Journal Club

DNA METABOLISM

5MC: WHAT GOES ON MUST COME OFF

In the mammalian genome, cytosine can undergo covalent modifications, leading to increased genetic and epigenetic diversity. The most well-studied cytosine modification is the addition of a methyl group at the 5 position to generate 5-methylcytosine (5mC). Almost all 5mC is found in CpG dinucleotides, where it has a crucial role in a number of physiological processes such as genomic imprinting, X-chromosome inactivation and transposon repression. Mammalian DNA methyltransferases, which convert C to 5mC, were first identified in 1982. Since then, their catalytic mechanism and co-factors have been fully elucidated.

Nonetheless, how this epigenetic modification is reversed remained a mystery. The dynamicity of 5mC levels during primordial germ cell reprogramming implicated both passive and active means of demethylation, and although decreased DNA methyltransferase 1 activity during DNA replication can result in passive demethylation, the agents responsible for active demethylation remained unknown.

There was no shortage of imaginative mechanisms proposed for active demethylation. Yet, none had endured the self-correcting process of scientific rigor until the discovery of TET proteins' ability to oxidize 5mC to 5-hydroxmethylcytosine (5hmC).

In this study, Tahiliani et al. drew a clever parallel between 5mC and β-D-glucopyranosyloxymethyluracil (base J), a modified base in trypanosomes that is found in repetitive sequences. To synthesize J, thymine sequentially undergoes hydroxylation and glucosylation of the methyl group. Hydroxylation is catalysed by JBP1 and JBP2, which belong to the Fe^{2+}- and α-ketoglutarate-dependent oxygenase family. With a plausible mechanism in hand, the authors identified three human paralogs: TET1, TET2 and TET3 and demonstrated that overexpression of TET1 decreased 5mC content by conversion to 5hmC. They went on to show that 5hmC is found in CpG dinucleotides, which suggested in situ conversion of 5mC to 5hmC. The authors also established the oxygenase activity in vitro and confirmed that Fe^{2+} and α-ketoglutarate are essential cofactors. Finally, the authors linked 5hmC levels in embryonic stem cells with TET1 expression.

> Tahiliani et al. drew a clever parallel between 5mC and … base J

Owing to this landmark study, we now recognize that TETs can act repeatedly to generate higher base oxidation states, which are removed by DNA base excision repair and replaced with an unmodified cytosine. Understanding this fundamental mechanism has enabled the discovery of the cause of hypermethylation phenotypes in certain cancers, and inspired the field to investigate the functions of TETs in health and disease.

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ORIGINAL ARTICLE Tahiliani, M. et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science* **324**, 930–935 (2009)

Journal Club

GENE REGULATION

TRANSPOSONS: CATCH THEM IF YOU CAN

Viruses mutate to evade host defences: once a topic for epidemiologists and virologists, the COVID-19 pandemic has turned the mutation rates of viruses into casual dinner conversation. As we encounter a new variant of SARS-CoV-2 in short intervals, a 2014 study led by David Haussler exemplified how transposons, which are virus-like genomic elements, evolve to escape host defence mechanisms, and how the host fights back with mutations of its own.

The study is of great importance as it shows the co-evolution of cellular defence mechanisms as a response to a genome invader. Different from an arms race with an external pathogen, different transposon escape routes are created within the same genome, which highlights that genomes are dynamically shaped instead of being static entities.

Jacobs et al. took advantage of a mouse–human hybrid cell line, which enables the screening of primate-specific factors that are responsible for the transcriptional silencing of human transposons in a mouse cellular environment. Using a candidate-based approach and reporter assays, they identified a specialized KRAB zinc-finger (KZNF) protein, ZNF91, as responsible for the silencing of SINE-VNTR-Alu (SVA) transposons. Tracing ZNF91 back in ancestral genomes showed that it has undergone structural changes in the lineage to humans to cope with the newly emerging SVA elements.

Similarly, ZNF93 was found to repress the activity of a primate-specific long interspersed nuclear element 1 (LINE1). Loss of the ZNF93-binding site on LINE1 about 12.5 million years ago led to a new wave of LINE1 expression and transposition in great ape genomes. Whereas ZNF91 represents the host genome taking the lead in the race, ZNF93 presents a remarkable escape of the transposons.

> This hide-and-seek play is central to genome evolution and speciation

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Jacobs et al. further showed that repression of retrotransposons by the host also affects the expression of nearby genes. Hence, it is crucial to consider the effects of retrotransposons when investigating the evolution of gene expression patterns of the host.

This type of arms race is probably not restricted to transcriptional silencing, as transposons are transcribed as parts of transcriptional units. Therefore, such transposon-derived transcripts should have evolved sequence features to escape processing by RNA maturation machineries. How and for what purpose these RNA-binding proteins come into contact with transposable elements embedded in the introns of protein-coding genes remains largely unclear.

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ORIGINAL ARTICLE Jacobs, F. M. J. et al. An evolutionary arms race between KRAB zinc-finger genes *ZNF91/93* and SVA/L1 retrotransposons. *Nature* **516**, 242–245 (2014)