



HAL
open science

Reaching the inaccessible DNA

Olivier Mathieu

► **To cite this version:**

Olivier Mathieu. Reaching the inaccessible DNA. *Nature Reviews Molecular Cell Biology*, 2022, 23, pp.388 - 388. 10.1038/s41580-022-00484-9 . hal-03722703

HAL Id: hal-03722703

<https://cnrs.hal.science/hal-03722703>

Submitted on 13 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

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



methylation depends on DRM2, and the DDM1 requirement is shifted to another nucleosome remodeller called DRD1 (also known as CHR35).

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.

Olivier Mathieu 

Institute of Genetics Reproduction and Development, CNRS UMR6293, Inserm U1103, University Clermont Auvergne, Clermont-Ferrand, France.

e-mail: olivier.mathieu@uca.fr

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)