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Histone variants: the artists of eukaryotic chromatin

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The eukaryotic genome is packaged into a complex nucleoprotein structure named chromatin, balancing the compactness of genome and the accessibility of regulatory proteins and RNA polymerases to DNA. The mechanisms of the regulation of chromatin dynamics include the post-translational modification of histones, alteration of nucleosome positions by chromatin remodelers, replacement of canonical histones by histone variants with the aid of histone chaperones, and dynamic organization of the three-dimensional genome in the small nucleus. Histone variants are different from canonical histones by substitution of several amino acid residues or changes in amino acid sequence. Histone variants perform specialized functions such as altering nucleosome stability, dynamics, structure, as well as playing critical roles in a range of biological processes like transcriptional regulation, DNA repair and recombination, development and immune responses. Here we discuss how histone variants, their modification and specific loading to chromatin are involved in transcriptional regulation, DNA repair and plant development.

histone variants, histone modification, gene regulation, DNA repair, stress responsiveness

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In the eukaryotic cell nucleus, the fundamental repeating unit of chromatin is the nucleosome, consisting of 147 bp of DNA left-handedly wrapped around a octameric histone core particle, which contains two copies of each of the four core histone proteins H2A, H2B, H3 and H4, and approximately another 20 bp DNA stretches between the neighbouring core particles coupled with the linker histone H1 [1,2]. The huge genomic DNA of eukaryotes is necessary to be densely packed into chromatin to fit within the small dimensions of the nucleus; however, the high order structures restrict the access of transcriptional factors and enzymes to DNA [3]. There are diverse mechanisms involved in breaking through the barriers, including the post-translational modification of histones, alteration of nucleosome positions by chromatin remodelers and replacement of histone variants. The canonical histones are specifically expressed during S-phase and deposited to the genome in a replication-coupled manner. The histone variants, however, are expressed not restricted to S-phase, but throughout the cell cycle, thus the incorporation of histone variants into chromatin is in a replication independent manner [4,5]. In metazoans, the canonical histones are encoded in gene clusters, which encode all four core histones and linker histone H1, for instance, HIST1, the large clusters of histone genes on human chromosome 6, contains 55 histone genes. In contrast, the histone variants are outside of gene clusters and encoded by individual genes [5,6]. In *Arabidopsis*, however, both the canonical histones and variants are not encoded by gene clusters, for example, there are 15 histone H3 genes in *Arabidopsis* genome: AT1g09200, AT3g27360, AT5g-10390, AT5g10400 and AT5g65360, which encode the canonical histone H3.1; AT4g40030, AT4g40040, AT5g-10980 and AT1g13370, AT1g19890, AT1g75600, AT1g-75610, AT5g12910, encoding H3.3 or H3.3-like his-

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tone variants [7]. These genes disperse in different chromosome positions. The histone variants can exchange the canonical histones and then form an architecturally divergent sub- chromatin domains for specific biological functions [8].

In addition to the canonical histones, the unstructured N-termini and the histone fold domains of histone variants are also subjected to a set of post-translational modifications (PTMs), including phosphorylation, acetylation, methylation and ubiquination. These modifications have important roles in regulating chromatin dynamics during diverse processes, such as DNA replication, transcription and DNA repair [9,10].

Here, we discuss the roles of histone variants and their PTMs in regulating gene expression, DNA repair, especially in DNA double strand break (DSB) repair pathway, and summarize their functions in plant development.

1 The universality of histone variants

Until now, histone variants have been identified in all core histones except histone H4. With increasing number of the known histone variants in recent years, the naming convention was established in 2012, which based on historical usage along with phylogenetic relationship [11], the nomenclature normalized the field and provided the convenience for database search. Histone H2A family has the largest number of variants, including H2A.X and H2A.Z evolutionarily conserved from yeast to mammals [12,13], macroH2A and H2A.Bbd found only in mammals [5,14] and H2A.W specific to plant [11]. H2A.W shows approximately 50% amino acid sequence identity with canonical H2A, and contains a SPKK motif at its C-terminal region, which can bind to DNA minor groove [15,16], and the C-terminal motif is responsible for the heterochromatin condensation *in vivo* and *vitro*, therefore, H2A.W is a heterochromatin-specific histone H2A variant [17]. H2A.Z is the most conserved variant in the H2A family [13,18], which differs from the canonical H2A at many amino acid positions throughout the full length sequence [19]. In contrast, H2A.X differs mainly in the carboxyl terminal, which contains a conserved SQ motif [20–22]. H2A.Z is involved in many biological processes, including transcriptional regulation, genome stability and the formation of heterochromatin boundaries [23]. H2A.Z preferentially occupies few nucleosomes around the transcription start sites (TSSs) of genes, which is conserved in yeast, *Drosophila*, plants and mammals [24–28]. The interaction between H2A.Z/H2B dimmer and H3/H4 tetramer is less stable than the H2A/H2B [29]. H2A.Z is incorporated into chromatin by a conserved complex termed SWR1 in yeast and SRCAP in mammals [30–32]. The SWR-like complex has also been found in *Arabidopsis*, which contains ARP6, PIE1 and SEF [33–35].

There are two H3 variants found in all eukaryotes: H3.3 and CenH3. H3.3 differs from H3.1 only in 4- or 5- amino acid positions. In *Arabidopsis*, the amino acid residues at positions 31, 41, 87 and 90 of H3.3 define its difference from H3.1 [36]. In *Drosophila*, the difference between H3.3 and H3.1 is defined by the sites of 31, 87, 89 and 90 [37]; however, in human, there are 5-aa residues of H3.3 different from H3.1, which are 31, 87, 89, 90 and 96 [38]. In *Arabidopsis*, a recent study has revealed that four amino acids guide the nucleosome assembly and disassembly: the amino acid residues 87 and 90 of H3.3 are critical for its deposition into rDNAs especially the site of 87, and amino acid residues 31 and 41 guide the disassembly of H3.3-containing nucleosomes [36]. The deposition of H3.3 into chromatin is mediated by H3.3 specific histone chaperones: HIRA, responsible for replication-independent H3.3 deposition at actively transcribed regions, DAXX-ATRX complex and DEK, mediating H3.3 incorporation at regulatory regions and heterochromatin respectively [39–41].

Centromere-specific histone H3 variant CenH3 is incorporated at centromeres and critical for centromeric functions. Sequence analysis revealed that CenH3 shares a similar C terminal histone fold domain to canonical histone H3, but there are replacements of amino acids in histone fold domain regions supposed to mediate the targeting to the centromeres [42]. In addition, the N terminal tail is hypervariable with CenH3 having a long N terminal tail which is not alignable to the canonical H3 [43,44], and the N terminal tail is essential for the correct localization of CenH3 during meiosis, which is critical for chromosome inheritance [45,46]. Interestingly, the haploid *Arabidopsis* plants were generated by CenH3-mediated genome elimination [47], which is a useful tool in molecular breeding [48,49]. CenH3 was given diverse names in different organisms, for example, Cna1 in *Tetrahymena thermophlia* [50], Cse4 in *Saccharomyces cerevisiae* [51], HCP-1 in *Caenorhabditis elegans* [52], CENP-A in humans [53] and HTR12 in *Arabidopsis thaliana* [54]. HJURP is believed to assemble CenH3 into centromeric chromatin [55]; its timely phosphorylation by cyclin-dependent kinases and proper localization to DNA are essential for CenH3 loading [56].

Compared to the core histones, linker histone H1 and its variants are less conserved in sequence and structure. FRAP experiments revealed the highly dynamic binding to chromatin *in vivo*, which might be important for regulating the genome functions [57,58]. Studies in unicellular eukaryotes have shown the roles of H1 in development, transcriptional regulation and the recombination at rDNA locus [59–61]. In contrast, high eukaryotes have multiple variants of linker histone H1, which function in nucleosome spacing in chicken cells [62] as well as in mouse cells and embryonic development in mice [63]. In *Arabidopsis*, histone H1 contributes to DNA methylation and gene imprinting [64,65].

In addition to the above mentioned universal functions of histone variants, histone variants are also involved in spe-

cialised functions, such as that for the sperm specific histones. In *Arabidopsis*, which has double fertilization during sexual reproduction, the H3.3 variant AT1g19890 is specifically expressed in male gametes. Live imaging revealed the replication-independent dynamics of H3.3 in the zygote and replication-dependent manner in the endosperm [66]. During gametogenesis, CenH3 could be observed on sperm chromatin but not the zygotic chromatin [67]. In mammals, the first zygotic divisions are also marked by replication independent dynamics of H3.3 [68,69]. In addition, H2B variant TH2B played a key role in genome-wide chromatin transition from histone to protamine and protamine to histone [70], indicating the important functions of histone variants in gametogensis.

The histone variants change the structure, dynamics and stability of nucleosomes in order to facilitate gene activation or inactivation. In the following section, we will focus on the specific loading of histone variants to the genome and their functions in transcriptional regulation and DNA repair, especially histone variants H2A.Z, H3.3 and H2AX.

2 Roles of histone variants in transcriptional regulation

2.1 H2A.Z

As early as 30 years ago, the role of H2A.Z in transcriptional regulation had been indicated in *Tetrahymena thermophila*, H2A.Z was specific to transcriptionally active macronucleus and absent from the inactive micronucleus, suggesting that H2A.Z plays an active role in genes regulation [71]. Then, the studies in yeast revealed that H2A.Z had effect on the transcriptional regulation and partially redundant with nucleosome remodelling complex SWI/SNF and Gcn-5 containing complex [72]. In addition, H2A.Z facilitates the recruitment of RNA polymerase II (RNP II) in certain genes under specific conditions [73], antagonizes telomeric silencing, which acts as a boundary element to protect euchromatin [74]. In human cells, CHIP-chip (chromatin immunoprecipitation-chip) experiments indicated that the correlation between H2A.Z and RNP II, H2A.Z is dynamically recruited to promoters before RNP II loading, suggesting its roles in transcription activation [75]. In addition, there were evidences showing the function of H2A.Z in transcription elongation in *Drosophila* [76] .

Apart from the function of H2A.Z in positively regulating gene expression, H2A.Z also plays a role in negatively regulating gene expression in *Drosophila* [77], *S. cerevisiae* [78] and human [79]. In yeast, H2A.Z may favor to stabilize the binding of the Sir complex to nucleosomes at HMR locus to mediate the silencing of HMR [78]. In mammals, H2A.Z directly interacts with HP1-α and works together to regulate the formation of heterochromatin domains [79].

Identification of the occupation of histone variants within genome helps us to understand their functions. The global views of the distribution of H2A.Z have been reported in many organisms, including yeast, *Drosophila*, *Arabidopsis* and human. In yeast, H2A.Z preferentially locates to the promoters of inactive genes. H2A.Z may also play a role in nucleosome positioning, for example, at the GAL4 model gene, H2A.Z-containing promoters define positions of nucleosomes in wild type, and H2A.Z-free promoters have a less organized chromatin structure in H2A.Z-null cells [24]. In *Drosophila*, the distribution of H2A.Z is not uniform, widely within the euchromatin and heterochromatin [80]. H2A.Z enrichment at 5′ regions of genes has been observed in many organisms, including yeast, *Drosophila*, human and plants, which affects the nucleosome density and the accessibility to DNA templates [26,27,81,82], suggesting that H2A.Z may contribute to form unique chromatin domains for transcription activation at TSSs [83]. H2A.Z in *Arabidopsis* was found to locate at gene bodies [27], implying its relation to gene responsiveness [84]. However, the mechanism of the role of H2A.Z in gene regulation remains largely unknown.

2.2 H3.3

The genome-wide distributions of H3.3 have been well understood in many organisms. In yeast, histone H3/H3.1 is more enriched at the promoter regions than coding regions and the positions at promoters are associated with transcriptional activity [85,86]. In contrast, H3.3 distributes not only at regions with transcriptional activity, but also at transposons in *Drosophila* [87]. Similar to mammals, the genome mapping of *Arabidopsis* H3.3 revealed that H3.3 is deposited at regions with transcriptional activity and is predominantly enriched at 3′ end of genes [88]. Recently, the genome-wide characterization of H3.3 in mammals revealed that H3.3 replaces the canonical H3 at gene bodies, *cis*-elements including promoters, enhancers and polycomb response elements, as well as telomeres and pericentromeric heterochromatin at different turnover rates, suggesting that there are different mechanisms involved to control the H3.3 replacement. Notably, the fast turnover rate of H3.3 at promoters is positively correlated with active histone modifications such as methylation of H3K4, acetylation of H3K9 and H3K27, and also associated with H2A.Z, which is responsible for both gene activity and inactivity [89].

The studies on the genome-wide distributions of histone variants indicated the functions of histone variants in transcriptional regulation; however, the molecular mechanisms involved are still mysteries. Histone variants may work via chromatin level such as modulating the high structure of chromatin, or cooperate with regulatory protein complexes to regulate gene expression.

3 Roles of histone variants in DNA repair

Due to the endogenous and exogenous DNA damage agents,

DNA damage occurs frequently in cells. In response to DNA damage, cells activate multiple processes, including gene regulation, cell cycle regulation, apoptosis and DNA repair. In the following section, we will focus on the role of histone variants H2A.X, H2A.Z as well as their modifications in DNA repair, especially in the double strand break (DSB) repair.

3.1 H2A.X

In the past few decades, many studies have contributed to revealing the molecular mechanism of DNA damage response (DDR) pathways, and H2A.X was found to be an important component of DDR. In response to DNA double strand break (DSB), H2A.X is rapidly phosphorylated at serine 139 in animals or serine 129 in yeast by a set of PI3-K-like kinases, including DNA-PK, ATM and ATR [90–93], the phosphorylated H2A.X was known as γ-H2A.X. In the presence of DNA DSB, γ-H2A.X rapidly accumulates around the DSB lesion, and other DNA damage response and repair related proteins also concentrate around the sites of DSBs; however, many of these actions are dependent on γ-H2A.X. For instance, γ-H2A.X interacts directly with MDC1 (mediator of damage checkpoint protein) [94], a mediator to recruit the MNR complex, including RAD51, MRE11, NBS1 (Nijmegen Breakage Syndrome 1) [95,96]. MDC1 stimulates ATM kinase activity and ATM further phosphorylate H2A.X, resulting in the spreading of γ-H2A.X around the DBSs [97]. In addition, the accumulations of other components of the repair machinery like Rad51, 53BP1 (p53-binding protein), BRCA1 (breast and ovarian cancer susceptibility protein 1) also rely on γ-H2A.X. Thus, γ-H2A.X is not simply a rapid and sensitive marker for DSBs in DDR, but an amplifier for the DNA damage signals. Upon damage, γ-H2A.X not only recruits the DNA damage repair proteins, but also the chromatin remodelers such as INO80. The mutated INO80 complex in yeast is hypersensitive to DNA damage agents [98], and impaired for the eviction of H2A.Z and γ-H2A.X, indicating that the chromatin remodelling driven by the INO80 is involved in DNA repair [99]. In addition to the phosphorylation of H2A.X which is required for DNA damage repair, recent studies have revealed that H2A.X ubiquitylation and acetylation are also involved in DDR [100].

During the DNA repair process, γ-H2A.X foci will gradually diminish [101]; however, how γ-H2A.X removes from the chromatin remains to be discovered. Research has indicated that there are multiple players involved in eliminating γ-H2A.X. In budding-yeast, γ-H2A.X is removed from chromatin before its dephosphorylation which is mediated by a three-protein complex named HTP-C containing the phosphatase Pph3 that regulates the phosphorylation status of H2A.X *in vivo* [102]. In animals, however, protein phosphatase 2A (PP2A) is responsible for the dephosphorylation of γ-H2A.X. When PP2A is inhibited, the γ-H2A.X foci always exists and the cells are hypersensitive to DNA damage [103]. In addition, there are many remodelling complexes involved in histone eviction, exchange and nucleosome reassembly in order to remove γ-H2A.X. For instance, the INO80 in yeast and NBS1 in mammals were found to have a function in histone eviction at DSBs [104,105]. Besides, the FACT, a heterodimer of Spt16 and SSRP1, has been reported to be involved in the replacement of nucleosomal H2A.X with H2A in human cells [106].

Without doubt, H2A.X is a key player in DNA repair, however, mild defects of DNA damage repair were observed in the H2A.X-deficient cells or animals, indicating that there are H2A.X-independent mechanisms in DDR.

3.2 H2A.Z

In addition to the role of H2A.X in DNA repair, recent work has made a breakthrough in discovering the role of H2A.Z in DSB repair. CHIP at a defined DSB site showed that H2A.Z functions directly in DSB, rather than by an indirect way through altered gene expression [107]. An open chromatin structure is critical to DNA repair process, enabling the repair machinery to access to the DNA damage sites, and the chromatin remodelling complex NvA4 is responsible for this process. NvA4 consists of two subunits—the p400 motor ATPase, which belongs to the INO80 family [108] and Tip60 acetyltransferase, which functions in acetylating the histone H2A and H4 [109]. The deposition of H2A.Z into nucleosomes at DSBs by p400 motor ATPase creates an open, accessible chromatin domain, which facilitates the acetylation and ubiquitination of histones, these modifications are required for altering the chromatin conformation and DSB repair [110]. GFP-HR (homologous recombination) reporter system indicated that loss of H2A.Z exchange leads to defect of the HR repair pathway [111]. In the H2A.Z and p400 inactive cells, the level of NHEJ (nonhomologous end-joining) significantly decreased [107]. These results suggested that H2A.Z participates in DNA repair pathway; however, the mechanism in detail remains to be discovered.

4 Histone variants in plants

Compared to mammals, plants continually face the changes of environments like temperature, drought, nutrition as well as pathogens, and have developed multiple mechanisms to overcome the changeable environmental conditions to adapt their developments. Here we summarize and discuss the roles of histone variants in regulating gene expression in response to developmental and environmental stimuli.

4.1 H2A.Z in *Arabidopsis*

Recent studies have suggested that H2A.Z and H3K4 meth-

ylation are involved in regulation of gene responsiveness [112]. For instance, in yeast *ino80* mutant, H2A.Z mislocalization results in the reduced responsiveness to transcriptional changes of gene KAR4 [113]. *Arabidopsis* H2A.Z not only enriches at TSSs which is in agreement with results from yeast and human, but also locates at gene bodies of genes that respond to environmental or developmental stimuli.

In a forward genetic screen, *ARP6*, a gene which encodes a critical subunit of SWR1 complex known to deposit H2A.Z, was found to control responses to ambient temperature in *Arabidopsis* [114]. Gene expression profiling revealed a significant constitutive warm temperature transcriptome in *arp6* mutants which defect in H2A.Z distribution. CHIP indicated that H2A.Z occupancy at TSSs of temperature responsive genes was reduced at 27°C compared to that at 17°C in wild type, suggesting that H2A.Z-containing nucleosomes perform dynamic responses to temperature [114]. Phosphate starvation response (PSR) genes, which always have H2A.Z-containing nucleosomes near their TSSs, show low expression in wild type at normal condition and are induced under phosphate deficiency. In contrast, PSR genes were highly induced in *arp6* mutants at the normal condition and showed phosphate starvation related phenotypes, indicating H2A.Z plays a role in maintaining the repressive state of the PSR [115]. Similarly, mutation in PIE, which codes a subunit of SWR complex, showed a constitutive induction of systemic acquired resistance (SAR) dependent genes in the absence of pathogen infection [116]. These data suggested that H2A.Z coupled with SWR plays repressive or inductive roles in *Arabidopsis*. In addition, H2A.Z occupancy at gene bodies has been reported to correlate with gene responsiveness [84]. However, the mechanisms of H2A.Z in the regulation of gene responsiveness remain unclear.

Arabidopsis H2A.Z also contributes to transcriptional regulation. For example, the FLC gene expresses during vegetative growth and stays silent before flowering, which is critical in the transition from the vegetative growth to flowing. This switch from the active to silent state is associated with various regulations at chromatin level, including the modification of histone H3, chromatin remodelling, deposition of histone H2A.Z and ubiquitination of histone H2B [117–120]. H2A.Z is deposited at the FLC locus, and loss of H2A.Z leads to reduced FLC expression and promoted flowering, indicating that H2A.Z positively regulates FLC to repress flowering [116].

Mutants in H2A.Z and SWR1 subunits exhibit many developmental phenotypes, including early flowering, small flowers, dwarf, curly leaves and reduced fertility [121]. Not surprisingly, both the male and female gametophyte developments are disturbed in these mutants. The mutants have a smaller size of anthers and less number of pollen grains resulting from the defect in male gametogenesis. Defects in female meiosis were also observed in the *arp6* mutant as a result from downregulation of meiotic genes, such as DMC1 (disrupted meiotic cDNA1). H2A.Z is deposited in the DMC1 gene body in wild type; however, in the *arp6* mutant, the occupancy of H2A.Z is significantly decreased at DMC1 gene body, supporting a role of H2A.Z in meiosis [122].

4.2 H3.3 in *Arabidopsis*

H3.3 is less understood in *Arabidopsis* than animals. Recently, genome-wide location maps of the *Arabidopsis* H3.3 revealed that H3.3 is distributed at gene bodies which correlate with transcriptional activity of related genes, promoter regions and the downstream of the 3′ end of active genes, suggesting a role of H3.3 in transcriptional regulation [123].

5 Perspective

Over the past few years, evidences have indicated the roles of histone variants in transcriptional regulation, DNA repair and plant development. The replacement of canonical histones by variants results in the alteration of nucleosome dynamics, stability, structure and the accessibility to DNA templates by transcription factors or enzymes like Pol II. In addition to histone variant replacement, transcriptional regulation at the chromatin level is frequently involved in histone variant-specific modifications; however, whether there are relationships between histone variant replacement and modifications in gene regulation is rarely reported. Moreover, DNA methylation coupled with histone variants in gene activation and inactivation is required for future investigation. The mechanisms for the roles of histone variants in DNA damage and plant development are also required for intensive studies.

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