Reaching the inaccessible DNA

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Journal Club

CHROMATIN

REACHING THE INACCESSIBLE DNA

In most eukaryotes, DNA methylation is crucial for proper gene expression and for keeping potentially mobile transposable elements in check. Various aspects of the processes that regulate DNA methylation may seem somewhat paradoxical. One is that heterochromatin, the most heavily methylated compartment of the genome, also turns out to be the least accessible. Yet, to maintain DNA methylation at these genomic regions, DNA methylation enzymes need to efficiently access DNA. A 2013 study led by Daniel Zilberman provided mechanistic insights that helped understand this conundrum.

It has been known since 1993 that DNA methylation of heterochromatin in *Arabidopsis thaliana* requires decrease in DNA methylation 1 (DDM1), a SWI2/SNF2-related chromatin remodeller whose mammalian orthologues likely ensure a similar function. However, despite the extensive use of *ddm1* mutants in many studies since then, how DDM1 specifically mediates methylation of heterochromatin has remained elusive.

In a study that took advantage of approaches that allow to profile DNA methylation patterns genome wide, Zilberman and colleagues found that *ddm1*-induced loss of DNA methylation in heterochromatin is greatly ameliorated by a concomitant loss of linker histone H1.

H1 is specifically enriched in heterochromatin and binds to both the nucleosome core and the linker DNA, ensuring compact nucleosome packaging. The authors showed that H1 hinders access of DNA methyltransferases to heterochromatin and that DDM1 overcomes this physical barrier to grant them access to DNA.

Adding a cherry on the top, the study also revealed that CMT2, a previously poorly characterized DNA methyltransferase, mediates the majority of methylation at CHH sequences, a type of methylation that is abundant in plant heterochromatin. At less heterochromatic regions, CHH methylation depends on DRM2, and the DDM1 requirement is shifted to another nucleosome remodeller called DRD1 (also known as CHR35).

> “H1 hinders access of DNA methyltransferases to heterochromatin and … DDM1 overcomes this physical barrier”

Although DRD1 and DDM1 act in distinct chromatin environments, DDM1 does not interact directly with H1, and what governs DDM1 specificity towards heterochromatin remains to be determined. One hint may lie in the recent discovery that DDM1 binds to the heterochromatin-specific histone variant H2A.W.

Whatever future work reveals, the paper by Zemach et al. nicely highlighted that nothing about the regulation of DNA methylation makes sense, except in the light of the chromatin environment.

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ORIGINAL ARTICLE Zemach, A. et al. The *Arabidopsis* nucleosome remodeler DDM1 allows DNA methyltransferases to access H1-containing heterochromatin. *Cell* **153**, 193–205 (2013)
RELATED ARTICLE Osakabe, A. et al. The chromatin remodeler DDM1 prevents transposon mobility through deposition of histone variant H2A.W. *Nat. Cell Biol.* **23**, 391–400 (2021)