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Contribution of the histone variant H2A.Z to expression of responsive genes in plants

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ABSTRACT

The histone variant H2A.Z plays a critical role in chromatin-based processes such as transcription, replication, and repair in eukaryotes. Although many H2A.Z-associated processes and features are conserved in plants and animals, a distinguishing feature of plant chromatin is the enrichment of H2A.Z in the bodies of genes that exhibit dynamic expression, particularly in response to differentiation and the environment. Recent work sheds new light on the plant machinery that enables dynamic changes in H2A.Z enrichment and identifies additional chromatin-based pathways that contribute to transcriptional properties of H2A.Z-enriched chromatin. In particular, analysis of a variety of responsive loci reveals a repressive role for H2A.Z in expression of responsive genes and identifies roles for SWR1 and INO80 chromatin remodelers in enabling dynamic regulation of H2A.Z levels and transcription. These studies lay the groundwork for understanding how this ancient histone variant is harnessed by plants to enable responsive and dynamic gene expression (Graphical Abstract).

1. Introduction

In eukaryotes, critical DNA-templated processes such as transcription, replication, and repair take place in the context of a nucleoprotein complex referred to as chromatin [1]. The foundational subunit of chromatin is the nucleosome, which consists of an octameric core of 8 histone proteins (an $(H3\text{-}H4)_2$ tetramer flanked by 2 H2A-H2B dimers) wrapped by ~147 bp of DNA [2]. It is well-established that both the composition of the nucleosome and its modification state play critical roles in these DNA-templated processes and the organization of the eukaryotic genome.

Eukaryotes have evolved a range of histone variants that are incorporated into nucleosomes in place of canonical histone proteins [3–5]. Incorporation of these variants can result in altered biochemical properties for nucleosomes as well as render it a better or worse substrate for factors that covalently modify nucleosomes or dynamically alter their position, composition, deposition, and turnover. Similarly, nucleosomes incorporating histone variants have different impacts with regards to both DNA-templated processes and genome organization and more emergent properties such as development, environmental responsivity, and disease [6]. Teasing out the specific contribution of a histone variant to immediate nucleosome-based events as well as more emergent chromatin-based traits is an active field of inquiry that is greatly complicated by the possibility of a variant playing multiple roles and concomitant indirect effects.

This review focuses on recent developments regarding the histone variant H2A.Z in plants. H2A.Z appears to have evolved once early in eukaryotic evolution and a number of aspects regarding its deposition and contribution to chromatin-based processes such as transcription are conserved in plants, animals, and yeast [7–9]. Ongoing developments, however, regarding our understanding of H2A.Z homeostasis in plants as well as its contribution to gene expression highlight that this conserved histone variant has been distinctively harnessed by plants to achieve regulatory outcomes. In particular, H2A.Z is enriched in the body of many genes in plants [7] where it appears to contribute to expression of responsive genes including those involved in stress and development. These studies, in combination with comparable studies in animals and yeast, illustrate how conserved chromatin-associated machinery can be harnessed to achieve distinct paths to regulated gene expression in different lineages of eukaryotes.

2. Plants have a distinct H2A.Z landscape

As in animals, different isoforms of H2A.Z exist in flowering plants,

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and varying numbers of genes code for them [10]. In Arabidopsis, there are three isoforms of H2A.Z that are encoded by three genes: *HTA8*, *HTA9*, and *HTA11* [11]. Extensive phylogenetic analysis and accompanying structural characterization have identified three key domains in histone H2A variants including H2A.Z: the acidic patch, the docking domain, and the L1 loop [6]. These and other sequence features of H2A.Z histones contribute to distinct biophysical properties of nucleosomes containing H2A.Z that may contribute to more emergent properties such as transcription. In particular, plant nucleosomes containing H2A.Z exhibit reduced thermostability relative to nucleosomes containing other histone variants [12]. Domain swapping experiments indicate that both the L1 loop and the docking domain of H2A.Z contribute to the reduced thermostability of plant nucleosomes containing this H2A variant [12].

Although the 3 isoforms of H2A.Z in Arabidopsis have sequence differences in both the L1 loop and docking domain, phenotypic characterization of single, double and triple mutant plants carrying defective versions of *HTA8*, *HTA9*, and/or *HTA11* suggest that they are somewhat functionally redundant [13,14]. In particular, the recent isolation of a triple mutant plants through CRISPR/Cas9-generated alleles revealed a much more severe growth phenotype relative to previously characterized *hta9 hta11* plants, which also exhibit extensive growth defects but are still fertile [13]. The respective contribution of each variant in wild-plant plants to patterns of H2A.Z distribution, gene expression, and other chromatin-associated traits remains to be determined. Recent characterization of the respective contributions of H2A.Z.1 and H2A.Z.2 to gene expression in human cells [15] raise the prospect that functional relationships of plant isoforms will similarly be complex.

Analysis of the distribution of H2A.Z in the plant genome reveals that H2A.Z is preferentially enriched adjacent to the nucleosome depleted region at the transcription start site of many loci as is observed in animals and yeast, with the noteworthy (and perhaps important) difference of the lack of enrichment of H2A.Z in the − 1 nucleosome in plants [16–22]. The presence of H2A.Z at the + 1 nucleosome has been shown to reduce the barrier for transcriptional elongation by RNA polymerase II at transcribed loci and is thereby thought to contribute to gene transcription [23,24]. Nevertheless, H2A.Z is found at the transcription start site of transcriptionally inactive genes as well and contributes to both transcriptional activation and repression [25–28]. Thus, the specific contribution of H2A.Z at the + 1 nucleosome is context-dependent and not solely determined by its inherent relative stability.

Plants also exhibit a distinct pattern of H2A.Z enrichment at many loci in which H2A.Z is enriched throughout the entire gene body [29, 30]. This pattern of enrichment is strongly correlated with genes exhibiting so-called responsive expression: expression that is dependent on endogenous and environmental cues including differentiation, hormone, nutrition, and general abiotic or biotic stress such as pathogens [30,31]. Further, expression of stress-responsive genes is misregulated in plants in which H2A.Z levels are decreased, indicating that H2A.Z does play a role in determining expression of these genes [14, 29–33]. Understanding how H2A.Z plays this role in plants is an active area of inquiry and will be addressed in detail later in this review.

3. Both conserved and plant-specific machinery is associated with homeostasis of H2A.Z-enriched nucleosomes in plants

SWR1 and INO80 are both members of the INO80 subfamily of ATP-dependent chromatin remodelers and play a well-established role in homeostasis of chromatin-associated H2A.Z in yeast and in animals [34, 35]. Characterization of the SWR1 complex in budding yeast, containing the conserved ATP-dependent chromatin remodeler SWR1 and thirteen other subunits, revealed that it exhibits the ability to exchange H2A-H2B dimers for H2A.Z-H2B dimers in nucleosomes in vitro and also promotes incorporation of H2A.Z into chromatin in vivo [36–38]. Animals have a related SWR1 complex, typically designated SRCAP, which has eleven subunits in common with yeast (including the SWR1-related remodeler SRCAP) and similarly exhibits H2A.Z exchange activity in vitro and promotes H2A.Z deposition in vivo [39–41].

There is strong genetic evidence that a SWR1 complex also plays an analogous role in promoting incorporation of H2A.Z into chromatin in plants. Mutations in genes corresponding to a number of conserved components of the SWR1 complex, including the SWR1 remodeler PIE1, ARP6, and SWC6 lead to similar plant phenotypes consistent with action in a common complex [42–47], but there are also substantial phenotypic differences that have been identified that indicate that the different components of the SWR1 complex in plants are playing distinct roles [32,48]. Unlike animals, Arabidopsis has only one ortholog of the SWR1 remodeler, PIE1. Comparative analysis of mutants carrying a null allele of *PIE1* versus a “near null” triple mutant of H2A.Z reveals severe but distinct developmental phenotypes [30], suggesting that PIE1 may play roles beyond incorporation of H2A.Z and/or the existence of PIE1-independent pathways by which some amount of H2A.Z is maintained in chromatin. In support of both possibilities, mutation of H2A.Z genes in *pie1* plants results in an enhanced phenotype and death of the plant shortly after germination [30], whereas recent images of “true” triple null *hta8 hta9 hta11* plants [13] suggest a much more severe growth defect than that associated with a null allele of *PIE1* and similarly suggest caution in interpreting the phenotype of the ”near null” triple mutant mentioned above [30].

Recent biochemical determination of the composition of the plant SWR1 complex reveals conservation of the core complex characterized in yeast and animals. In total, three groups have independently used affinity purification coupled with mass spectrometry in conjunction with confirmatory approaches such as two-hybrid to identify components of the plant SWR1 complex [49–51]. Importantly, the eleven conserved subunits that are found in the SWR1 complex in yeast and the SRCAP complex in animals are also components of the plant SWR1 complex (Fig. 1). Further, evaluation of specific protein-protein interactions indicates that PIE1 acts as a scaffolding protein in the plant SWR1 complex in agreement with previously published data in plants [14,42,43,45] and as previously characterized for the complexes from yeast and metazoans. These relationships reveal a robust conservation of the core chromatin remodeling machinery involved with exchange of H2A.Z in eukaryotes.

Additional interactions with other factors were also identified, suggesting the existence of plant-specific versions of SWR1 and/or functional submodules that direct/alter/complement plant SWR1 complex activity. All three groups identified MBD9 and two related proteins TRA1A and TRA1B as interacting with the canonical SWR1 complex in their studies [49–51]. MBD9 has a variety of putative binding domains associated with chromatin [52–54], including a non-functional methyl-CpG-binding domain (MBD) that it derives its name from. TRA1A and TRA1B are also components of the SPT module of SAGA complex in Arabidopsis [55]. The interaction of these three proteins with the plant SWR1 complex appears to be of functional relevance: analysis of the corresponding mutants by ChIP-seq revealed reduced incorporation of H2A.Z. In particular, loss of *MBD9* affected expression and H2A.Z levels at a subset of genes, implying that MBD9 was preferentially required for H2A.Z at certain loci [49,50]. Characterization of the SWC4 and AL4/5/6/7 subunits of the plant SWR1 complex to date also demonstrate or reveal possible links to targeting of the SWR1 complex [48,56, 57]. SWC4 is a homolog of a conserved component of SWR1 complexes in eukaryotes and binds AT-rich DNA sequences [48] , whereas ALFIN1-like (AL) 4/5/6/7 proteins belong to a plant-specific family of proteins containing a PHD domain that have previously been linked to stress tolerance and have the ability to bind to di- and tri-methylated lysine 4 of histone H3 (H3K4me2/3) [56,57].

One group also identified a robust MBD9-dependent interaction of the plant SWR1 complex with ISWI chromatin remodelers [51]. This interaction is of interest because ISWI remodelers contribute to nucleosome positioning in yeast, metazoans, and plants [58–60]. Thus, the implication of the observed association between SWR1 and ISWI is that

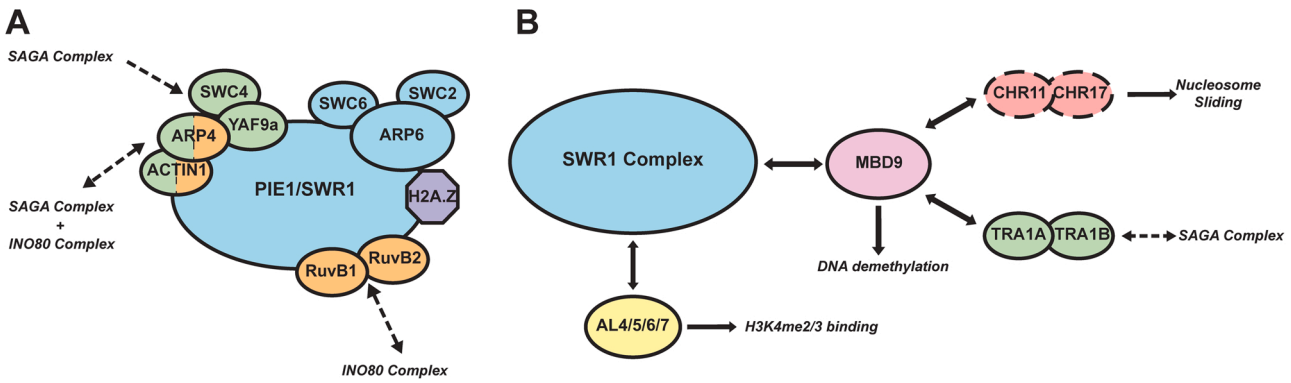

Fig. 1. Identification of the subunits of the plant SWR1 complex reveals multiple opportunities for functional and/or biochemical interactions. A) 11 subunits of the plant SWR1 complex are conserved in yeast and animals. The ovals are assigned different colors based on identified role(s) for the subunits. Blue indicates core subunits of the remodeling complex. Green subunits are shared between SAGA and SWR1 complexes. Subunits that are present in both INO80 and SWR1 complexes are indicated by orange. The two subunits that are associated all three complexes (SWR1, INO80, and SAGA) are indicated by ovals that are colored green and orange. The H2A.Z/H2B dimer is depicted as a purple octagon. B) A number of plant-specific components of the SWR1 complex have been identified in Arabidopsis that expand opportunities for functional crosstalk and recruitment of SWR1, as indicated. The dashed lines around CHR11/17 denote identification of this interaction by only one of three groups, as described in the text. Double-headed arrows denote interactions between subunits of SWR1 whereas single-headed arrows denote interactions/activities identified for specific subunits.

the ISWI remodelers help to generate the final chromatin product. Analysis of both H2A.Z levels and nucleosome positioning to date do not support this model, however. H2A.Z levels exhibit a modest reduction at best in *ISWI* mutants, and loss of *MBD9* (which is necessary for association of ISWI with the SWR1 complex in plants) does not appear to substantially perturb nucleosome positioning either globally or specifically at H2A.Z-enriched loci [51].

Characterization to date of the INO80 remodeler in plants is consistent with previous characterization in other eukaryotes but reveals a less dramatic impact on genome-wide enrichment of H2A.Z. In both yeast and animals, in vitro and in vivo data indicate that INO80 remodelers promote the exchange of H2A.Z-H2B dimers for H2A-H2B dimers in nucleosomes [61–63], and thus acts in opposition to SWR1. Characterization of INO80 in Arabidopsis reveals that it physically interacts with H2A.Z-H2B dimers and contributes to DNA damage repair pathways in plants [64], much as it does in yeast and animals [65]. However, in comparison to impairment of SWR1 machinery, loss of *INO80* results in indistinguishable or relatively modest changes in the distribution of H2A.Z globally in the genome [66,67]. Recent work, however, highlights the contribution of INO80 to H2A.Z removal and regulated gene expression at specific loci, which will be described later in this review.

Histone chaperones that specifically contribute to H2A.Z homeostasis have been identified in both yeast and animals. CHZ1 contributes to H2A.Z deposition in yeast and functions redundantly with the canonical histone chaperone NAP1 [68,69] whereas ANP32E acts to remove H2A.Z in association with DNA damage response [70–73]. Recent characterization of the histone chaperone OsCHZ1, which associates with both H2A.Z-H2B and H2A-H2B dimers and promotes deposition of H2A.Z in rice [74], suggests that similar pathways are at work in plants alongside chromatin remodeler-mediated exchange of H2A.Z. Similarly in Arabidopsis, the NAP1-related histone chaperones NRP1 and NRP2 have been strongly implicated in removal of H2A.Z from chromatin [75].

4. Other chromatin-based machinery contributes to transcriptional properties of H2A.Z-enriched loci

The viability of Arabidopsis mutants that strongly perturb chromatin-based pathways that are essential in animals has enabled novel insights into how H2A.Z contributes to transcriptional activation and repression in plants. A comprehensive set of genome-wide analyses in Arabidopsis revealed a complex interplay between H2A.Z-enriched + 1 nucleosomes and the ATP-dependent SWI2/SNF2 chromatin remodeling factor, BRAHMA (BRM), with regards to both properties of the + 1 nucleosome and expression of the corresponding locus [76]. BRM belongs to a class of remodelers that slide nucleosomes and disrupt histone-DNA interactions and has been linked to expression of a wide range of loci that contribute to numerous developmental pathways in plants [77]. Characterization of differential expression of direct targets of SWR1 (as defined by *ARP6*-dependent H2A.Z enrichment) and BRM in WT, *arp6*, *brm1* and *arp6 brm1* plants revealed 8 different classes of expression that included both coordinated and antagonistic behavior of these two chromatin-based pathways with regards to transcriptional activation and repression.

Combining these expression data with an examination of chromatin-based features revealed the conditional combinatorial nature of these pathways [76]. Depletion of H2A.Z resulted in both increased and decreased stability (occupancy/fuzziness/positioning) of the corresponding H2A.Z-enriched nucleosomes. Thus, the behavior of the H2A.Z-enriched nucleosome was determined by context rather than solely by the intrinsic biophysical properties of the H2A.Z-enriched nucleosomes. Intriguingly, the presence of H2A.Z in the + 1 nucleosome can influence the role of BRM. In H2A.Z-enriched + 1 nucleosomes, loss of *BRM* is more likely to result in an increase in nucleosome stability relative to non-enriched + 1 nucleosomes. These and other observations indicate that the effect of the presence of H2A.Z to + 1 nucleosome dynamics, BRM-dependent remodeling, and transcription is contextually emergent and that other chromatin-associated factors are likely to play critical roles in these processes at H2A.Z-enriched loci.

A distinct chromatin pathway that has been functionally associated with H2A.Z is the transcriptionally repressive histone modification trimethylation of lysine 27 of histone H3 (H3K27me3). This mark plays a critical role in generation of facultative heterochromatin in both animals and plants [78,79]. Several studies have noted that numerous loci are enriched for both H3K27me3 and H2A.Z at the + 1 nucleosome as well as the gene body [80–82]. A recent study revealed that mutation of the SWR1 remodeler *PIE1* results in reduction of both H2A.Z and H3K27me3 as well as elevated expression of H3K27me3-enriched loci [82]. Further, reduction of H3K27me3 was also observed at loci with no detectable change in expression, indicating that the reduction was not an indirect effect of expression. These data thus suggest that the presence of H2A.Z can facilitate deposition of H3K27me3 at some loci. It is striking to note that H2A.Z and H3K27me3 co-localize in mouse embryonic stem cells and that loss of H2A.Z results in loss of H3K27me3 and elevated expression of some affected loci [83,84], suggesting the existence of a

conserved pathway by which H2A.Z can contribute to H3K27me3 in plants and animals.

PRC1, a histone modification complex that is associated with H3K27me3-mediated repression [85,86], has recently been demonstrated to contribute to H2A.Z-mediated transcriptional repression [87]. The conserved PRC1 component BMI promotes monoubiquitination of both H2A [88,89] and H2A.Z [87] in plants as previously observed in animals, where it contributes to generation of higher order structure for chromatin and transcriptional repression in addition to facilitating recruitment of PRC2, the histone methyltransferase complex that promotes H3K27me3 [90,91]. With regards to ubiquitylation and H2A.Z, site-directed mutation of the BMI-targeted lysine residue of an H2A.Z in plants severely impairs its ability to confer H2A.Z-associated transcriptional repression. The authors conclude that transcriptional repression conferred by H2A.Zub is not dependent on PRC2 activity (and by implication H3K27me3) based on a number of correlative observations such as that 64% of genes with decreased H2A.Z levels and increased transcript levels in *hta9 hta11* plants are not enriched for H3K27me3. Reanalysis of their data, however, to focus on genes that specifically exhibit increased transcript levels in transgenic *hta9 hta11* plants expressing HTA9 that lacks the ubiquitylation site (thus specifically impaired in H2A.Zub) suggests a different possible relationship. Examining the intersection of these derepressed loci with previously characterized H2A.Z- and H3K27me3-enriched loci [82] revealed that 16% of genes (total = 495) that exhibit increased transcript levels in H2A.Zub-defective plants relative to wild-type plants are enriched for H2A.Z but not H3K27me3 in the gene body whereas 31% of this same set of genes are enriched for H3K27me3. This analysis raises the prospect that loss of H2A.Z-associated PRC1-dependent ubiquitylation contributes in some fashion to H3K27me3-associated transcriptional repression (Fig. 2).

Two studies featuring in-depth characterization of distinct loci illustrate both that the characterized contributions of H2A.Z to transcriptional repression identified above are context-dependent and reveal a similarly emergent combinatorial role with regards to H3K4me3, a histone modification that is linked to transcriptional activation [92,93]. Loss of ARP6, a core component of the SWR1 complex, leads to increased expression of anthocyanin biosynthetic genes and loss of both H2A.Z and H3K27me3 at the corresponding loci [93]. Surprisingly, although disruption of PRC2 also leads to reduction of H3K27me3 at these loci, it does not result in increased expression. The authors instead find that loss of H2A.Z at the biosynthetic loci results in increased levels of H3K4me3, which the authors find is necessary for increased expression of corresponding transcripts. These studies thus suggest that H2A.Z represses expression of these loci by preventing deposition of H3K4me3 rather than through promoting H3K27me3, loss of which is insufficient to derepress these loci. In contrast, H2A.Z appears to promote high expression of the MIR156A and MIR156C, microRNAs that contribute to post-transcriptional regulation of a number of genes involved in phase change, by promoting H3K4me3 and either promoting (MIR156A) or having no detectable effect (MIR156C) on H3K27me3. Different histone methyltransferases have been linked to modification and expression of these loci, SDG2 for anthocyanin biosynthetic genes and ATXR7 for MIR156A/C, which may account for the distinct functional relationships identified [92,93].

5. H2A.Z plays a critical role in expression of loci that respond to environment stimuli

The presence of H2A.Z at loci that exhibit environmentally-responsive expression [30] raises the prospect that H2A.Z contributes in some fashion to that responsivity. Recent work confirms such a role for H2A.Z, primarily by contributing to transcriptional repression of the locus, and has identified mechanisms by which the level of H2A.Z is altered at a locus that thereby likely contribute to its transcriptional regulation.

An analysis of genes associated with drought response revealed that mutation of *ARP6*, a component of the plant SWR1 complex, results in extensive misregulation of drought-responsive genes [31]. Remarkably, the level of enrichment of H2A.Z in the gene body correlates with the magnitude of change of the transcript level in response to drought stress, both up and down. Nevertheless, the primary impact of H2A.Z on transcription appears to be repression. Drought-responsive genes that exhibit increased transcript levels in *arp6* plants are over-represented for loci containing H2A.Z in the gene body. In contrast, genes that exhibit decreased transcript levels are not over-represented. Further, loci that exhibit increased expression in response to drought stress concurrently exhibit modestly reduced levels of H2A.Z in the gene body under drought stress. In contrast, loci that exhibit decreased expression in response to drought stress exhibit either no change or perhaps a slight increase in enrichment of H2A.Z. Enrichment of H2A.Z at the +1 nucleosome was not strongly predictive of expression changes in the absence of ARP6 for drought-responsive genes, suggesting that it is the presence of H2A.Z in the gene body that plays the primary role in enabling responsive gene expression.

Whereas the effect of drought stress on transcript levels was examined 7–10 days after treatment, another group examined the effect of heat shock on gene expression and H2A.Z enrichment as soon as 15 min after treatment [94]. Shifting plants from 17 °C to 27 °C revealed a group of genes (14% of those with altered expression) that exhibited substantially increased transcript levels at 15 min that then returned to basal levels within four hours. This group of genes exhibits an accompanying rapid loss of H2A.Z at the transcription start site (TSS) as well as throughout the gene body at 15 min and a return to basal levels by 4 h. The responsivity of expression of these genes is altered in *arp6* plants, consistent with a role for H2A.Z in determining their ability to be transcribed. The authors observed that reduction of H2A.Z is associated with an alteration in stability of the +1 nucleosome and propose that this alteration enables increased expression of the locus. Taken together, both papers are consistent with a H2A.Z-enriched chromatin enabling responsive genes to switch rapidly between expression states, with H2A.Z-enriched chromatin more refractory to transcription and H2A.

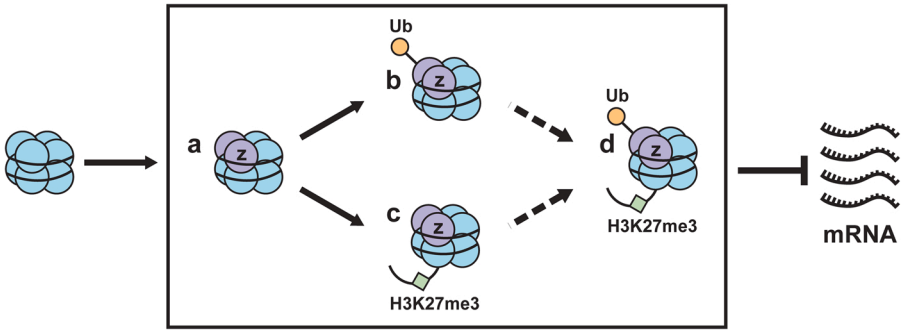

Fig. 2. H2A.Z-enriched chromatin is also associated with transcriptionally repressive histone modifications promoted by PRC1 and PRC2. The PRC1 component BMI1 promotes ubiquitylation of H2A.Z (b) and ChIP-seq and genetic analyses suggest that H2A.Z nucleosomes can also be modified by PRC2 to promote H3K27me3 (c). Analysis of RNA-seq and ChIP-seq data raise the possibility (dashed line) that all three epigenetic marks may be present at some loci (d). These three modification states and unmodified nucleosomes incorporating H2A.Z (a) are linked to transcriptional repression.

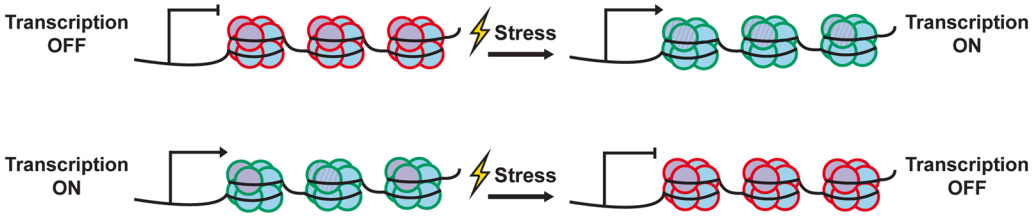

Fig. 3. The presence of H2A.Z enables transcriptional regulation of stress-responsive loci. Both drought-responsive and heat shock-responsive loci have been identified at which H2A.Z is present at the locus, necessary for transcriptional repression of the locus, and relative depletion of H2A.Z at the locus is associated with expression [31,94] (top). In addition, numerous loci for which expression is strongly induced by drought stress that are also enriched for H2A.Z prior to induction [31] (bottom). Given that the presence of H2A.Z at a locus does not appear to be sufficient to confer repression, nucleosomes are outlined in red or green to indicate expression status of the locus (repressed and active respectively) which may reflect additional modifications of chromatin (see Conclusions). Observation of relatively reduced enrichment of H2A.Z in nucleosomes at loci in a given stress-dependent transcriptional response is indicated by purple and blue stripes.

Z-depleted chromatin more permissive to transcription, and the potential for a given enrichment state to support transcription likely substantially influenced by post-translational modifications of H2A.Z and other histones (Fig. 3).

6. SWR1 and INO80 contribute to H2A.Z dynamics at responsive loci

Recent papers that primarily examine light-responsive expression are largely consistent with the proposed transcriptionally repressive role for H2A.Z and further identify both the SWR1 and INO80 remodelers as playing key roles in switching between H2A.Z enrichment states (Fig. 4). ELF3 is a component of the Evening Complex, which represses expression of target genes at the end of the day and is an integral component of the circadian clock in Arabidopsis [95,96]. New studies reveal that ELF3 interacts with the SWR1 complex subunit SWC6 by both yeast two-hybrid and in planta bimolecular fluorescence complementation [97]. Further, H2A.Z enrichment at both the TSS and the gene body of ELF3 targets peaks at dusk (when these genes are repressed), and this enrichment is dependent on *ELF3*. Critically, the circadian rhythm of ELF3 target gene expression is compromised in *hta9 hta11* plants, indicating that it is the incorporation of H2A.Z rather some other action of SWR1 that promotes repression of these loci. In short, the investigators provide compelling data that the transcription factor ELF3 directly recruits SWR1 to mediate incorporation of H2A.Z and thereby facilitate repression of targeted genes.

A recent spate of papers raises the prospect that other light-responsive factors repress gene expression using the same general strategy of facilitated recruitment of SWR1. *arp6* and/or *hta9 hta11* plants are defective in a number of light-dependent responses, including the ratio of red to far-red light (R/FR), and light-responsive genes are observed to be misregulated in these mutants [98–100]. The transcription factor ELONGATED HYPOCOTYL 5 (HY5), which plays a major role in photomorphogenesis by modulating expression of light responsive genes [101,102], interacts with ARP6 and SWC6 [99]. Consistent with the hypothesis that HY5 recruits SWR1 to target loci, the authors observed that *HY5* is necessary for H2A.Z deposition and enrichment of SWC6 at target genes as well as blue light mediated repression of these loci. Similarly, a separate study revealed that the trimeric NF-Y transcription complex interacts with ARP6 and contributes to both H2A.Z enrichment and transcriptional repression at red light responsive target loci [98].

The INO80 complex appears to act in a complementary fashion to the SWR1 complex and has been strongly implicated in enabling regulated removal of H2A.Z from responsive loci and thereby promoting expression of target genes. It was recently observed that PHYTOCHROME-INTERACTING FACTORS (PIFs) mediate transcriptional activation of genes in response to a decreased ratio of red (R) to far-red (FR) light in part through recruitment of INO80 and reduction of H2A.Z [103]. The investigators observed that increased expression of genes at dusk in conditions of low R:FR is accompanied by reduction of H2A.Z enrichment. Characterization of PIF7, which the investigators found plays a major role in determination of growth response, revealed similar kinetics of PIF7 association and also of depletion of H2A.Z at a number of loci, as soon as 5 min after altering light conditions. Multiple PIFs, including PIF7, were revealed to interact with EIN6 ENHANCER (EEN), a subunit of the INO80 complex. *ino80* plants are defective in removal of H2A.Z at low R:FR-activated loci, consistent with a role for PIF7 in promoting expression of these loci in part by recruitment of INO80, ensuing depletion of H2A.Z, and thus alleviation of this repressive state.

Analysis of another PIF-responsive locus reveals a similar regulatory circuit and also linked transcriptional elongation to INO80 and removal of H2A.Z. *PIF4* contributes to thermomorphogenesis in Arabidopsis in part by promoting expression of genes involved in auxin biosynthesis and responsiveness [104]. Xue and colleagues observed that increased expression of these *PIF4*-dependent loci is accompanied by decreased enrichment of H2A.Z [66]. They also observed that PIF4 interacts with both EEN and the INO80 remodeler and that reduction of H2A.Z at these

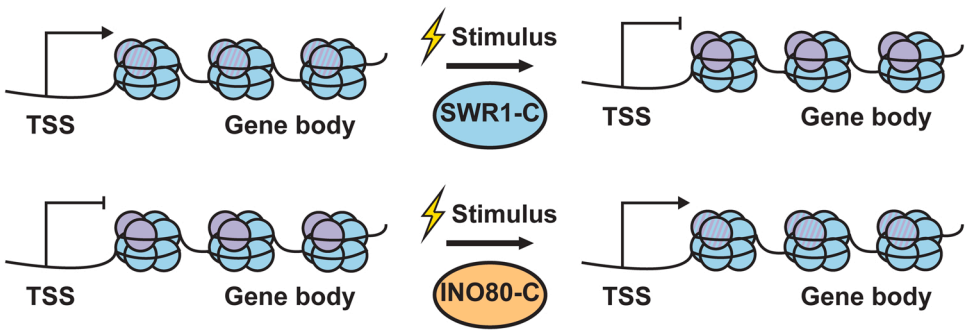

Fig. 4. SWR1 and INO80 complexes contribute to altered levels of H2A.Z at distinct light-responsive loci. Light-responsive loci have been identified at which the SWR1 remodeling complex promotes incorporation of H2A.Z and transcriptional repression in response to light and for which recruitment of the complex is likely directly mediated by transcription factors (ELF3 and HY5) [97,99] (top). Similarly, other responsive loci have been identified in which recruitment of the INO80 remodeling complex by a PIF transcription factor (e.g. PIF4 or PIF7) facilitates depletion of H2A.Z and transcriptional activation [66,103] (bottom). Observation of relatively reduced enrichment of H2A.Z in nucleosomes at loci in a given stress-dependent transcriptional response is indicated by purple and blue stripes. TSS denotes transcription start site.

loci is compromised in *pif4* and *ino80* plants.

In addition, the authors observed that EEN also interacts with factors associated with active transcription, the histone methyltransferase subunit WDR5A [105,106] and the transcription elongation factor SPT4 [107,108]. Analysis of *ino80* plants revealed both reduced H3K4me3 and reduced association with the phosphorylated form of RNA polymerase II associated with transcriptional elongation at target loci [66]. These and other data raise the prospect that INO80 may contribute to regulated expression of these loci through facilitating transcription activation of the locus and that transcription itself contributes to depletion of H2A.Z. Such a direct role for INO80 in interacting with transcriptional machinery may in part account for its contribution to expression and chromatin-associated features at these and other loci [67].

In light of the proposed joint contribution of H2A.Z and H3K27me3 to transcriptional repression at some loci, it is worth highlighting an analysis of the contribution of *INO80* to expression of *ETHYLENE-INSENSITIVE2* (*EIN2*), which plays a pivotal role in the plant hormone ethylene signal transduction pathway [109,110]. Treatment of plants with ethylene results in *INO80*-dependent loss of H2A.Z at *EIN2* [111]. In addition, plants carrying defective alleles of both *EEN* and *REF6/EIN6*, which promotes demethylation of H3K27me3 [112], exhibit elevated levels of both H3K27me3 and H2A.Z in the 5′ UTR of *EIN2* and transcriptional repression. Genome-wide analyses of H3K27me3 and H2A.Z did not reveal other loci that behave in a similar fashion to *EIN2* in response to loss of *EEN* and *REF6/EIN6*, however, suggesting that these two pathways are not generally redundant for ectopic repression of loci in this fashion [111].

7. Conclusions

Recent advances have shed new light on how the presence of the histone variant H2A.Z in gene bodies contributes to responsive gene expression in plants. Combining genome-wide analyses with detailed analysis of specific response pathways highlights both the association of enrichment of H2A.Z at a gene with transcriptional repression and the role of targeted action of SWR1 and INO80 complexes in: 1) H2A.Z incorporation and accompanying repression of a locus (SWR1); and 2) H2A.Z removal and accompanying transcriptional activation of a locus (INO80). In both types of transcriptional regulation, it is important to keep in mind that these studies address dynamic regulation of loci in response to cues and thus reveal different outcomes from ablation of the respective remodelers under constant conditions (a substantial loss of H2A.Z enrichment in the absence of *SWR1* [82,113] as opposed to a much more modest alteration in enrichment in the absence of *INO80* [66,67]). Identification of plant-specific subunits of the SWR1 complex suggests possible routes by which SWR1 may be targeted to certain loci, and the identification of H3K27me3 and ubiquitylated H2A.Z suggest additional chromatin-based pathways that may contribute to H2A.Z-associated transcriptional repression.

With regards to repression, characterization of drought responsive loci strongly suggests that the presence of H2A.Z is not sufficient to ensure transcriptional repression [31]. H2A.Z is strongly enriched in the gene body of loci that exhibit robust transcriptional repression as well as those that exhibit substantial activation. Possible implications of this observation include: 1) H2A.Z-enriched chromatin requires additional modifications and/or components to repress transcription; 2) H2A.Z-enriched chromatin can be modified to be permissive to transcription; and 3) expressed loci recruit a transcription apparatus that is capable of reading through otherwise repressive H2A.Z-enriched chromatin. Ubiquitylation of H2A.Z by BMI1 and H3K27 trimethylation of H2A.Z nucleosomes by PRC2 are clear candidates for modifications that may contribute to H2A.Z-associated repression at some loci as described in the first option [82,87]. Further characterization of the chromatin of H2A.Z-enriched loci in various expression states is clearly needed to clarify the role of these and possibly other chromatin-based pathways in determining the transcriptional properties of H2A.Z-enriched loci.

H2A.Z has previously been suggested to function as a molecular rheostat for control of transcription in animals [9]. The findings summarized here are consistent with a similar role for H2A.Z in plants and further suggest that plants in particular have harnessed this property to enable responsive gene expression in a varying environment. Further, the observed overlap between H2A.Z and H3K27me3, which is strongly associated with differentiation [114], implies that plants have similarly harnessed this H2A.Z-based rheostat to enable environmentally-responsive growth and development in plants. Further characterization of H2A.Z-based transcriptional switches is likely to generate considerable insight into how plants respond in such a dynamic fashion to environmental stimuli. The existence of genes that are similarly enriched for H2A.Z and H3K27me3 in mouse embryonic stem cells [84] raises the prospect that such insight may also be relevant to understanding the contribution of H2A.Z to changes in gene expression associated with differentiation in animals as well.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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