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All Packed Up and Ready to Go

Yannick Jacob and Rob Martienssen

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA

Rob Martienssen: martiens@cshl.edu

Abstract

Gene silencing depends on the higher-order structure of heterochromatin as well as repressive biochemical modifications.

In eukaryotes, the two states of chromatin were first distinguished cytologically according to their different levels of condensation. Euchromatin has an open conformation that correlates with an active state of gene expression, whereas the transcriptionally silent heterochromatin is tightly packaged. On page 1448 of this issue, Moissiard *et al.* describe the identification of proteins that are specifically required for the condensed structure of heterochromatin in flowering plants (1). And on page 1445 of this issue, Qian *et al.* (2) identify a plant protein that binds to biochemically modified DNA and itself modifies histones to generate a chromatin state that allows active DNA demethylation (and gene expression).

Heterochromatin can be facultative or constitutive. Facultative heterochromatin is associated with repressed genes that can be turned on and off during development (3). By contrast, constitutive heterochromatin is a more permanent state and is associated with repetitive sequences and transposons that need to be continually silenced to protect the integrity of the genome. Constitutive heterochromatin is readily distinguishable cytologically as densely stained structures characteristic of condensed chromatin. Many epigenetic marks (DNA methylation, histone posttranslational modifications, and histone variants) have now been identified that uniquely localize to constitutive heterochromatin and functionally contribute to its specification (4). In terms of chromatin compaction, how do these epigenetic marks make some regions of the chromatin more or less likely to interact and condense to form heterochromatin? Epigenetic marks do this in several ways, such as by affecting the physical properties of the chromatin (3) and by serving as signals for the recruitment of chromatin-remodeling proteins (5).

Through a screen for genes required to suppress the activity of a promoter containing tandem repeats, Moissiard *et al.* have found two homologous proteins that are involved in heterochromatin condensation and transposon silencing in the model plant *Arabidopsis thaliana*. AtMORC1 [also called COMPROMISED RECOGNITION OF TCV-1 (CRT1)] and AtMORC6 [also called CRT1 HOMOLOG-6 (CRH6)/DEFECTIVE IN MERISTEM SILENCING 11 (DMS11)] both contain a GHKL (gyrase, Hsp90, histidine kinase, MutL)–type adenosine triphosphatase (ATPase) domain. Eukaryotic proteins containing this domain were hypothesized to be involved in large-scale chromatin remodeling through detection of epigenetic marks (6). This information implies that heterochromatin decondensation is likely to be the primary defect in *atmorc1* and *atmorc6* mutant plants, and that transcriptional

reactivation of transposons can be construed as a secondary effect of the loss of heterochromatin structure. Moissiard *et al.* found support for this idea by applying chromatin conformation capture technology, which indicated that close interactions within condensed heterochromatic regions were disrupted in the mutants. Future work will focus on the subsequent interactions with euchromatin in *atmorc1* and *atmorc6* mutant plants.

Interestingly, Moissiard *et al.* show that two repressive epigenetic marks—histone H3 lysine 9 dimethylation (H3K9me2) and DNA methylation—are maintained genome-wide in *atmorc1* and *atmorc6* mutants. This is an important finding, as it suggests that the process of compacting heterochromatin is directly responsible for the loss of gene silencing. It is possible, therefore, that AtMORC1 and AtMORC6 function downstream of H3K9me2 and DNA methylation, but they must be recruited to heterochromatin indirectly, as these proteins do not contain known methylation binding domains. Both *atmorc1* and *atmorc6* single and double mutants have near-identical phenotypes, suggesting that they both function in the same pathway (see the figure), but their impact on the silencing of transposons is relatively modest relative to mutants of the genes coding for the chromatin remodeler DECREASE IN DNA METHYLATION 1 (DDM1) and the maintenance DNA methyltransferase MET1, which also lose heterochromatin condensation (7).

In an independent study, Lorkovi *et al.* found that a mutation in *AtMORC6* impairs RNA-directed DNA methylation by partially affecting DNA methylation in the CHH (where H is A, C, or T) sequence context—a hallmark of this pathway in plants (8). Thus, AtMORC6 might have local effects on DNA methylation, and in support, Lorkovi *et al.* show that AtMORC6 interacts with DEFECTIVE IN MERISTEM SILENCING 3 (DMS3) when both proteins are coexpressed in bacteria. DMS3 is an integral part of the DDR complex (which also contains the proteins DRD1 and RDM1), required for RNA-directed DNA methylation, although AtMORC6 was not previously found in this complex purified from plants (9). Interestingly, DDR interacts with the plant-specific RNA polymerase Pol V, and plants with inactive Pol V or DRD1 also have defects in heterochromatin condensation (10). This indicates that AtMORC6 could control large-scale structural organization of heterochromatin in a complex with DDR and Pol V. It will be important to assess whether the DDR complex or only DRD1 is involved in heterochromatin condensation. As RNA-directed DNA methylation is not required for heterochromatin condensation (10), AtMORC6 would play another role in the DNA methylation pathway. Alternatively, it is possible that the effect of AtMORC6 on CHH DNA methylation is a consequence of its role in structurally organizing heterochromatin.

AtMORC1 and AtMORC6 proteins are part of a seven-member family in *Arabidopsis*, and homologs are also present in animals. Deletion of the mouse gene homolog *Microrchidia* (*Morc1*) produces mice with defects in meiosis and spermatogenesis, closely resembling mice lacking either the *Miwi2* or *Dnmt3L* gene, which also have defects in RNA interference-guided DNA methylation (11–14). Moissiard *et al.* show that the single ortholog of *MORC1* in the worm *Caenorhabditis elegans* (*morc-1*) is also required for gene silencing, although it still remains to be tested whether this is due to heterochromatin decondensation. The mouse protein SMCHD-1 has N-terminal and C-terminal domains related to AtMORC6 and DMS3, respectively (8). Heterozygous mice engineered to lack

one allele of *SMCHD-1* have defects in heterochromatic gene silencing, but homozygous female embryos lacking both alleles are lethal because of defects in X inactivation—a dramatic example of chromosome condensation in mammals (15). Because it occurs only upon cellular differentiation, X inactivation is considered a paradigm for facultative heterochromatin (3). The fact that facultative and constitutive heterochromatin rely on related proteins suggests that they may have more in common than previously supposed.

Little is known about how active demethylation of DNA is regulated. In *Arabidopsis*, it is carried out in a base excision repair process that involves DNA glycosylases. Qian *et al.* identify an *Arabidopsis* protein called IDM1 (in mutant plants, it causes increased DNA methylation 1) that functions as a histone acetyltransferase, which may promote or even guide demethylation via DNA glycosylases (such as Repressor of Silencing 1) in plants. IDM1 contains domains that recognize a combination of epigenetic marks on DNA and histones. Determining how it activates glycosylases should further clarify the relationship among histone modifications, active demethylation of DNA, and protection from gene silencing.

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Figure. Heterochromatin condensation

AtMORC1 and AtMORC6 function similarly in heterochromatin condensation, and both colocalize to the same regions in the nucleus, which suggests that they are in the same pathway and may interact. Recombinant AtMORC6 protein interacts with DMS3, an integral part of the DDR complex. The DDR complex protein DRD1 also regulates chromatin compaction with Pol V independently of their role in RNA-directed DNA methylation.