H2A Variants in *Arabidopsis*: Versatile Regulators of Genome Activity

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ABSTRACT

The eukaryotic nucleosome prevents access to the genome. Convergently evolving histone isoforms, also called histone variants, form diverse families that are enriched over distinct features of plant genomes. Among the diverse families of plant histone variants, H2A.Z exclusively marks genes. Here we review recent research progress on the genome-wide distribution patterns and deposition of H2A.Z in plants as well as its association with histone modifications and roles in plant chromatin regulation. We also discuss some hypotheses that explain the different findings about the roles of H2A.Z in plants.

Key words: histone H2A.Z, transcription, *Arabidopsis*, histone variant, histone modifications

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INTRODUCTION

Nucleosomes are a distinguishing feature of eukaryotes. They consist of two copies of each of the four core histones H2A, H2B, H3, and H4. Each nucleosome prevents accessibility to ~147 bp of DNA (Luger et al., 1997). As a consequence, nucleosomes act as general repressors of transcription. Post-translational modifications of core histones have been associated with transcriptional regulation but the extent to which chromatin directly controls the transcriptional machinery remains a matter of controversy. Histone variants are isoforms of core histones that acquired comparable properties and functions through convergent evolution (Talbert et al., 2012; Talbert and Henikoff, 2017). Histone variants are found primarily among the families of histones H3 and H2A. Although isoforms of histone H2B exist, they do not currently qualify as variants because there is a lack of evidence of functional convergence.

In both plants and animals, the histone H3 family consists of three major types of variants, replication-dependent H3, which is generally referred to as H3.1 and H3.2 in vertebrates and as H3.1 in plants, the replacement histone H3.3, and the centromeric H3 (CenH3/CENP-A) (Henikoff and Ahmad, 2005; Muller and Almouzni, 2014). The sequence of CenH3/CENP-A is highly divergent from other H3 variants and it is incorporated specifically at the centromeric region (Malik and Henikoff, 2009; Fukagawa and Earnshaw, 2014). H3.1 and H3.3 are distinguished from each other by only four to five amino acids and act as replication-dependent and replacement histones, respectively (Malik and Henikoff, 2003; Talbert et al., 2012; Filipescu et al., 2014). In animals, the properties of H3 variants and their roles in development and disease has been reviewed extensively (Filipescu et al., 2014; Buschbeck and Hake, 2017). In plants, replication-dependent H3.1 and H3.3 variants also differ from each other by only two to four amino acid residues (Ingouff and Berger, 2010; Talbert et al., 2012; Borg and Berger, 2015; Lu et al., 2018). They show distinct genome localization, with H3.3 more abundant over gene bodies of highly expressed genes (Stroud et al., 2012; Wollmann et al., 2012). In addition, H3.3 appears to antagonize H1 deposition and promote the deposition of gene body methylation (Wollmann et al., 2017) while H3.1 is essential for the deposition of H3K27me1 (Jacob et al., 2014) and the propagation of the epigenetic memory carried by H3K27me3 through cell division (Jiang and Berger, 2017). In addition to these three major H3 variants, plants also evolved additional H3 variants with amino acid substitutions at the N-terminal tail that are predicted to impact deposition of lysine modifications (Borg and Berger, 2015). At least two of these variants show a cell-specific expression pattern. The *Arabidopsis* H3 variant H3.10 is specifically and abundantly deposited into sperm cell chromatin and H3.14 is specifically expressed in the sperm companion cell in pollen and in endosperm (Ingouff et al., 2010), suggesting that they play specific developmental roles.

Variants in the H2A family are primarily distinguished by motifs in their C-terminal tail. Most eukaryotes share several types of H2A variants, including H2A,Z, H2A.X, and replicative H2A (Bonisch and Hake, 2012; Talbert et al., 2012; Weber and Henikoff, 2014; Kawashima et al., 2015). In contrast with H3 variants, the link between replication and H2A variants is not as clearly reviewed extensively (Filipescu et al., 2014; Buschbeck and Hake, 2017). In plants,
established in plants, neither at the level of transcriptional control nor protein deposition. Unique types of H2A variants have also evolved in animals and plants (Talbert et al., 2012; Kawashima et al., 2015). Metazoans encode macroH2A, which contains a ~25-kDa “macro-domain” at its C-terminal and may act as a transcriptional repressor (Buschbeck and Hake, 2017; Sun and Bernstein, 2019). H2A.B is a mammalian-specific H2A variant that is strongly expressed in the testis, and to a lesser extent in the brain, and affects nucleosome structure (Arimura et al., 2013; Molaro et al., 2018; Anuar et al., 2019).

In addition to H2A.Z, H2A.X, and the replicative H2A, the H2A.W variants evolved in land plants and are characterized by the motif KSPKK in the C-terminal tail (Talbert et al., 2012; Kawashima et al., 2015). Constitutive heterochromatin and transposons are occupied by H2A.W, which is also absent from genes (Yelagandula et al., 2014; Lorkovic et al., 2017). The bodies of expressed genes are covered by H2A and H2A.X, while the first nucleosomes are occupied by H2A.Z (Yelagandula et al., 2014). H2A.X is essential for the response to DNA damage in Arabidopsis (Lorkovic et al., 2017) similar to reports in other eukaryotes (Foster and Downs, 2005). DNA damage triggers H2A.X phosphorylation on the serine residue of the SQEF motif by the conserved DNA damage responsive kinase ATM. Another kinase, ATR, is responsible for a minor fraction of H2A.X phosphorylation (Donia and Mittelsten Scheid, 2015; Lorkovic and Berger, 2017). It remains unclear whether the histone chaperone FACT is involved in H2A.X deposition in Arabidopsis as was previously shown in mammalian cells (Piquet et al., 2018). H2A.Z acts as a general boundary between noncoding chromatin and transcription start sites (TSS) and is enriched over bodies of transcriptionally repressed genes that, together, constitute facultative heterochromatin (Coleman-Derr and Zilberman, 2012; Yelagandula et al., 2014; Carter et al., 2018). Hence, H2A variants differentiate expressed genes, non-expressed genes, and silenced transposons that are no longer accessible to transcription (Figure 1 A).

At the DNA replication fork, nucleosomes are deposited by dedicated chaperones that assemble a tetramer containing two H3, two H4, and chaperones that deposit two H2A-H2B heterodimers. The chaperone NAP1 mediates deposition of the H2A-H2B heterodimer regardless of the H2A variant present in the heterodimer (Zlatanova et al., 2007; Gurard-Levin et al., 2014; Sauer et al., 2018). At present, in plants, no chaperone has been identified that deposits a specific type of H2A variant at the DNA replication fork. Hence, at the time of nucleosome deposition at the DNA replication fork, some proportion of newly deposited nucleosomes likely contain two different H2A variants (heterotypic nucleosomes). Yet, homotypic nucleosomes are overwhelmingly dominant in differentiated cells of the model plant species Arabidopsis thaliana (Osakabe et al., 2018). This implies that yet unknown dedicated mechanisms catalyze the exchange of specific types of H2A variants to convert heterotypic nucleosomes deposited after DNA replication into homotypic nucleosomes.
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| Locus     | Gene   | Protein | Locus     | Gene   | Protein | Locus     | Gene   | Protein |
|-----------|--------|---------|-----------|--------|---------|-----------|--------|---------|
| H2A       | At5g54640 | HTA1 | H2A.1 | YDR225W | HTA1 | H2A.1 | SPCC622.08c | hta1 | H2A.2 |
|           | At4g27230 | HTA2 | H2A.2 | YBL003C | HTA2 | H2A.2 | SPAC19G12.06c | hta2 | H2A.5 |
|           | At1g51060 | HTA10 | H2A.10 |       |       |       |       |       |       |
|           | At3g20670 | HTA13 | H2A.13 |       |       |       |       |       |       |
| H2A.X     | At1g54690 | HTA3 | H2A.X.3 |       |       |       |       |       |       |
|           | At1g08880 | HTA5 | H2A.X.5 |       |       |       |       |       |       |
| H2A.Z     | At4g13570 | HTA4 | H2A.Z.4 | YOL012C | HTZ1 | H2A.Z | SPBC11B10.10c | pht1 | H2A.Z |
|           | At2g38810 | HTA8 | H2A.Z.8 |       |       |       |       |       |       |
|           | At1g52740 | HTA9 | H2A.Z.9 |       |       |       |       |       |       |
|           | At3g54560 | HTA11 | H2A.Z.11 |       |       |       |       |       |       |
| H2A.W     | At5g59870 | HTA6 | H2A.W.6 |       |       |       |       |       |       |
|           | At5g27670 | HTA7 | H2A.W.7 |       |       |       |       |       |       |
|           | At5g02560 | HTA12 | H2A.W.12 |       |       |       |       |       |       |

Table 1. List of Histone H2A Nomenclature in Arabidopsis, Budding Yeast, and Fission Yeast.

Each type of H2A variant confers distinct biophysical properties to nucleosomes in plants (Osakabe et al., 2018) and animals (Abbott et al., 2001; Arimura et al., 2013; Chakravarty et al., 2005; Park et al., 2004; Watanabe et al., 2013). Nucleosomes cause stalling of RNA PolII and it has been proposed that transcriptional initiation is required to overcome the energy barrier imposed by nucleosomes (Bintu et al., 2012; Bondarenko et al., 2006; Kireeva et al., 2005). This energy barrier is decreased when the first nucleosome encountered by RNA PolII contains the histone variant H2A.Z, suggesting that this variant plays an essential role in directing transcription (Rudnizky et al., 2016; Subramanian et al., 2015; Weber et al., 2014) (Figure 1B). In fission yeast, it has been proposed that H2A.Z participates in the initiation and termination of transcription (Rainsier et al., 2005; Albert et al., 2007; Venter et al., 2011; Weber and Henikoff, 2014). In animals, the loss of H2A.Z affects transcriptional activity in a complex manner that awaits clarification (Bonisch and Hake, 2012; Giammo et al., 2019). This review is focused on the roles of H2A.Z in plants. For nearly a decade there has been a strong increase in the number of studies, mostly based on genetic approaches, unveiling a link between H2A.Z and responsiveness (Jarillo and Pineiro, 2015; Kumar, 2018). However, the factual links between genetic studies and mechanistic insights remain unclear and further directions for this field of research will be outlined.

HOW TO IDENTIFY H2A.Z VARIANTS IN PLANTS?

H2A.X and H2A.W harbor the specific motifs SQEF and KSPK, respectively, but this is not the case for H2A.Z (Figure 1C). Most H2A.Z variants have the shortest C-terminal tails among H2A variants. In addition, they differ from all other variants by their L1 loop, which resides in the conserved histone fold domain and mediates interaction via hydrogen bonds between the two H2A proteins within the nucleosome (Andrews and Luger, 2011; Bonisch and Hake, 2012; Luger et al., 1997) (Figure 1C). Sequences of the H2A.Z L1 loop are highly diverged from other H2A variants, which enable the clear identification of H2A.Z. In flowering plants, the sequence of the H2A.Z L1 loop, with the consensus sequence A/S/T/QAN/H/SG, is not fully conserved (Kawashima et al., 2015). The docking domain of histone H2A, placed at the DNA entry/exit point, interacts with H3/H4 and directs the H3 N-terminal helix to interact with DNA (Andrews and Luger, 2011; Bonisch and Hake, 2012; Shaytan et al., 2015). In H2A.Z variants, the docking domain is very conserved and distinct from other H2A variants, consistent with its role in H2A.Z-specific mechanisms of deposition and exchange (Tarbell et al., 2012; Kawashima et al., 2015) (Figure 1C). In summary, the short C-terminal tail, docking domain, and L1 loop sequences are distinctive features for identifying H2A.Z variants.

HOW MANY H2A.Z ISOFORMS EXIST?

During the evolution of streptophytes, from single-cell algae to flowering plants, H2A variants diversified. In addition to the acquisition of the plant-specific class H2A.W, the number of genes encoding each type of H2A variant increased, leading to distinct isoforms (Table 1). This variation does not correlate with either genome size or genome duplication events, likely reflecting positive evolutionary selection (Kawashima et al., 2015). This is clearly the case for H2A.Z, which is represented by a single gene and protein in the charophyte Klebsormidium nitens and extant representatives of early land plants, including Marchantia polymorpha. In bryophytes, the number of genes encoding H2A.Z vary but they encode the same protein. In flowering plants, the number of H2A.Z genes vary, and they encode distinct isoforms (Figure 1C and Table 1), although it is not yet clear whether these isoforms show distinct properties and play distinct roles. In Arabidopsis, three genes encode the three isoforms H2A.Z.8 (At2g38810), H2A.Z.9 (At1g52740), and H2A.Z.11 (At3g54560). The increasing severity of phenotypes in single, double, and triple mutants (Choi et al., 2007; March-Díaz et al., 2008; Nie et al., 2019) suggests a wide degree of...
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redundancy between the H2A.Z isoforms in Arabidopsis. Despite this, their expression patterns are distinct (https://www.arabidopsis.org), with H2A.Z.9 and H2A.Z.11 seeming to be expressed in a replication-dependent manner (https://cyclebase.org/CyclebaseSearch and March-Díaz and Reyes, 2009). These aspects merit further in-depth studies to investigate the potential sub-functionalization of H2A.Z in plants, as has been reported in mammals (Dryhurst et al., 2009).

H2A.Z CON芙ES SPECIFIC BIOPHYSICAL PROPERTIES TO THE NUCLEOSOME

Although heterotypic nucleosomes containing two different H2A variants were reported in animals and yeast (Viens et al., 2006; Luk et al., 2010; Nekrasov et al., 2012), Arabidopsis chromatin consists primarily of homotypic nucleosomes of each type of H2A variant (Osakabe et al., 2018), suggesting that each variant confers specific properties to the nucleosome.

Regarding the stability of the H2A.Z nucleosomes, contrasting results have been reported in animals and yeast (Abbott et al., 2001; Park et al., 2004; Horikoshi et al., 2013; Watanabe et al., 2013). In Arabidopsis, H2A.Z confers lower stability compared with other H2A variants as H2A.Z-H2B disassociated from the nucleosome at lower temperatures than H2A-H2B in vitro (Osakabe et al., 2018). This is consistent with previous results with human H2A.Z nucleosomes (Horikoshi et al., 2016). As shown in animals (Thakar et al., 2009), the stability differences observed between H2A.Z and other H2A variants in Arabidopsis are likely due to the short C-terminal tail, which can barely bind to linker DNA in contrast to H2A (Osakabe et al., 2018). The low stability of H2A.Z homotypic nucleosomes also results from changes in charge, which potentially influence loop-loop and/or loop-DNA interactions, in line with data from molecular dynamic simulations of the L1 loop from mammalian H2A.Z (Bowerman and Wereszczyński, 2016).

GENOMIC LOCALIZATION OF H2A.Z

In yeast, H2A.Z occupies the +1 nucleosome while the remaining gene body is occupied by H2A.X (Figure 1B). As in yeast, H2A.Z is absent from transposons and repeats in flowering plants, but it shows two types of enrichment patterns over gene bodies (Coleman-Derr and Zilberman, 2012; Yelagandula et al., 2014). One pattern is similar to that described in yeast, with H2A.Z enriched in the first nucleosome while the rest of the gene body is occupied by H2A and H2A.X. The other pattern is distinctive, with H2A.Z occupying the entire gene body with sharp boundaries at both the 5' and 3' ends. These patterns described in Arabidopsis are also observed in rice (Zahraefard et al., 2018) and are thus likely present in all flowering plants.

H2A.Z enrichment over gene bodies is anticorrelated with enrichment in the histone variant H3.3 (Wollmann et al., 2017), linker histone H1 (Wollmann et al., 2017), and DNA methylation in CG contexts (Zilberman et al., 2008). The anticorrelation between CG methylation and H2A.Z is still not fully explained. Complete loss of H2A.Z causes local hypermethylation over genes and intergenic regions and these differentially methylated regions are associated with the recruitment of the DNA demethylase ROS1 by H2A.Z (Nie et al., 2019). However, overall gene body methylation is not perturbed in either partial (Coleman-Derr and Zilberman, 2012) or complete loss-of-function H2A.Z mutants (Nie et al., 2019). In contrast, loss of CG methylation in the met1 mutant causes a strong increase in H2A.Z toward the 3' end of highly expressed genes (Zilberman et al., 2008), but the significance of this change and the mechanism involved remain unclear. This anticorrelation between H2A.Z and CG methylation is also observed in other eukaryotes (Zemach et al., 2010; Murphy et al., 2018) although there are exceptions (Bewick and Schmitz, 2017).

The relative enrichment of the three types of H2A variants over gene bodies varies depending on the level of gene expression (Yelagandula et al., 2014). Whereas contrasting reports were made relative to the correlation between H2A.Z at the TSS and gene expression, occupancy of the entire gene body by H2A.Z is clearly associated with gene repression (Coleman-Derr and Zilberman, 2012; Yelagandula et al., 2014; Dai et al., 2017; Sura et al., 2017; Carter et al., 2018; Gómez-Zambrano et al., 2019). This association is further supported by a tight correlation between H2A.Z occupancy and the repressive histone modifications H3K27me3, deposited by the Polycomb repressive complex 2 (PRC2) (Dai et al., 2017; Carter et al., 2018; Gómez-Zambrano et al., 2019), and H2A.Z monoubiquitination through the PRC1 subunit AtBMI1 (Gómez-Zambrano et al., 2019). Hence, in plants, H2A.Z is primarily associated with repressive marks and low gene expression. However, a minor proportion of H2A.Z is associated with H3K36me3 in the first nucleosomes after the TSS of genes expressed at high levels (Sequeira-Mendes et al., 2014), as reported in other eukaryotes. These two contrasting patterns of H2A.Z occupancy suggest that different isoforms of H2A.Z show different distribution patterns, or that distinct mechanisms regulate the dynamics of H2A.Z along the gene body, or that these patterns are the consequence of transcriptional activity.

DEPOSITION OF H2A.Z IN PLANTS

The predominance of homotypic nucleosomes for each type of Arabidopsis H2A variant suggests that each variant carries specific residues or domains responsible for their specific deposition (Osakabe et al., 2018). As H2A.Z diverged early during eukaryotic evolution, specific deposition mechanism have co-evolved, consisting of specific chaperones and chromatin remodelers (Buschbeck and Hake, 2017; Talbert et al., 2019).

This is illustrated by studies in budding and fission yeast that possess only one H2A.Z and one replicative H2A variant, which harbors the SQ motif and also functions as H2A.X (Table 1). Typically, yeast genes are covered by H2A.X with the exception of one or two homotypic H2A.Z nucleosomes at the TSS (Tramantano et al., 2016). The chromatin remodeler INO80 enables the eviction of H2A.Z (Brahma et al., 2017; Morrison and Shen, 2009), while specific deposition of H2A.Z is achieved by the chromatin remodeler SWR1 complex, which acts together with the chaperones FACT and Spt6 that favor the exchange of H2A.Z to H2A and with the chaperone Chz1 that favors the deposition of H2A.Z (Gerhold and Gasser, 2014; Gómez-Zambrano et al., 2018; Luk et al., 2007; Morrison and
Table 2. List of SWR1 Complex in Arabidopsis, Budding Yeast, and Fission Yeast.

Shen, 2009; Zhou et al., 2016a (Tables 2, 3, and 4). Besides Chz1 in fungi, the mammalian Anp32e is the only other chaperone with a specific affinity for H2A.Z and it is involved in eviction of H2A.Z after nucleosome deposition (Mao et al., 2014).

The Swi/Snf helicase superfamily possesses a Swi/Snf (SWITCH helicase-related sequence motifs. The Swi/Snf catalytic domain serves as a motor that alters histone-DNA interactions within nucleosomes (Hamiche et al., 1999; Langst et al., 1999; Whitehouse et al., 1999; Jaskelioff et al., 2000). Chromatin remodelers enhance nucleosome sliding, histone removal/exchange, and nucleosome replacement (Flaus et al., 2006; Ho and Crabtree, 2010; Narlikar et al., 2013; Gerhold and Gasser, 2014). Most chromatin remodelers form large complexes with accessory factors, which select from among a broad range of remodeling activities and guide the remodeling complex to precise genomic regions. The Swi/Snf superfamily is further divided into subfamilies based on differences within their Swi/Snf-specific motifs (Wang et al., 1996; Clapier and Cairns, 2009; Ryan and Owen-Hughes, 2011). In budding and fission yeast, 13 remodelers are represented by five major subfamilies, including the H2A.Z chromatin remodelers SWR1 and INO80. The structure of these remodelers has been obtained but the exact mechanism of exchange remains debated (Hong et al., 2014; Ranjan et al., 2015; Willhoft et al., 2018; Singh et al., 2019).

The Swi/Snf helicase superfamily has expanded during animal and plant evolution, reaching 43 proteins in the model plant Arabidopsis thaliana (Knizewski et al., 2008). The physiological and developmental impacts of several chromatin remodeler mutants have been studied in Arabidopsis (Archacki et al., 2013, 2017; Jegu et al., 2017; Jerzmanowski, 2007; Ojolo et al., 2018; Peirats-Llobet et al., 2016; Walley et al., 2008). Biochemical studies have identified the overall conservation of the SWR1 complex in Arabidopsis (Nie et al., 2019; Potok et al., 2019; Sijacic et al., 2019) (Table 2). Three recent reports have clarified the mechanism involved in targeting SWR1 in Arabidopsis, which includes PIE, the ortholog of the catalytic subunit of SWR1 and ACTIN PROTEIN RELATED 6 (ARP6). Additional interacting proteins have been uncovered from immunoprecipitates from plants expressing flag-tagged (Potok et al., 2019; Sijacic et al., 2019). These include METHYL BINDING DOMAIN 9 (MBD9). Analysis of H2A.Z enrichment in immunoprecipitates from plants expressing flag-tagged (Potok et al., 2019; Sijacic et al., 2019).
chromatin states favor or repel MBD9-dependent H2A.Z enrichment (Sijacic et al., 2019). The loss of MBD9 primarily affects H2A.Z deposition over genes that show a strong enrichment of H2A.Z at the TSS but not over the gene body, which are active genes (Potok et al., 2019). Size-exclusion chromatography experiments indicate that MBD9 is not a core component of SWR1, but likely associates temporarily with the complex, a conclusion also supported by genetic interactions between SWR1, but likely associates temporarily with the complex, a conclusion also supported by genetic interactions between mbd9 and arp6 mutants (Sijacic et al., 2019). MBD9 occupies the nucleosome-depleted region upstream of the TSS of active genes marked by H3 acetylation and devoid of H3K27me3 (Nie et al., 2019). This indicates that other mechanisms are involved in the deposition of H2A.Z. These could include other chromatin remodelers, such as ISWI, encoded by the redundant genes CHR17 and CHR11 in Arabidopsis, which is involved in maintaining the regular spacing of nucleosomes in gene bodies (Li et al., 2014). MBD9 associates with CHR17 and CHR11 (Potok et al., 2019) and could thus recruit an H2A.Z-specific chaperone, which remains to be characterized in plants. Interestingly, CHR17 and CHR11 do not interact with ARP5, suggesting that MBD9 interacts with these two complexes (SWR1 and ISWI) separately (Potok et al., 2019).

Other proteins associated with SWR1 are NPX1, which contains a bromodomain that binds H3 peptides acetylated at K14, K18, and K23 (Nie et al., 2019), and TRA1A and TRA1B (Potok et al., 2019; Sijacic et al., 2019) (Table 2). NPX1 is involved in the recruitment of SWR1 and shows patterns of enrichment in the 5’ and 3’ UTR of genes coincident with high levels of acetylation (Nie et al., 2019). TRA1A and TRA1B, are components of the SAGA acetyltransferase complex (Pfab et al., 2018) and of the NuA4 complex (Cai et al., 2003; Doyon and Cote, 2004; Qian et al., 2012; Lang et al., 2015; Duan et al., 2017), providing another link between histone acetylation and H2A.Z deposition. Histone acetylation is also mediated by the INCREASED DNA METHYLATION (IDM) complex that binds methylated DNA (Qian et al., 2012; Lang et al., 2015; Wang et al., 2015; Duan et al., 2017). Genetic interaction studies suggest that the function of the IDM complex initiates a series of events that promotes H2A.Z recruitment, which then recruits ROS to promote DNA demethylation and the loss of silencing (Nie et al., 2019).

Interestingly, the loss of SWR1 subunits causes only a partial loss of H2A.Z (Potok et al., 2019) and phenotypes that are much milder (Choi et al., 2005, 2007; Martin-Trillo et al., 2006; March-Diaz et al., 2007) than the total loss of H2A.Z, which is barely viable (Nie et al., 2019). This indicates that other mechanisms are involved in the deposition of H2A.Z. These could include other chromatin remodelers, such as ISWI, encoded by the redundant genes CHR17 and CHR11 in Arabidopsis, which is involved in maintaining the regular spacing of nucleosomes in gene bodies (Li et al., 2014). MBD9 associates with CHR17 and CHR11 (Potok et al., 2019) and could thus recruit an H2A.Z-specific chaperone, which remains to be characterized in plants. Interestingly, CHR17 and CHR11 do not interact with ARP5, suggesting that MBD9 interacts with these two complexes (SWR1 and ISWI) separately (Potok et al., 2019).

Although much emphasis has been placed on SWR1 activity, very less is known about the roles of recently identified INO80 ortholog in plants (Zhou et al., 2016b), which also binds to H2A.Z (Zhang et al., 2015). A recent report has shed new light on its function with the identification of EIN6 ENHANCER (EEN), the ortholog of IES6 from budding yeast and human INO80C, a component of the INO80 complex (Table 3) (Shen et al., 2003; Morrison et al., 2004; Zhang et al., 2015; Zander et al., 2019). IES6 forms the nucleosome recognition module of the INO80 chromatin remodeling complex, which also contains ACTIN-RELATED PROTEIN5 (ARP5) (Eustermann et al., 2018). This module is crucial for the remodeling activity of the INO80 complex (Tosi et al., 2019).
**Table 4. List of H2A/H2B Chaperones in Arabidopsis, Budding Yeast, and Fission Yeast.**

| Locus          | Gene   | Protein | Locus          | Gene   | Protein | Locus          | Gene   | Protein |
|----------------|--------|---------|----------------|--------|---------|----------------|--------|---------|
| H2A/H2B chaperones |        |         | Arabidopsis thaliana |        |         | Saccharomyces cerevisiae |        |         | Schizosaccharomyces pombe |
| At4g26110      | NAP1.1 | NAP1.1  | YKR048C        | NAP1   | Nap1    | SPCC364.06     | nap1   | Nap1    |
| At2g19480      | NAP1.2 | NAP1.2  |                 |        |         | SPBC2D10.11c   | nap2   | Nap2    |
| At5g56950      | NAP1.3 | NAP1.3  |                 |        |         |                 |        |         |
| At3g13782      | NAP1.4 | NAP1.4  |                 |        |         |                 |        |         |
| At1g74560      | NRP1   | NRP1    |                 |        |         |                 |        |         |
| At1g18800      | NRP2   | NRP2    |                 |        |         |                 |        |         |
| At4g08310      | CHZ1A  | CHZ1A   | YER030W        | CHZ1   | Chz1    | SPAC4G9.06c    | chz1   | Chz1    |
| At1g44780      | CHZ1B  | CHZ1B   |                 |        |         |                 |        |         |
| At4g10710      | SPT16  | SPT16   | YGL207W        | SPT16  | Spt16   | SPBP8B7.19     | spt16  | Spt16   |
| At3g28730      | SSSL1  | SSSL1   | YMLD69W        | POB3   | Pob3    | SPBC6O9.05     | pob3   | Pob3    |
|                 |        |         |                 |        |         | YML246W        | VPS75  | Vps75   |

**ROLE OF H2A.Z IN TRANSCRIPTION**

A clear involvement for H2A.Z in transcription was provided from studies in yeast where H2A.Z assists in recruiting RNA PolII and promotes elongation (Santisteban et al., 2000, 2011). In *Drosophila*, H2A.Z occupancy is anti-correlated with RNA PolII stalling during transcription (Weber et al., 2014) and it has been proposed that H2A.Z-H2B heterodimers are more easily displaced from nucleosomes lost when RNA PolII unwraps the nucleosomes (Weber and Henikoff, 2014). In plants, there is ample evidence that H2A.Z function is tightly coupled with transcription, especially in response to environmental signals (Deal and Henikoff, 2011; Jarillo and Pineiro, 2015; Kumar, 2018). In response to shifts in temperature, the transcription factor HEAT SHOCK FACTOR 1 (HSF1) is required for the temporary eviction of H2A.Z from the bodies of repressed genes (Cortijo et al., 2017). HSF1 might recruit chaperones of remodeling complexes involved in transcriptional regulation, such as the chromatin remodeling factor BRAHMA (BRM), which occupies thousands of genes (Archacki et al., 2017). The loss of BRM (Archacki et al., 2017) or of SWR1 (Sura et al., 2017) causes up- and downregulation of thousands of loci. A study that combined analyses of transcriptome of *arp5* and *bmr* with H2A.Z, BRM, and nucleosome occupancy shows that distinct configurations lead to a complex involvement of H2A.Z and its associated remodelers in transcriptional regulations (Torres and Deal, 2019). In brief, eight types of promoters are distinguished by antagonistic or coordinated roles of H2A.Z and BRM on the stability of the +1 nucleosome and of the impact of BRM on nucleosomes flanking the nucleosome-depleted region upstream of the TSS. The complex regulation explains previous contrasting results summarized in (Torres and Deal, 2019) and this complexity likely results from other factors including SPLAYED another chromatin remodeler, which is partially redundant with BRM in genetic studies (Bezhani et al., 2007; Sang et al., 2012) and possibly as well from distinct chromatin modifications associated with each type of promoter. Genes regulated jointly by BRM and H2A.Z are involved in response to light, defense, temperature, and growth, reinforcing the conclusion that H2A.Z is not a sensor of a specific factor, such as temperature as proposed in older studies (Kumar and Wigge, 2010).

In plants, the majority of H2A.Z homotypic nucleosomes are associated with repressive facultative heterochromatin marked by H3K27me3 while a small fraction is associated with H3K27ac (Klein et al., 2018). YAF9 recruits the acetyltransferase complex Nu4A, which acetylates H4, H2A, and H2B. YAF9 contains a YEATS (Yaf9/GAS41-ENL-AF9-TAF14-SAS5) domain. In budding yeast, the YEATS domain of Yaf9 selectively binds to H3K27ac (Klein et al., 2018). YAF9 recruits the acetyltransferase complex Nu4A, which acetylates H4, H2A, and H2A.Z (Auger et al., 2008), and the SWR1 complex (Wu et al., 2009). Hence, YAF9 likely participates in coordinating the action of these two complexes at the +1 nucleosome (Lu et al., 2009). The important motif GWGEF, in which the E residue is crucial for the selective recognition of H3K27ac, is conserved in *Arabidopsis* orthologs and it is thus likely that YAF9A and YAF9B also recognize this mark in *Arabidopsis*. *Arabidopsis* YAF9 is also associated with Nu4A (Crevillon et al., 2019) and SWR1 (Gómez-Zambrano et al., 2018) and participates in controlling FLC expression, where it is responsible for...
deposition of H2A.ZAc, H4Ac, and H2A.Z over the gene body (Crevillon et al., 2019). YAF9 interacts with the SWC4 module, which is common to both the Nu4A and SWR1 complexes and is involved in the genome-wide recruitment of SWR1 (Gómez-Zambrano et al., 2018). Interestingly, YAF9B was not found in association with SWR1 subunits, suggesting that it is primarily associated with Nu4A (Sijacic et al., 2019). In plants, it is likely that the conserved YAF9-SWC4 module is more generally involved in assisting transcriptional activation, or at least activity, through H2A.Z acetylation (Gaiamo et al., 2019).

Recent publications are beginning to detail the potential roles of the SWR1 and INO80 complexes in the interaction between H2A.Z and H3K27me3 (Wang et al., 2019). Curiously, the loss of INO80 does not cause a genome-wide increase in H2A.Z levels, suggesting that other mechanisms are involved in the eviction of H2A.Z. In mammals, the chaperone Anp32E plays also a role in H2A.Z eviction, but no ortholog of this chaperone has been reported in plants (Obri et al., 2014). SWR1 promotes the deposition of H3K27me3. Yet the Arabidopsis ortholog of the INO80 complex subunit IES6, EEN, binds to responsive genes and an increased enrichment of H2A.Z is observed in mutants deficient for INO80 function, suggesting that INO80 function depends on other regulatory pathways associated with responsive genes (Zander et al., 2019). The chromatin state of responsive genes is associated with H2A.Z and H3K27me3 (Coleman-Derr and Zilberman, 2012; Carter et al., 2018; Xu et al., 2018) and an interaction between INO80 and the H3K27me3 demethylase REF6 has been reported (Smaczniak et al., 2012). The ref6 and een double mutant shows increased levels of H2A.Z and H3K27me3 at the gene ETHYLENE INSENSITIVE 2 (EIN2) (Zander et al., 2019), which encodes a member of the ethylene response pathway (Alonso et al., 1999). Very few other genes are affected in either H3K27me3 or H2A.Z levels and only the gene At3g35585 shows a similar joint increase of H2A.Z and H3K27me3 as observed at EIN2, suggesting redundancies with other pathways. Although nearly unique, EIN2 can be used as a model locus to study the dialogue between H2A.Z and H3K27me3. This interaction is also illustrated by the genetic interactions between SWR1 and CURLY LEAF, which encodes the catalytic subunit of the PRC2, which is responsible for H3K27me3 deposition (Carter et al., 2018). In the absence of H2A.Z deposition by SWR1, H3K27me3 levels decrease over ~3000 genes (Carter et al., 2018). A further link between H2A.Z and Polcomb is the monoubiquitination of H2A.Z by the PRC1 component AtBmi1 (Gómez-Zambrano et al., 2019). Together with AtRING1, AtBmi1 forms a module responsible for monoubiquitination of H2A.K121, H2A.Z.K129, and H2A.Z.K132 (Bratzel et al., 2010; Gómez-Zambrano et al., 2019). Monoubiquitination of H2A.Z.K129 directly controls silencing of a subset of genes silenced by PRC1, suggesting that this modification might connect H2A.Z with transcriptional repression or its maintenance in contrast to the role of presumably non-modified H2A.Z present at the +1 nucleosome on active genes. Profiling H2A.Z.K129ub together with H2A.K121ub will be crucial for gaining direct mechanistic insight into the dual role of H2A.Z in transcription, which is still missing in plants. This duality, together with the wide range of loci affected, most likely explains the complex phenotypes resulting from the perturbation of H2A.Z dosage in plants.
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