenine methyltransferase genes. These genes were matched to their respective target motifs by expressing each methyltransferase individually in a methyltransferase-deficient strain and analysing the sites that became methylated.

Of particular interest was the adenine methyltransferase M.EcoGIII, which is encoded by a genomically integrated phage. This phage is responsible for pathogenicity in this strain of *E. coli*, as it also encodes the Shiga toxin. As expected, the presence of the methyltransferase (along with its paired restriction endonuclease) increased adenine methylation at target sites and decreased susceptibility to infection by various other phages. Interestingly, it also caused widespread gene expression changes and repressed the replication of integrated sequences from other phages; this indicates additional broad roles for 6mA, although the relevance to virulence is currently unclear.

In a related paper, Murray *et al.* used SMRT to characterize the methylomes of six bacterial species, and they identified widespread 6mA and 5mC marks in all species. These studies have set the scene for more extensive characterization of the roles of DNA methylation beyond 5mC, and it will be interesting to see whether SMRT will also facilitate global insights into eukaryotic DNA methylation.

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ORIGINAL RESEARCH PAPER Fang, G. *et al.* Genome-wide mapping of methylated adenine residues in pathogenic *Escherichia coli* using single-molecule real-time sequencing. *Nature Biotech.* 8 Nov 2012 (doi:10.1038/nbt.2432)
FURTHER READING Murray, I. A. *et al.* The methylomes of six bacteria. *Nucleic Acids Res.* 2 Oct 2012 (doi:10.1093/nar/gks891)