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-hydroxymethylcytosine (5hmC).

In this study, Tahiliani et al. drew a clever parallel between 5mC and β-d-glucopyranosylxylohexuronic acid (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 Fe²⁺- 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 Fe²⁺ and α-ketoglutarate are essential cofactors. Finally, the authors linked 5hmC levels in embryonic stem cells with TET1 expression.

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.

Angela H. Ting✉ and Byron H. Lee
Genomic Medicine & Department of Urology, Cleveland Clinic, Cleveland, OH, USA.

“Tahiliani et al. drew a clever parallel between 5mC and ... base J.”

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

Tuğçe Aktaş
Otto Warburg Laboratory, Max Planck Institute for Molecular Genetics, Berlin, Germany.

“This hide-and-seek play is central to genome evolution and speciation.”