Histone modifications and dynamic regulation of genome accessibility in plants

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Summary

In all eukaryotes chromatin physically restricts the accessibility of the genome to regulatory proteins such as transcription factors. Plant model systems have been instrumental in demonstrating that this restriction is dynamic and changes during development and in response to exogenous cues. Among the multiple epigenetic mechanisms that alter chromatin to regulate gene expression, histone modifications play a major role. Recent studies in Arabidopsis have provided the first genome-wide histone modification maps, revealed important biological roles for histone modifications, and advanced our understanding of stimulus-dependent changes in histone modifications.

Introduction

Within each cell, the genetic information encoded by DNA is compacted into chromatin. The fundamental unit of chromatin is the nucleosome, which is formed by wrapping 147 bp of DNA around a histone octamer (two copies each of histones H2A, H2B, H3 and H4). Nucleosomal DNA presents a barrier for proteins that need to contact the DNA, including those regulating gene expression. Constitutively expressed genes in plants and other organisms often have nucleosome free regions in their promoters[1,2]. Expression of many other genes is regulated by altering these chromatin constraints in response to endogenous and exogenous cues, which ultimately creates a cell- or stimulus-specific accessible genome. How is this achieved? Within the context of chromatin, three processes act in concert to regulate gene expression and thus should be considered together (Table 1). First, histone modifiers covalently alter amino acids primarily in the exposed N-terminal tails of histones, which changes the histone-DNA interaction and creates or blocks protein binding sites (Table 1)[3]. Second, chromatin remodeling ATPases use the energy derived from ATP hydrolysis to alter position or composition of nucleosomes (Table 1)[2]. Finally, methylation of cytosine residues in the DNA interferes with binding of some proteins (including transcription factors) and recruits other proteins (Table 1)[4,5].

Here we focus on the role of covalent histone modifications in regulation of gene expression in euchromatin. These modifications can activate or repress transcription by generating more ‘open’ or ‘closed’ chromatin configurations, respectively. Generally, open chromatin increases the accessibility of the genome to transcription factors and/or the general transcription machinery, thereby activating transcription, while closed chromatin represses transcription by limiting the accessibility of the genome to these proteins (Table 2). Within a histone, the amino acid modified, the type of modification and the degree of modification (for example mono-,
di- or trimethylation) all affect whether a given modification is activating or repressive[3] (Table 2). The roles of the individual histone modifications are conserved between the plant and animal kingdoms.

In this review we will discuss genome-wide elucidation of the distribution of histone modifications in plants, identification of the processes regulated by histone modifications, and how histone modifiers are recruited to their targets in plants. A unique advantage of studying chromatin regulation in plants is that functional and molecular studies are usually conducted in context of the multicellular organism, not in cell lines. While this can be technically challenging (see conclusions), it facilitates identification of biologically relevant changes in histone modifications. That very few chromatin regulators are essential in plants is a significant advantage for elucidating the in vivo role of these regulators.

**Genome-wide distribution of covalent histone modifications**

In addition to the type of histone modification present, the effect on gene expression depends on the spatial distribution of a given modification across a gene region (the histone modification landscape[6]) and the combinatorial presence of other modifications[3,7,8]. Two examples from yeast and mammalian cell lines highlight this point. Tri-methylation of histone H3 on lysines 9 and 36 (H3K9me3 and H3K36me3) is repressive when found in the promoter region but activating when found in gene proper (reviewed in[3,7,8]). These modifications close chromatin to prevent transcription initiation. Thus, when present within genes, this stimulates full-length transcript production by preventing internal initiation from cryptic start sites. Genome-wide binding and expression studies showed that presence of an activating histone modification such as H3K4me at the promoter alone is not sufficient to trigger transcriptional activation, additional histone modifications present at the same locus affect gene expression in a combinatorial fashion (reviewed in [3,6,7], see also[9,10]).

Recent studies in plants also address these topics. Genome-wide analyses of H3K27me3 were recently published for Arabidopsis[1,11]. This is a repressive histone modification established by SET-domain containing histone methyl transferases of the Polycomb Repressive Complex 2 (PRC2). H3K27me3 is required for proper expression of several important transcriptional regulators[12–18]. Chromatin immunoprecipitation studies with H3K27me3 antibodies followed by hybridization of the precipitated genomic DNA to whole genome Arabidopsis tiling arrays (ChIP on chip) revealed that H3K27me3 is associated with many individual genes (18% of all genes), especially transcription factors and developmental regulators that are not expressed at the developmental stage examined (ten-day-old seedlings)[1]. The modification is limited to the transcribed regions of genes, with a slight bias towards the 5’ end and the proximal promoter[1,11](Figure 1), suggesting that regulatory sequences in the DNA may be the primary targets of H3K27me3 repression. In metazoans H3K27me3 also represses expression of transcription factors and developmental regulators, but is generally associated with large multigene chromatin domains instead of single genes[19,20]. The reduced tendency of plants to form large compacted chromatin domains may be the basis for their high developmental plasticity and the ease with plant cells can change developmental programs and even de-differentiate.

H3K27me3 was found to be the in vivo binding site for the only Arabidopsis thaliana Heterochromatin Protein 1 (HP1) homolog, LHP1/TFL2[11], which plays a role in repressing gene expression in euchromatin[21,22]. This contrasts with the situation in metazoans, where instead of HP1, Polycomb Repressive Complex 1 (PRC1) recognizes H3K27me3[19,20] and generates large multigene silenced domains. Intriguingly, a homolog of PRC1 is not present in plants [18], thus LHP1/TFL2 may functionally substitute for PRC1-mediated repression in...
The strong, pleiotropic phenotypes of lhp1/tfl2 mutants are consistent with a role for LHP1/TFL2 as an important repressor of gene expression [23].

A comprehensive analysis of multiple histone modifications was recently reported for H3K9me2, H3K9me3, and H3K27me3 using a chromosome 4 tiling array[11]. As previously described, H3K9me2 was exclusively associated with repetitive heterochromatic regions[24]. Both H3K27me3 and H3K9me3 were present in small dispersed but largely non-overlapping regions in euchromatin with a similar 5’ concentrated distribution over genes[11](Figure 1). The mutually exclusive presence of these two histone modifications suggests that they are part of distinct repressive mechanisms and perhaps regulate different groups of genes or respond to different types of cues.

Role of histone modifications in the organism

Histone modifications in plants regulate gene expression in response to diverse exogenous stimuli including stress, pathogen attack, temperature, and light[25]. For example, the histone acetyltransferase (HAT) HAC1 is required for transcriptional upregulation of the heat shock gene HSP17 and accumulation of HSP17 after heat shock[26]. The histone deacetylase (HDAC) HDA19 regulates expression of pathogenesis related genes and promotes resistance to a fungal pathogen[27]. Prolonged exposure to cold silences the flowering time repressor FLOWERING LOCUS C (FLC) in Arabidopsis winter annuals by histone deacetylation and repressive histone methylation (reviewed in [28,29]). HDA19 and two HATs (HAF2 and GCN5) have negative and positive roles, respectively, in light-responsive gene expression and in photomorphogenesis[30]. Thus, histone modifications control expression of important regulators in response to environmental signals in plants.

Histone modifications also play a central role in developmental regulation (reviewed in [17, 18,25,28,31]). In a recent study, three-dimensional fluorescence in situ hybridization of the locus encoding the homeodomain transcription factor GLABRA2 (GL2) revealed cell-type-specific hybridization of a GL2 probe in atrichoblast cells (which express GL2 and do not form root hairs) but not in root-hair forming trichoblast cells[32]. This hybridization and hence accessibility of the locus changes dynamically when a cell perceives positional cues that cause a switch from trichoblast to atrichoblast fate, apparently by resetting of the responsible epigenetic marks during the cell cycle[32]. A second study showed that certain histone modifications (high levels of H3K9me2, low levels of H3K9me3, and low H3 acetylation) at the proximal promoter of GL2 are required for repression of this gene[33]. Because these histone modifications can also be reset during the cell cycle[33], it is possible that they cause the differential GL2 locus accessibility. It is intriguing that the H3K9me2 modification is readily reversible upon perception of altered positional cues. As described above, H3K9me2 is nearly exclusively heterochromatic[11,24], and thus likely associated with tightly compacted chromatin.

Recruitment and regulation of histone modifying activities

An important, largely unanswered, question is how histone-modifying activities are recruited to their targets. One mechanism is recruitment by transcription factors. As discussed below, transcription factors can directly bind and recruit histone-modifying complexes or recruit them indirectly, via co-regulators. In addition, existing histone modifications can affect recruitment of histone modifiers. Several plant transcription factors are known to interact with histone modifying complexes. The cold-inducible C-REPEAT BINDING FACTOR (CBF1) is proposed to recruit the GCN5 HAT complex via direct interaction with the HAT complex subunits ADA2a and ADA2b[34]. The C2H2 zinc-finger transcription factor SUPPRESSOR OF FRIGIDA4 (SUF4) is thought to recruit the histone methyl transferase EARLY
FLOWERING IN SHORT DAYS (EFS) to the FLC promoter[35,36]. The APETALA2/EREBP-type transcription factor AtERF7, which mediates ABA responses, likely recruits HDA19 via its interaction with the HDAC complex subunit SIN3[37]. The seed specific ABI3-like transcription factor ALF appears to recruit a HAT activity to the bean phaseolin promoter[38]. A steroid inducible system revealed that ALF binding causes promoter potentiation through increased histone acetylation. Full promoter activation after subsequent exposure to the hormone ABA correlates with altered histone acetylation, and increased H3K4 levels[38], indicating that a step-wise sequence of histone modifications is necessary for phaseolin activation. Although more recruiting factors need to be identified to better understand what types of transcription factors play this role, the available data suggests that expression and/or activity of the recruiting transcription factors is cell- or stimulus-specific.

The LEUNIG (LUG) co-repressor complex bridges interactions between transcription factors and chromatin regulators. LUG is recruited by certain MADS-domain transcription factors to the promoter of the floral homeotic regulator AGAMOUS(AG) and represses AG expression in the outer whorls of flowers via recruitment of the HDA19 HDAC[39–41]. TOPLESS (TPL), a protein with limited similarity to LUG, was recently identified as pivotal in embryo patterning in Arabidopsis. Among the earliest patterning events in the embryo are establishment of an apical (shoot) pole and a basal (root) pole. Dominant negative mutations in TPL inactivate all five TPL family members in Arabidopsis and convert the apical pole into a basal pole, which can lead to a dramatic double root phenotype[42]. Elegant genetic interaction studies indicate that the TPL family of proteins likely works in conjunction with HDA19 to repress genes required for basal fate in the apical half of transition stage embryos[42].

Once a histone modification has been added, it can serve to recruit or inhibit recruitment of additional histone modifying complexes. For example, GENERAL TRANSCRIPTION FACTOR 6 (GTE6) contains a domain that binds acetylated lysines on histone tails. GTE6 is recruited to the promoter of the MYB transcription factor ASYMMETRIC LEAVES 2 (AS2) and is required for histone acetylation of the AS2 promoter via positive feedback, perhaps by recruiting a HAT complex[43].

Specific recruitment of histone modifying complexes enables them to regulate particular target genes in response to endogenous and exogenous cues. Formation of multiple histone modifier complexes also contributes to their target specificity. For example three distinct PRC2 complexes exist in Arabidopsis that regulate unique target genes through H3K27 trimethylation[18]. Specificity of histone modifiers can also be regulated posttranslationally, the maize HDAC Hda1 is activated by proteolytic cleavage during seed germination[44].

**Conclusion**

Ultimately many histone modifications are directed at coordinating gene expression. As summarized above the recent genome-wide studies in plants have provided tantalizing glimpses into how this coordination is actually achieved. These studies have revealed that in Arabidopsis repressive histone modifications (such as H3K27 me3) occupy smaller domains than in metazoans, likely making these modifications more readily reversible. The observation that factors binding this histone modification may also be distinct further underscores that fundamental differences may exist in chromatin-mediated regulation between the two kingdoms. These differences may reflect the higher developmental plasticity of plants and allow these sessile organisms to respond rapidly to fluctuating environmental conditions. It is the expectation that the coordinated gene expression enabled through these histone modifications patterns would be target of environmental or developmental cues. Indeed, as discussed above, histone modifications change rapidly in response to diverse exogenous cues and during patterning and differentiation to control expression of important regulators of the
processes triggered by these cues. The precise patterns of histone modifications observed genome-wide as well as the dynamic changes in histone modifications observed at the single gene level suggest presence of an accurate recruitment mechanism for histone modifiers. As evidenced from the studies described here, this likely involves a combination of sequence specific DNA binding proteins, co-regulator complexes, feedback mechanisms as well as regulation of histone modifier activity.

The challenge for the future is to detect the global, dynamic changes in multiple histone modifications in the organism that occur within subpopulations of cells, to further delineate how these modifications are triggered by exogenous and endogenous cues at specific genes, and to determine how they correlate with gene expression. This will require new approaches and techniques, including inducible systems to dissect the responses to endogenous cues, better cell fractionation methods, and increased sensitivity of techniques such as ChIP. Genetic analyses will continue to be instrumental in deciphering the biological significance of the observed alterations in histone modifications.

Understanding chromatin-mediated regulation of genome accessibility will ultimately require expanding these studies to include other chromatin regulatory mechanisms such as chromatin remodeling and DNA methylation. The intricate epigenetic regulation of FLC [28,31] clearly demonstrates that histone modifications and chromatin remodeling act together to control expression of this master regulator. Other chromatin remodeling complexes play important roles in chromatin-mediated control of gene expression[45,46]. Similarly, genome-wide DNA methylation maps[47–51] suggest that in addition to its role in heterochromatin, DNA methylation may affect transcription in plants. Because of the viability of null mutants, plants are ideally suited to sort out how these processes coordinately regulate genome accessibility.

Acknowledgements

We apologize to all researchers who contributed this field and whose work could not be cited here due to space limitations. We wish to thank John D. Wagner, Chang Seob Kwon, Kim Gallagher, Scott Poethig, Stewart Gillmor, and Nick Kaplinsky for critical comments on this manuscript. DW is supported by National Institutes of Health grant R01 GM64650-01 and National Science Foundation grant IBN 0516622, JP is supported by National Institutes of Health NSRA grant F32-GM076933.

References

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32. Costa S, Shaw P. Chromatin organization and cell fate switch respond to positional information in Arabidopsis. Nature 2006;439:493–496. [PubMed: 16362059]** Using 3D fluorescence in situ hybridization, the locus for GLABRA 2, a regulator of root epidermal cell fate, was shown to be accessible only in non hair-forming cells. Altered positional cues cause cell cycle linked resetting of this differential chromatin-mediated locus accessibility and altered cell fate.


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**Abbreviations**

ac  
acetylation  

ChIP  
chromatin immunoprecipitation  

H3K9  
histone H3 Lysine 9  

HAT  
histone acetyl transferase  

HDAC  
histone deacetylase  

HMT  
histone methyl transferase  

HMD  
histone demethylase  

HP1  
Heterochromatin Protein 1  

me  
methylation  

me2  
demethylation  

me3  
trimethylation  

LHP1  
LIKE HETEROCHROMATIN PROTEIN 1 (also called TFL2); *Arabidopsis* HP1 ortholog  

ph  
phosphorylation  

PRC1  
Polycomb Repressive Complex 1  

PRC2  
Polycomb Repressive Complex 2  

sme2  
symmetric dimethylation  

SWR1  
chromatin remodeling complex that mediates histone exchange of the histone variant H2A.Z for the canonical histone H2A
Figure 1. Spatial arrangement of chromatin modifications important for gene expression

Shown is a generic euchromatic *Arabidopsis thaliana* gene in the context of chromatin modifications known to affect gene expression. Relevant gene regions are indicated. Histone octamers are shown as purple cylinders. The histone variant H2A.Z incorporated by the SWR1 chromatin remodeling complex[75–77] is shown as a green ellipse. The promoter is partially depleted of nucleosomes, which is observed in many constitutively expressed genes and in inducible genes after the combined activity of chromatin remodeling ATPases and histone modifiers. Above the graphic grey shading indicates the promoter region, the 5′ end of the gene, the central gene region, the 3′ end of the gene, and the 3′ intergenic region. The spatial distribution of covalent histone modifications is indicated relative to these five regions. Modifications for which distribution was determined by global binding studies are indicated in bold[1,11,47,48,50], to distinguish them from those for which information is only available from studies of a limited number of genes (see Table 2 for examples). Note that H3K27me3 and H3K9me3 do not overlap, genes repressed by H3K27me3 are devoid of H3K9me3 and vice versa[11]. Spatial distribution of DNA methylation and of the Heterochromatin Protein 1 homolog LHP1/TFL2, two other chromatin regulators whose distribution was mapped genome-wide, is also indicated.

1 H3K9me3 and H3K36me2 may have different roles on transcription dependent on their location[3].
### Table 1

Types of chromatin alterations that regulate gene expression

<table>
<thead>
<tr>
<th>Chromatin alteration</th>
<th>Subtype</th>
<th>Acts upon</th>
<th>Mechanism</th>
<th>Outcome for transcription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histone Modifications</td>
<td>Ubiquitination</td>
<td>Lysine (K)</td>
<td>Distances histones from DNA (bulky moiety)</td>
<td>Activation (H2B) or repression (H2A)²</td>
</tr>
<tr>
<td>Methylation</td>
<td>Lysine, Arginine (R)</td>
<td>Recruitment of other chromatin regulators</td>
<td>Activation (H3K4, H3K36³) or repression (H3K9⁴, H3K27, H4K20, H4R3)</td>
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</tr>
<tr>
<td>Acetylation</td>
<td>Lysine</td>
<td>Charge neutralization⁴, recruitment of other chromatin regulators</td>
<td>Activation</td>
<td></td>
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<tr>
<td>Phosphorylation</td>
<td>Serine (S), Threonine (T)</td>
<td>Charge neutralization⁴, recruitment of other chromatin regulators</td>
<td>Activation</td>
<td></td>
</tr>
<tr>
<td>Chromatin remodeling</td>
<td>SWI/SNF</td>
<td>Nucleosome position and occupancy²</td>
<td>Sliding to new position, histone octamer eviction²</td>
<td>Activation and repression</td>
</tr>
<tr>
<td>SWR1</td>
<td>Histone exchange</td>
<td>H2A.Z histone variant incorporation</td>
<td>Activation</td>
<td></td>
</tr>
<tr>
<td>DNA methylation</td>
<td>CG and non-CG</td>
<td>Promoter</td>
<td>Inhibition of transcription factor binding</td>
<td>Repression</td>
</tr>
<tr>
<td></td>
<td>CG</td>
<td>Gene (less at 5’ and 3’ ends)</td>
<td>May reduce transcription elongation</td>
<td>Repression</td>
</tr>
</tbody>
</table>

¹ These and additional chromatin alterations also play a role in heterochromatic silencing of repetitive DNA and transposons, genome integrity, and chromosome stability, which are reviewed elsewhere [24,49,51].
² Not yet demonstrated for plants.
³ May activate transcription when localized in transcribed region, but repress transcription when localized in the promoter region.
⁴ Charge neutralization decreases the affinity of positively charged histones for negatively charged DNA.
⁵ For simplicity, only a subset of the chromatin remodeling complexes that regulate transcription are listed here.
# Table 2

<table>
<thead>
<tr>
<th>Modification</th>
<th>Location</th>
<th>Effect</th>
<th>Transcription</th>
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<th>Removed by</th>
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<td>open</td>
<td>activation</td>
<td>Ring-Type E3 ligases [HUB1, HUB2]</td>
<td>Deubiquitinases SUP32/UBP26 [54]</td>
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<td>activation</td>
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<td>LSD1-type of histone demethylases (HDMs) [3, 8]</td>
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<td>activation</td>
<td>ATX1 [56]</td>
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<td>ATX1 [56]</td>
<td>EFS/SDG8 [57]</td>
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<td>JmjC-domain and LSD1-type HDMs [3, 8]</td>
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<td>SUVH2 [58]</td>
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<td>HDA4 [70]</td>
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<td>HD2 family: HD2A, HD2B [72], HD2C [73]</td>
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<td>H2T11ph</td>
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</table>

Histone modifications, their locations in the genome and their effects on chromatin (open/closed) as well as on transcription (where known) are listed. Also listed are the enzymes known to add and remove each modification. Plant histone modifiers are listed in bold type.

* denotes all modifications of a certain type, for example, H3K9me* denotes mono, di, and tri-methylation of lysine nine of histone H3, while H3*ac denotes general acetylation of lysines in histone H3.
These introns contain cis regulatory elements important for transcriptional regulation.

The role of histone phosphorylation in the cell cycle is described elsewhere [24, 74].