Minireview

Plant chromatin – epigenetics linked to ATP-dependent remodeling and architectural proteins

Jan Brzeski, Andrzej Jerzmanowski*

Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Pawinskiego 5A, 02-106 Warsaw, Poland

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Abstract Studies in organisms belonging to different eukaryotic kingdoms have revealed that the structural state of chromatin is controlled by interactions of DNA, small RNAs and specific proteins, linked to a self-reinforcing complex network of biochemical activities involving histone and DNA modifications and ATP-dependent nucleosome remodeling. However, these findings must now be reinterpreted in light of the recent discovery of the highly dynamic character of interphase chromosomes exemplified by the constant flux of enzymatic and structural proteins through both eu- and heterochromatin and by short- and long-range chromosome movements in the nucleus. The available data on chromosome organization in *Arabidopsis thaliana* and links between proteins influencing chromatin structure and DNA and histone modifications documented in this model plant provide strong supportive evidence for the dynamic nature of chromosomes.

Keywords: Chromatin; ATP-dependent remodeling; DNA methylation; Linker histone; *Arabidopsis*

1. Introduction

Several excellent reviews concerning chromatin in general and plant chromatin in particular have recently been published; a normal situation in a rapidly developing area in which new discoveries are announced almost every month. We will focus on two aspects of chromatin in plants: one is the interdependence of the RNA interference (RNAi) system, chromatin remodeling and DNA and histone modifications in establishing and maintaining heterochromatin, the other is the role of linker histones in the emerging dynamic model for chromatin.

*Corresponding author. Fax: +48-22-658-4636.
E-mail address: andyj@ibb.waw.pl (A. Jerzmanowski).

Abbreviations: DDM1, decrease in DNA methylation 1; H3K9, histone H3 at position lysine 9; H3K9Met, histone H3 methylated at the position lysine 9; HDA, histone deacetylase; HMT, histone methyltransferase; HP1, heterochromatin protein 1; KYP, kryptonite; LSH, lymphoid-specific helicase; MET1, DNA methyltransferase 1; Pc, polycomb; PEV, position effect variegation; SNF2, sucrose nonfermenting 2

2. Major determinants of chromatin state

Eukaryotic chromosomes in interphase nuclei are organized into domains that can be distinguished by high resolution light microscopy. These regions are composed of two chromatin forms: the loosely packed euchromatin containing most of the actively expressed genes and the more condensed heterochromatin, predominantly associated with transcriptionally inactive, gene-poor sequences. However, heterochromatin is not restricted to microscopically distinguishable areas and this term is often used to describe domains that differ greatly in size, structure, stability, extent of condensation and degree of transcriptional silencing [1]. The permanently condensed and largely inactive, constitutive heterochromatin is concentrated at the centromeres and pericentromeres, and around telomeres. The facultative heterochromatin, which can be difficult to distinguish microscopically, occurs at different locations within euchromatic areas [2] and may be transcriptionally inactive in certain cell lineages or developmental stages while active in others. For example, in vertebrates, stem cells differ considerably from terminally differentiated cells in their amount of heterochromatin [3]. Since the definition of heterochromatin is rather vague, even a normally euchromatic region can be considered heterochromatinized, provided it is transcriptionally silenced due to structural changes in the chromatin. Apart from transcriptional silencing, other characteristic features of typical heterochromatin include late replication during S phase and an inhibitory effect on meiotic recombination [4]. Heterochromatin can act as a matchmaker in mitotic alignment of homologous chromosomal regions and in recognition, pairing and proper segregation of homologous chromosomes at meiosis [5]. A heterochromatic state is capable of spreading: for example it can exert a silencing effect on nearby euchromatic genes, a phenomenon known as position effect variegation (PEV) [6]. Most importantly, heterochromatin can be transmitted through mitosis, thus forming the basis of epigenetic inheritance and cellular memory.

What are the biochemical markers of typical heterochromatin? Constitutive and facultative heterochromatin differ greatly in the type of DNA sequences they encompass (see below) but they share some common features with regard to protein components and DNA modifications. In eukaryotes, ranging from *Schizosaccharomyces pombe* to man and including plants, heterochromatin is marked by modification of the histone H3 tail by methylation of residues Lys 9 (H3K9Met)

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and Lys 27 and low levels of core histone acetylation. In contrast, euchromatic regions are marked by methylation of histone H3 on Lys 4 and a high level of core histone acetylation. In evolutionary lineages in which DNA modification by cytosine methylation occurs, it is predominantly associated with a transcriptionally inactive, heterochromatic states. Heterochromatin is also marked by the occurrence of specific non-histone proteins. The most characteristic are chromodomains containing heterochromatin protein 1 (HP1), found predominantly in centromeric and telomeric regions, and polycomb (Pc), associated mostly with silenced euchromatic genes that are involved in developmental regulation (although HP1 has also been linked with silencing of euchromatic genes [1]). Both proteins are capable of forming higher order oligomeric or multimeric networks. HP1 and Pc were shown to be recruited by histone H3 methylated on lysines 9 and 27, respectively [7]. Recent evidence indicates that the initiation and maintenance of silenced centromeric heterochromatin and of the heterochromatic region in the yeast mating-type *locus* requires the normal functioning of the RNAi pathway [8].

3. The effect of nuclear architecture

The location of genes in relation to nuclear architecture is now seen as another key factor in determining their transcriptional state. New information has been obtained by tracking specific chromosomal sites marked by integrated *lac* operator arrays in cells expressing GFP-*lac* repressor [9]. It appears that while structurally distinct chromatin domains (i.e., eu- and heterochromatin) can be assigned to discrete territories or compartments within the 3-D nuclear space (determined by tethering to specific sites in the nuclear scaffold and nuclear envelope, and by connections to other nuclear compartments), there is a substantial degree of intermingling and movements of mobile domains from one chromosome to another and between separate nuclear compartments [10]. Regulatory changes may be associated with the migration of chromatin domains between different compartments. In vertebrate cells, it has been shown that the transition of genes from active to inactive transcriptional states is accompanied by relocation from eu- to heterochromatic nuclear compartments [11]. Thus, the heritable epigenetic state of chromatin probably results from a combination of the molecular determinants required for initiation and maintenance (repressor–co-repressor binding, histone and DNA modifications, association of specific proteins) and the position of chromatin domains in the 3-D nuclear space.

In mammalian species, the complex nature of chromosomes makes analysis of the relationship between DNA sequence, chromatin structure and gene activity difficult. In contrast, *Arabidopsis thaliana* (5*n*) has a surprisingly simple overall chromosome arrangement. As recently documented in an elegant study by Fransz et al. [12] each interphase chromosome consists of a single, strongly condensed chromocentre, containing all of the constitutive heterochromatin, with euchromatin loops extending from the chromocentre. Chromocentres contain centromeres consisting of a specific 180 base-pair (bp) tandem repeat (representing several percent of the whole genome) and pericentromeric regions rich in other repetitive DNA, including a tandem arrangement of 5S rDNA genes and many transposons. Nucleolar organizing regions (NORs) with tandem arrays of 45S rDNA are also found in chromocentres. The DNA of chromocentres is hypermethylated and the associated histone H4 shows low levels of acetylation. There is also an increased level of histone H3 methylation on Lys 9. Gene-rich euchromatic loops of between 200 and 2000 kb emanate from the chromocentres. The loops are characterized by undermethylation of DNA, high levels of histone H4 acetylation and a low level of Lys 9 methylation in histone H3. Given the propensity of chromatin domains to change positions in nuclear space, it is conceivable that local movements resulting in physical association of the elements of the loops with nearby heterochromatic chromocentres may induce gene silencing.

4. Chromatin is an assembly of elements in fluid (metastable) equilibrium

Exploitation of the fluorescence recovery after photobleaching (FRAP) method, allowing real-time measurements of protein mobility in living cells, has changed an earlier perception of heterochromatin as an inert stable complex resulting from the tight association of individual protein components of the 'silencing apparatus' with nucleosomes. Not only the linker histones, thought to stabilize higher-order chromatin structures [13], but also the HP1-type proteins have been shown to turn-over surprisingly rapidly in both eu- and heterochromatin [14]. The short residence time of HP1 in heterochromatin indicates the phenotypically stable heterochromatic state is not the result of a static association but rather the outcome of a competition among available factors for existing binding sites. Thus, upon initiation, for example by binding of a sequence-specific repressor–co-repressor complex [11], the maintenance of a heterochromatin state would require a high local concentration of factors mediating silencing, such as HP1, histone deacetylases (HDAs) and histone methyltransferases (HMTs). This could be achieved by relocation of euchromatic region to nuclear compartments rich in constitutive heterochromatin. The competition model of establishing heterochromatic states is in agreement with recent findings on the dynamics of single nucleosomes. In particular, it was shown that the SWI/SNF-type ATPase subunits can generate multiple distinct remodeled nucleosomes, each with different fragment of DNA sequence exposed, securing the stochastic access of the activators and repressors [15]. As was recently shown in cultured mammalian cells, even a transient recruitment of an initiating factor (a repressor–co-repressor complex) can result in a stable heterochromatic state that is mitotically heritable over many generations in the absence of the initiating factor [11]. It seems that at least some epigenetic phenomena can result from stochastic processes at the chromatin level. The fluid equilibrium state of chromatin constantly creates windows of opportunity for the binding of initiating factors. The uncertainty of the outcome originates from the stochastic fluctuations in local concentrations of both the initiating factors and other chromatin components determining conditions for binding. External parameters, for example temperature, should exert measurable effects on the functioning of such a system. A good example of such an effect is provided by the observation of altered DNA methylation status in cold-stressed plant cells [16].

5. Decrease in DNA methylation 1 (DDM1)-mediated chromatin remodeling

Early genetic screens for *Arabidopsis* mutants impaired in DNA methylation [17] and transgene silencing [18,19] provided the first insights into the molecular mechanisms of epigenetic gene repression. Two of the identified *loci* were analyzed in detail and shown to encode DNA methyltransferase 1 (MET1) and a sucrose non-fermenting 2 (SNF2)-class protein DDM1 [20] that has recently been shown to act as a chromatin remodeling factor [21]. The effects observed in the mutant background included transcriptional derepression of pericentromeric heterochromatin transcriptionally silent information (TSI) [22], retrotransposons [23,24] and protein coding genes [25]. In some cases, transposon reactivation correlated with enhanced transposition frequency [26]. Even though both *ddm1* and *met1* mutations caused dramatic reductions in DNA methylation level, further analyses revealed striking differences between them. First, *met1* mutations caused a reduction in DNA methylation at both repetitive and single-copy *loci* whereas *ddm1* mutations led to immediate hypomethylation of repetitive sequences and only a gradual and delayed loss of methylation in single-copy sequences [17,27]. Second, *ddm1* mutations did not cause hypomethylation at the haploid stage [17,28], whereas MET1 seemed to act on the haploid gametophyte genome [29,30]. Third, the hypomethylation induced by *ddm1* was stably inherited and maintained when introduced into a wild-type background by genetic crosses [17,28,31]. In contrast, genomic sequences demethylated in *met1* underwent slow remethylation when transmitted to *MET1* plants [30]. Despite these differences, *met1* and *ddm1* mutations had two surprising similarities. First, both affected the chromosomal pattern of methylation of histone H3 on lysine 9, even though the overall level of this modification was not reduced [32,33]. Second, the global loss of cytosine methylation was coupled to hypermethylation in *AGAMOUS*, *SUPERMAN* and presumably other *loci* [34]. In other words, both mutations exerted two effects on cytosine methylation: a global DNA de-methylation and the resetting of the pattern of persisting methylation. Thus, an aberrant H3K9Met pattern might parallel the redistribution of methylcytosine. A similar phenomenon, although observed with a much lower frequency, was associated with the formation of epialleles in wild type plants. This could reflect the metastability of epigenetic modifications.

A number of scenarios can be envisaged that explain the altered patterns of cytosine methylation and H3K9Met in *met1* and *ddm1* backgrounds. It has been suggested that an overall loss of DNA methylation could activate hypothetical rescue mechanisms promoting cytosine methylation which, however, are unable to assure its correct targeting. According to another scenario, uncontrolled transcriptional derepression caused by hypomethylation could lead to the synthesis of numerous aberrant RNAs providing substrates for the production of siRNAs capable of targeting chromatin modifications to random complementary *loci*. The involvement of siRNA finds support in the genetic analysis of the model *clark kent SUPERMAN* epiallele system. A genetic screen for *clark kent* supressors identified mutations in *ARGONAUTE 4*, which belongs to a family of proteins involved in RNAi processes [35]. Another mutation found in this survey mapped to the *KRYPTONITE* (*KYP*) gene which encodes one of the SET-domain HMTs specific for histone H3 at position lysine 9 (H3K9) [36]. Interestingly, *kyp* mutants show strong reduction in the level of H3K9Met only in chromocentres, suggesting that the main function of KYP is restricted to heterochromatic domains and that other H3K9-specific HMTs act in euchromatic regions ([37], Olczak, J. Brzeski, A. Jerzmanowski, unpublished). Very similar patterns of H3K9 methylation have been observed in *ddm1* and *met1* mutants [31]. These observations led to a suggestion that disruption of any one component in the complex network of interdependences between DNA methylation and H3K9 methylation results in mis-targeting of the whole system.

How can the DDM1 chromatin remodeling activity contribute to the formation of heterochromatin? A frequently postulated model assumes that DDM1 unwinds nucleosomal DNA to permit modification of cytosine and H3K9 [20,38]. As DNA methylation presumably occurs immediately after DNA is replicated, DDM1 would have to act at the very early stages of chromatin assembly. According to this model, DDM1 acts primarily on the replication of heterochromatin which contains the vast majority of repetitive sequences in the genome and is the main acceptor of DNA methylation. Thus, the global DNA demethylation in *ddm1* mutants could be satisfactorily explained by the inefficient methylation of heterochromatic nucleosomal DNA. The delayed and gradual loss of DNA methylation in euchromatin, which contains mostly single-copy sequences, would result from some accessory function of DDM1 during euchromatin replication. Consistent with this model, a mouse homolog of DDM1–lymphoid-specific helicase (LSH) associates with recently replicated heterochromatin [39]. This model can also explain why DDM1 is not required at the haploid stage, where heterochromatin is presumably not yet completely formed.

Heterochromatin maturation takes several days and DDM1 function appears to be vital in this process [40]. This observation suggests that DDM1 is mostly active in non-dividing rather than meristematic tissues. Indeed, it was shown that DDM1 is required for the silencing of viral genes in non-dividing cells [41]. The above observations led to an alternative model in which it was proposed that DDM1 acts as a folding factor that creates a condensed chromatin environment which prevents disruption of heterochromatin. Such continuous chromatin remodeling might preserve its modification status counteracting active histone replacement or DNA de-methylation. Although the participating enzymes have not yet been identified so far, active DNA de-methylation has been suggested by several observations [16,42] and is probably involved in the activation of transposons [43].

Consistent with the latter model, LSH has been shown to dissociate from heterochromatin following treatment with inhibitors of histone deacetylases [39]. Histone acetylation/deacetylation has a very high turn-over rate and is therefore unlikely to serve as a stable epigenetic marker. This again indicates the continuous targeting and action of DDM1. Recent analysis of DNA and H3K9 methylation in the histone deacetylase mutant *sil1* supports this hypothesis [44]. In the *sil1* background DNA and H3K9 methylation were lost in a number of the analyzed *loci*. However, after backcrossing into a wild-type background re-methylation occurred immediately. Interestingly, the *ddm1* mutation causes an additional effect on post-replicative histone deacetylation in heterochromatin [31]. An attractive hypothesis explaining these observations is that

SIL1-mediated histone deacetylation is required for DDM1 targeting.

The two models discussed above are not mutually exclusive. In dividing cells DDM1 could participate in replication of the DNA methylation pattern of heterochromatic *loci*. After differentiation it could act continuously to prevent heterochromatin decondensation. The latter function of DDM1 might explain the delayed loss of methylation in single-copy sequences observed in *ddm1* mutants.

Why is the hypomethylation caused by *ddm1* mutations stably maintained after backcrossing into a wild-type background? One explanation is that DNA methylation is a semiconservative process and once the methylation pattern has been erased, the modification machinery is unable to remethylate DNA. A feedback loop has been proposed that targets DDM1 to hemimethylated DNA where it is required for methylation of the newly replicated strand. However, this explanation assumes that de novo DNA methylation is very inefficient, when it is known that epigenetic silencing (for example, after polyploidization or introduction of a transgene) occurs very rapidly. It also does not answer the question why the *met1*-induced hypomethylation can undergo re-methylation, albeit slowly. In addition, the feedback loop hypothesis is contradicted by the observation that de-methylation of DNA by treatment with azacytidine does not affect the association of LSH with heterochromatin [39]. It is tempting to ask whether other, as yet unidentified, genomic imprints are erased or changed in *ddm1* mutants but persist in *met1*. According to this very speculative idea, DDM1 might act upstream of the methylation of DNA and H3K9 and be involved in setting up this hypothetical imprint. This would explain the striking difference in the re-modification of chromatin demethylated in *ddm1* and *met1* backgrounds.

6. Epigenetics and linker histones

For a long time the role in chromatin of H1 (linker) histones remained poorly understood. H1 is an abundant chromatin protein represented by multiple non-allelic variants. In animals the down regulation of any particular variant is immediately compensated by up regulation of the other variants, without visible effects on major cellular or organismal functions. In plants, in which the compensation effect among variants is also strongly manifested, the reversal of the normal proportion of major to minor variants achieved in tobacco using an antisense strategy, led to severe disturbances in chromosome segregation during male meiosis and subsequent male sterility [45]. This result may be explained by the recent demonstration in yeast that the equivalent of H1, Hho1p, suppresses DNA repair by homologous recombination [46,47]. This function of H1, if universally conserved, could have profound effects on genomic stability. However, as homologous recombination is of particular importance during sexual reproduction, it is possible that there is a meiosis-specific mechanism which allows frequent DNA exchange in the presence of H1. It is conceivable that an aberrant proportion of H1 variants in tobacco chromatin during meiosis could have affected such a mechanism and disturbed the normal pairing and segregation of homologous chromosomes. However, is it possible that linker histones, in addition to a role in homologous recombination, have a more general function in plant chromatin? Some hints come from the observation that lowering the expression of the entire complement of linker histones genes in *Arabidopsis* to below 95% using RNAi led to alterations in the DNA methylation pattern of a number of sequences as well as to pleiotropic phenotypes which were inherited in a non-Mendelian fashion, similar to that previously described in plants defective in DNA methylation or histone deacetylation (A. Wierzbicki, A. Jerzmanowski, unpublished). This finding indicates a more global role for linker histones as structural elements influencing the outcome of epigenetic processes in chromatin.

With this in mind it is tempting to speculate on the importance of linker histone variants in chromatin. There is increasing evidence that variants of core histones, particularly of H3 and H2A, are used to mark nucleosomes and, through the nucleosome assembly pathway, serve to transmit epigenetic information [47]. Regarding the typical linker histones of animals and plants, two levels of variation should be considered. The first is minor variation represented within each group by non-allelic variants. The role of this variation is not clear, although the fact that the expression of an evolutionarily old plant-specific variant positively correlated with stress [48], may indicate that in plants the differences in variant content may be important in modulating the global chromatin response to changing external conditions. The second level of variation among linker histones results from a major difference between animal and plant H1s. The globular domain (GH1) of plant H1 lacks a five amino acids extension of the "Wing" subdomain, that is present in animal GH1 [49]. Since this subdomain has been implicated in binding to nucleosomes, its different length in plant H1 could result in a global change in the stability of chromatin higher order structures. It should be noted that the difference between histone H3 and its more transcriptionally permissive H3.3. variant also results from a minor three amino acids substitution in the histone fold domain [47]. Whether this characteristic structural feature of plant H1 is linked with decreased stability of chromatin epigenetic marks in plants, as compared to animals, remains an exciting possibility that is open for experimental verification.

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