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## REVIEW PAPER

# Chromatin regulation of somatic abiotic stress memory

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## Abstract

**In nature, plants are often subjected to periods of recurrent environmental stress that can strongly affect their development and productivity. To cope with these conditions, plants can remember a previous stress, which allows them to respond more efficiently to a subsequent stress, a phenomenon known as priming. This ability can be maintained at the somatic level for a few days or weeks after the stress is perceived, suggesting that plants can store information of a past stress during this recovery phase. While the immediate responses to a single stress event have been extensively studied, knowledge on priming effects and how stress memory is stored is still scarce. At the molecular level, memory of a past condition often involves changes in chromatin structure and organization, which may be maintained independently from transcription. In this review, we will summarize the most recent developments in the field and discuss how different levels of chromatin regulation contribute to priming and plant abiotic stress memory.**

**Keywords:** Abiotic stress, chromatin regulation, heat stress memory, histone modifications, priming, transcriptional memory, vernalization.

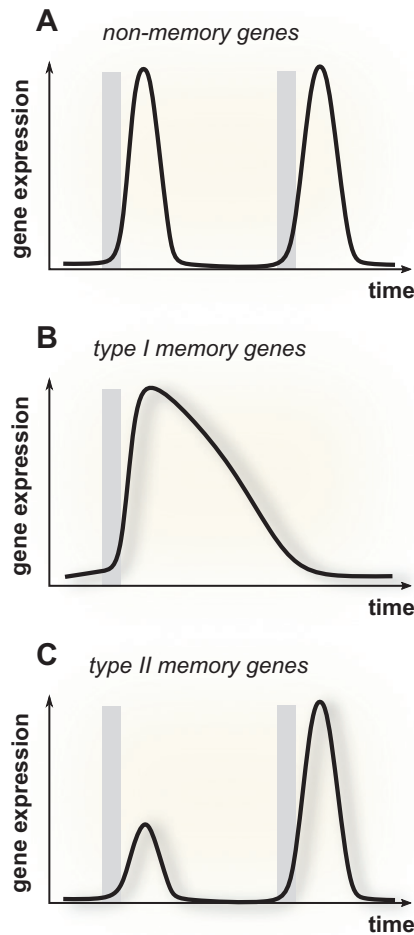
## Introduction

Plant growth and development are highly dependent on the surrounding environment, which can have a strong impact on overall fitness. In order to cope with environmental challenges, plants have developed a series of responses to different types of acute abiotic stress, which have been widely studied. To date, several regulatory pathways have been identified that result in the activation of genes involved in plant development and metabolism, which mediate increased tolerance to stress conditions (for comprehensive reviews, see Yamaguchi-Shinozaki and Shinozaki, 2006; Zhu, 2016; Ohama *et al.*, 2017).

However, in nature, single stress events are not the norm. Instead, in specific seasons, plants are frequently subjected to multiple periods of adverse conditions intercalated by times of recovery. To cope with recurrent stress, plants have developed the ability to remember a past stress and be better prepared to survive a subsequent one, a process known as priming (Hilker *et al.*, 2016). At the somatic level (within the same generation),

the effects of priming can be maintained/memorized for a few days or weeks, suggesting that information can be stored during this period (Bäurle, 2018). So far, only a few stress-inducible genes, known as ‘memory/trainable genes’, have been linked to stress memory (Charng *et al.*, 2006, 2007; Ding *et al.*, 2012a; Lämke *et al.*, 2016; Liu *et al.*, 2018). Based on their transcriptional profile, memory genes can be classified into two groups (Fig. 1): type I—genes that are up-regulated upon a first stress and show sustained expression during the recovery phase (Fig. 1B); and type II—genes that are hyperinduced upon a recurrent stress (Fig. 1C) (Bäurle, 2018). However, how these genes are regulated and which features distinguish them from so-called non-memory genes (Fig. 1A) remains to be elucidated.

Chromatin regulation has recently emerged as a key feature of plant responses to abiotic stress and it has been associated with the storage of information of a previous condition, given that



**Fig. 1.** Transcriptional behaviour of stress memory genes. (A) Non-memory genes are induced by stress and their expression quickly returns to pre-stress levels after the stress subsides; these genes behave identically upon a first or recurrent stress. (B) Type I memory genes are characterized by a sustained induction, which is maintained at elevated levels throughout the memory phase. (C) Type II memory genes are induced upon a first stress and hyperinduced upon a recurrent stress separated by a few days or weeks of recovery under stress-free conditions. Grey bars represent a stress stimulus of limited duration.

chromatin states may be maintained independently from transcription. Chromatin is composed of positively charged histone octamers, around which 147 bp of negatively charged DNA is wrapped, forming nucleosomes (Luger *et al.*, 1997). Each nucleosome consists of an octamer of two molecules of each four histones, H2A, H2B, H3, and H4, linked by a strand of DNA with which the linker histone H1 may be associated (Kornberg, 1974; Thoma *et al.*, 1979). Plants have multiple genes coding for the canonical (more conserved) histone forms, as well as variants that contain minor differences in their amino acid sequences and often have distinct functions (reviewed in Jiang and Berger, 2017). Histones are composed of a globular domain and an N-terminal tail, which is highly conserved and can be modified at the post-translational level, resulting in altered protein charge, thus changing the affinity with which the DNA is wrapped around nucleosomes. Histone modifications may also create or occlude binding sites of other chromatin regulators. Changes in chromatin organization can have a strong impact on gene expression through the regulation of DNA accessibility for

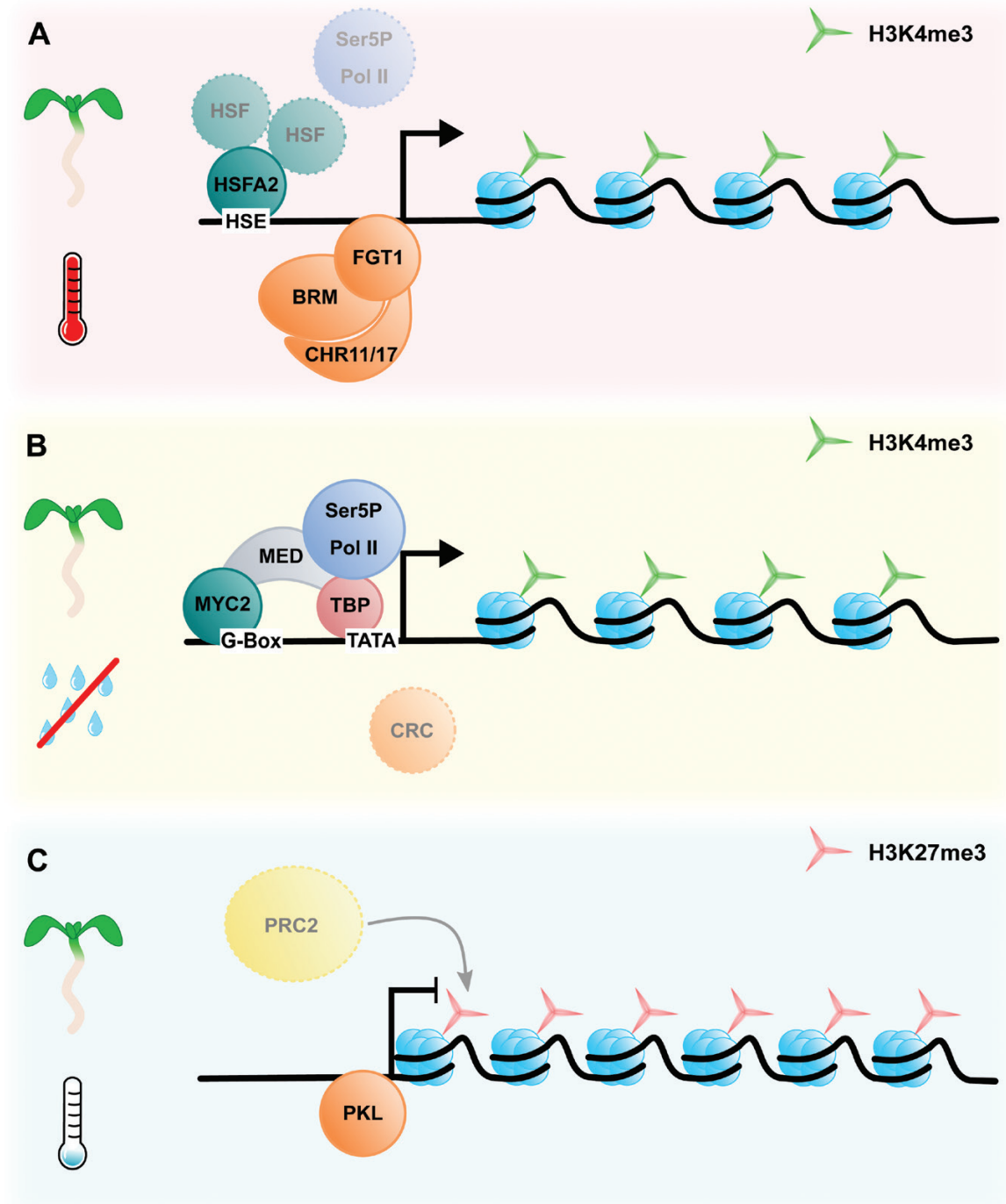
the transcriptional machinery or for regulatory proteins. Based on a combined analysis of different features, such as genomic location, histone modifications, and nucleosome occupancy, nine chromatin states have been identified in *Arabidopsis thaliana* (Sequeira-Mendes *et al.*, 2014). Adding to this complexity, chromatin compaction inside the nucleus is not random. Instead, chromosomes occupy a defined space in the nuclear matrix and form stable interactions with different nuclear regions (reviewed in Gibcus and Dekker, 2013). Interestingly, these domains are often associated with specific chromatin states (Feng *et al.*, 2014; Liu *et al.*, 2016; Bi *et al.*, 2017) and are therefore relevant for transcription regulation.

In this review we will discuss some of the latest findings on how different levels of chromatin regulation, ranging from histone post-translational modifications to structure, impact plant responses to abiotic stress. The role of chromatin in priming and abiotic stress memory will be highlighted by presenting recent work in plants or by drawing comparisons with other organisms. Finally, we will discuss some open questions that we believe are likely to shape the near future of research in the field.

## The role of H3K4me3 in dehydration and heat stress memory

One of the best studied histone post-translational modifications is the trimethylation of lysine 4 of histone H3 (H3K4me3), which is widely accepted to be associated with active chromatin states (Zhang *et al.*, 2009). Recently, this modification was also linked to transcriptional memory at several abiotic stress-responsive genes. Ding *et al.* (2012a) identified a subset of type II dehydration memory genes at which H3K4me3 accumulates upon a first priming stimulus and is maintained during the memory phase, when the genes are expressed at basal levels. A similar accumulation of H3K4me2/3 after a first triggering stress was observed in *A. thaliana* plants primed with the biotic stress hormone jasmonic acid (JA; Liu and Avramova, 2016) or primed by heat stress (HS; Lämke *et al.*, 2016; Liu *et al.*, 2018). Together, these observations suggest that enhanced H3K4 methylation may be a general mechanism to mark recently active genes for stronger reactivation upon a recurrent stress/signal (Fig. 2A, B). The exact mechanism is still not fully understood, but it seems to be related to a faster and, in some cases, more pronounced induction of memory genes upon a second stress.

In plants subjected to repeated dehydration, the enrichment of stalled RNA polymerase II (Ser5P Pol II) was detected at memory genes during the entire memory phase (Ding *et al.*, 2012a). Nuclear run-on assays confirmed that the transcription of these genes occurred at a three times higher rate during a recurrent stress, when compared with a first stress. Additionally, Liu and Avramova (2016) reported an increased occupancy of the TATA-binding protein (TBP), a key step in the formation of the pre-initiation complex (PIC), at the promoters of memory genes during the recovery phase (Fig. 2B). This suggests that the transcriptional machinery is maintained at these promoters, probably facilitating their faster or higher expression upon recurrent stress. It is therefore tempting to speculate



**Fig. 2.** Transcriptional memory of abiotic stress is regulated at the chromatin level. (A) In response to HS, HSFs, probably in a complex with other HSFs, binds heat shock elements (HSEs) at the promoters of HS memory genes and triggers the deposition of H3K4me3, which is sustained throughout the memory phase. Additionally, FGT1, in a complex with the chromatin remodellers BRM and CHR11/17, is required to maintain low nucleosome occupancy around the +1 nucleosome, keeping chromatin in an active state, thus probably facilitating the recruitment or activity of RNA Pol II. (B) Similar mechanisms, such as the accumulation of H3K4me3 and reduction of nucleosome occupancy (through the activity of an as yet unidentified chromatin-remodelling complex, CRC), regulate dehydration memory genes. The binding of MYC2 to the promoters of dehydration memory genes is also required for transcriptional memory. MYC2 interacts with the Mediator complex through the MED25 subunit, which in turn recruits the pre-initiation complex (here represented by TBP and Ser5P RNA Pol II), allowing a faster re-activation upon a recurrent stress cue. (C) The chromatin remodeller and transcriptional repressor PKL, which is known to be involved in the deposition and maintenance of the repressive histone mark H3K27me3, is required for cold stress priming. H3K27me3 plays a key role in long-term cold memory (vernalization) and was recently suggested to be involved in short-term memory as well. Dashed circles represent regulators whose direct involvement in abiotic stress memory remains to be validated.

that the deposition of H3K4me3 may create the necessary chromatin environment for the accessibility of the transcriptional machinery. Accordingly, in yeast mutants where Lys4 of histone H3 was replaced by either alanine or arginine, RNA

Pol II was not recruited to target genes during the memory phase (D'Urso *et al.*, 2016). However, in *A. thaliana*, the accumulation of this mark at the transcriptional start site (TSS) of a subset of genes occurs downstream of the recruitment of



PIC and is required for transcription elongation (Ding *et al.*, 2012b), suggesting a somewhat different mechanism.

The majority of H3K4me is deposited by the COMPASS-like complex, which is known to regulate different aspects of plant development (Jiang *et al.*, 2011). Upon induction of the unfolded protein response (UPR), the COMPASS-like complex was recruited by the bZIP28/60 transcription factors (TFs), which are required for the deposition of H3K4me<sub>3</sub> at a subset of genes (Song *et al.*, 2015). The UPR is a common response to abiotic stresses (Liu and Howell, 2010); therefore, it is conceivable that the same mechanism might trigger the deposition of this mark at some HS and dehydration memory genes. Alternatively, the COMPASS-like complex might be recruited to these genes by alternative stress-specific TFs (see below). In yeast, both COMPASS and Mediator complexes are required for the transcriptional memory of the inositol-1-phosphate synthase-encoding gene *INO1*, which also exhibits increased levels of H3K4me upon activation (Light *et al.*, 2013; D'Urso *et al.*, 2016). Interestingly, the protein composition of these complexes is altered under memory and non-memory conditions, allowing them to perform different functions during poised and active transcription (D'Urso *et al.*, 2016).

However, the question remains of whether any specific enzymes are responsible for the deposition of H3K4me at memory genes. Plants defective in the H3K4me<sub>3</sub> methyltransferase *ARABIDOPSIS TRITHORAX1* (*ATX1*) are more sensitive to dehydration than the wild type, due to impaired abscisic acid (ABA) production and consequently increased stomatal opening under stress (Ding *et al.*, 2011). On the other hand, *atx5* and *atx4* mutants showed an increased tolerance to dehydration and hypersensitivity to ABA treatment, thus acting as negative regulators in these processes (Y. Liu *et al.*, 2018). However, these proteins do not target exclusively memory genes, suggesting that other factors may provide memory specificity.

Some stress-induced TFs have been identified as key components of transcriptional memory and are likely to account for this specificity and recruit specific chromatin-regulatory proteins to target loci. For instance, the HS-dependent deposition of H3K4me was dependent on HEAT SHOCK FACTOR A2 (*HSFA2*; Fig. 2A; Lämke *et al.*, 2016). The *A. thaliana* HSF gene family consists of 21 members and, so far, only *HSFA2* is known to have a controlling function in somatic HS memory (Charng *et al.*, 2007; Lämke *et al.*, 2016). Genetic evidence, however, suggests that additional factors dependent on the *HSFA1* master regulators are also involved in this process (Liu *et al.*, 2018). Interestingly, the promoter of the type II memory gene *ASCORBATE PEROXIDASE 2* (*APX2*) is sufficient for transcriptional memory (Liu *et al.*, 2018), indicating that TF binding and *cis*-regulatory motifs are key elements in this process. As heat shock factors (HSFs) act in trimeric complexes together with other HSFs (reviewed in Scharf *et al.*, 2012), one exciting possibility is that HS memory specificity is a property of certain complexes and not of individual TFs.

ABA-dependent dehydration memory genes show a similar requirement for TFs. Priming plants by dehydration induces transient binding of MYC2, which is required for the transcriptional memory of a subset of genes (Liu and Avramova,

2016). Interestingly, this binding correlates with the accumulation of Ser5P RNA Pol II and involves the recruitment of the Mediator complex by direct interaction of MYC2 with the subunit MED25 (Fig. 2B; Liu and Avramova, 2016). The Mediator complex is a key integrator between TF binding to target genes and RNA Pol II transcriptional activity, and it has been shown to affect different aspects of plant development and responses to biotic and abiotic stress (reviewed in Samanta and Thakur, 2015). Whether the binding of MYC2–MED25 is also required for H3K4me<sub>3</sub> deposition at dehydration memory genes remains to be elucidated.

## Memory of short and prolonged exposure to low temperature

Stress priming of plants by low temperature has been reported in several plant species (Byun *et al.*, 2014; Li *et al.*, 2014; Zuther *et al.*, 2019). However, knowledge of the role of chromatin regulation in this process is still scarce. Exposure to cold leads to an open chromatin environment at several loci in potato, characterized by reduced nucleosome occupancy and the presence of bivalent H3K4me<sub>3</sub> (active) and H3K27me<sub>3</sub> (repressive) chromatin marks (Zeng *et al.*, 2019). In metazoans, bivalent marks are frequently found in undifferentiated cells and are correlated with poised genes that can be quickly switched on/off upon specific triggering stimuli (Voigt *et al.*, 2013). However, the dynamics of these marks upon exposure to low temperatures remain to be elucidated. Co-existence of both marks at stress-responsive loci has been previously reported upon dehydration, where genes were activated by stress-induced deposition of H3K4me<sub>3</sub>, despite exhibiting high levels of H3K27me<sub>3</sub> (Liu *et al.*, 2014). Additionally, in *A. thaliana*, the cold-induced activation of *COLD RESPONSIVE* (*COR*) genes was shown to involve the accumulation of histone acetylation as well as reduced nucleosome occupancy at these loci (Pavangadkar *et al.*, 2010; Park *et al.*, 2018). In maize, cold also induced activation of repetitive elements by increasing their histone acetylation, which was also accompanied by changes in nucleosome occupancy (Hu *et al.*, 2012). However, both histone acetylation and nucleosome occupancy return to pre-stress levels during the recovery period, when gene expression is back to baseline levels, suggesting that these changes may be a consequence of active transcription. Therefore, the question remains of how cold stress memory is regulated at the chromatin level.

The most detailed knowledge of cold-induced epigenetic regulation comes from vernalization in *A. thaliana*, the mechanism by which plants can remember a previous prolonged exposure to low temperatures and flower only when the conditions are favourable. At the molecular level, vernalization consists of the chromatin-mediated silencing of the flower repressor *FLOWERING LOCUS C* (*FLC*) by the Polycomb Repressive Complex 2 (*PRC2*; Michaels and Amasino, 1999; Bastow *et al.*, 2004), which deposits H3K27me<sub>3</sub> at target loci (Schubert *et al.*, 2006). *FLC* silencing occurs in two different phases (Yang *et al.*, 2017): nucleation of H3K27me<sub>3</sub> during the exposure to cold; and spreading of the mark to the gene body upon return to warmer temperatures. H3K27me<sub>3</sub>

nucleation takes place in a specific region downstream of the TSS (Finnegan *et al.*, 2007; Angel *et al.*, 2011) and it occurs digitally, meaning that an individual *FLC* allele is either ON (enriched in H3K36me3) or OFF (enriched in H3K27me3), with the intensity of silencing being achieved by a cell population average (Angel *et al.*, 2011, 2015; Yang *et al.*, 2014). The coordinated switch between the active and repressive states depends on the expression from the 3' end of a set of anti-sense transcripts collectively named COOLAIR (Swiezewski *et al.*, 2009; Csorba *et al.*, 2014; Rosa *et al.*, 2016). Two PHD proteins, VERNALIZATION INSENSITIVE 3 (VIN3; Sung and Amasino, 2004) and VERNALIZATION 5 (VRN5; Greb *et al.*, 2007), and a sense non-coding RNA named COLDAIR (Heo and Sung, 2011) also play a key role in cold-induced silencing of *FLC* by recruiting PRC2 to the locus through interaction with its core components VRN2 and CURLY LEAF (CLF; Wood *et al.*, 2006; de Lucia *et al.*, 2008; Heo and Sung, 2011). Consistently, *vin3*, *vrn5*, and *vrn2* mutants are all unable to completely silence *FLC* during exposure to cold, and all show reactivation upon return to warmer temperatures (Yang *et al.*, 2017). In *A. thaliana*, *VIN3* expression is activated only after a long period of cold in the absence of warmer temperatures, which is the first trigger for the epigenetically stable repression of *FLC* (Hepworth *et al.*, 2018). Additionally, *VIN3* is itself required for the recruitment of *VRN5* (de Lucia *et al.*, 2008). Upon return to warmer temperatures, *VIN3* binding is quickly reduced, while *VRN5* acquires a broader distribution throughout the *FLC* gene body, accompanying the spreading of H3K27me3 (Yang *et al.*, 2017). Interestingly, different PRC2 components seem to be required for each of the *FLC* silencing phases (Yang *et al.*, 2017). For instance, while the methyltransferase SWINGER (SWN) was shown to be predominantly required for the nucleation, CLF and the Polycomb-associated LIKE HETEROCHROMATIN PROTEIN 1 (LHP1) seem to be more important for the spreading of the mark (Yang *et al.*, 2017). This change in function by altering the composition of regulatory complexes resembles in part the regulation of transcriptional memory by the yeast COMPASS described in the previous section.

Vernalization responses in temperate cereals, such as wheat and barley, involve distinct molecular mechanisms (Dennis and Peacock 2009), indicating that vernalization evolved separately in different plant groups. Prolonged exposure to cold in cereals leads to the stable induction of *VRN1* (Trevaskis *et al.*, 2003; Yan *et al.*, 2003), a TF related to the *A. thaliana* APETALA1. This process is accompanied by a decrease in H3K27me3 and accumulation of H3K4me at the *VRN1* locus (Oliver *et al.*, 2009; Huan *et al.*, 2018), indicating a possible similar requirement for chromatin regulation in long-term memory of cold in cereals. However, further studies are required to confirm this hypothesis, and to identify the participating chromatin regulators.

## Impact of nucleosome composition and density

Changes at the nucleosome level, through the incorporation of specific histone variants or alterations in nucleosome

occupancy, may impact DNA accessibility and therefore transcription. Some of these mechanisms have been shown to be triggered under specific environmental conditions and could play a role in abiotic stress memory.

Besides the canonical H2A histone, three other variants have been identified in *A. thaliana*: H2A.Z which is mostly associated with euchromatin; H2A.W linked to constitutive heterochromatin; and H2A.X which has a broad localization in the genome (Yelagandula *et al.*, 2014). Notably, phosphorylated H2A.X, but not the widely distributed unphosphorylated form, marks sites of DNA damage (Lang *et al.*, 2012; Waterworth *et al.*, 2019). H2A.Z has been implicated in responses to environmental stimuli, particularly in the perception of temperature. Binding of H2A.Z at several loci is disrupted by a temperature increase within the ambient temperature range (Kumar and Wigge, 2010). At these loci, H2A.Z-associated chromatin is generally less open and accessible to digestion with micrococcal nuclease compared with regions occupied by the canonical H2A (Kumar and Wigge, 2010). Interestingly, in *A. thaliana*, this histone variant has been associated with both active and repressive chromatin states, depending on the genic region it occupies (Coleman-Derr and Zilberman, 2012; Sura *et al.*, 2017). However, the repressive role of H2A.Z depends at least in part on its monoubiquitination (H2A.Zub) by AtBMI1, a core component of PRC1 (Gómez-Zambrano *et al.*, 2019). The temperature-induced eviction of H2A.Z was additionally shown to be dependent on the activity of HSFA1 (Cortijo *et al.*, 2017). However, the dynamics of this process remain unknown. H2A.Z is deposited at target loci mainly through the activity of the SWR1 chromatin-remodelling complex (Mizuguchi *et al.*, 2004), but there is still poor knowledge on how it is evicted. H2Bub1 may stabilize the H2A.Z-chromatin association at inducible enhancers by preventing the binding of INO80 (Segala *et al.*, 2016), suggesting a possible role for histone post-translational modifications in this process. In yeast, H2A.Z eviction seems, at least in part, to rely on the chromatin remodeller INO80, which counteracts the action of SWR1 (Papamichos-Chronakis *et al.*, 2011). No equivalent mechanism has yet been reported in plants, but it will be interesting to see whether HSFA1 TFs could be involved in the recruitment of identical complexes. In *A. thaliana*, the MYB-like TF SWR COMPLEX 4 (SWC4) interacts with and is required for SWR1 recruitment and H2A.Z deposition at developmental genes (Gómez-Zambrano *et al.*, 2018). In *suc4* mutants, several HS-responsive genes, including *HSFA6A*, are up-regulated (Gómez-Zambrano *et al.*, 2018), suggesting that they are repressed by the SWC4-SWR1 complex under non-stress conditions. Nevertheless, a possible role for this complex under stress conditions requires further validation.

*Arabidopsis thaliana* also has three variants of the linker histone H1. Besides a role in heterochromatin formation, H1 influences nucleosome mobility at euchromatic sites and the maintenance of histone post-translational modifications (Rutowicz *et al.*, 2019). One of these variants (H1.3 in *A. thaliana* and H1-S in tomato) is induced by dehydration (Ascenzi and Gantt, 1999; Scippa *et al.*, 2000). In *A. thaliana*, two pools of H1.3 were identified: a constitutive one that localizes to stomata under non-stress conditions; and a broader

stress-inducible pool (Rutowicz *et al.*, 2015). Although tomato plants depleted of this variant performed less well than the wild type under progressive water deprivation (Scippa *et al.*, 2004), no differences were observed in the responses of *A. thaliana h1.3* mutants subjected to a similar treatment (Ascenzi and Gantt, 1999). However, upon exposure to combined dehydration/low light conditions, the *h1.3* mutant displayed altered patterns of stress-induced DNA methylation, suggesting that this variant might be important for the accessibility of DNA methyltransferases under more complex stress regimes (Rutowicz *et al.*, 2015).

Nucleosome assembly and disassembly are achieved through the activity of highly conserved histone chaperones (reviewed in Hammond *et al.*, 2017), which can also regulate plant responses to abiotic stress. Mutants in the NUCLEOSOME ASSEMBLY PROTEIN 1 (NAP1), an H2A–H2B chaperone, exhibit altered responses to the drought stress hormone ABA and to salt stress (Liu *et al.*, 2009). Plants with lower levels of SSRP1 and SPT16, both subunits of the FACT (facilitates activation of transcription) complex, show reduced induction of anthocyanin biosynthesis genes upon exposure to high light (Pfab *et al.*, 2018). The H2A–H2B chaperone complex FACT has also been related to responses to abiotic stress in other organisms. Yeast mutants depleted in SPT16 showed increased thermotolerance, which correlated with an impaired recovery of nucleosome occupancy and increased binding of RNA Pol II at HS-responsive genes (Erkina and Erkin, 2015). The opposite effect was observed for the H3–H4 chaperone ANTI-SILENCING FUNCTION 1 (ASF1) in *A. thaliana* (Weng *et al.*, 2014); *asf1* mutants showed increased sensitivity to high temperatures and lower expression of HS-inducible genes, which was accompanied by reduced removal of H3 and reduced accumulation of RNA Pol II (Weng *et al.*, 2014).

Orthologues of additional histone H3 chaperones such as the histone regulator A (HIRA) and the chromatin assembly factor 1 (CAF1) have also been identified in *A. thaliana* (Duc *et al.*, 2015; Muñoz-Viana *et al.*, 2017). In contrast to other chaperones, HIRA and CAF1 act preferentially on specific histone variants; while the former is responsible for the deposition of the replication-independent histone H3.3, the latter acts mostly on the replication-specific H3.1 variant (Tagami *et al.*, 2004). *Arabidopsis thaliana* mutants depleted in *FASCIATA 2* (*FAS2*), a core subunit of CAF1, show a reduction in nucleosome occupancy at a subset of defence response genes (Mozgová *et al.*, 2015; Muñoz-Viana *et al.*, 2017), mimicking primed plants. A similar phenomenon was observed for HS-activated DNA repeats in *fas1* mutants, where restoration of nucleosome occupancy during the recovery phase was impaired, indicating a role for CAF1 in re-silencing of repeats (Pecinka *et al.*, 2010). Fission yeast HIRA is involved in priming (cross-tolerance) by promoting nucleosome eviction and enhancing RNA Pol II occupancy at a subset of stress response genes (Chujo *et al.*, 2012). As similar chromatin features have been reported in plants primed for different abiotic stresses, it will be interesting to see whether HIRA is also required for these processes in plants. In *Caenorhabditis elegans*, the knockout of all five H3.3-encoding genes led to increased mortality upon HS (Delaney *et al.*, 2018). However, these differences were abolished when

the worms were subjected to a prior priming treatment with a milder HS, suggesting that H3.3 in this organism is mostly required for the immediate responses to high temperature (Delaney *et al.*, 2018). The high degree of conservation of histones in different organisms allows us to speculate that some of the mechanisms uncovered in other species may be conserved. To what extent histone variants and chaperones are involved in abiotic stress memory in plants remains unresolved.

Transcriptional changes in response to stress are often accompanied by changes in nucleosome occupancy. Accordingly, several ATP-dependent chromatin-remodelling complexes of the subfamilies ISWI, Switch/Sucrose Non-Fermentable (SWI/SNF), and CHD (reviewed in Han *et al.*, 2015) are required for priming in different organisms. In a forward genetic screen for regulators of HS memory, Brzezinka *et al.* (2016) isolated FORGETTER1 (FGT1) as a key element of type I HS transcriptional memory in *A. thaliana*. FGT1 interacts with the chromatin remodellers BRAHMA (BRM) and CHR11/17, forming a complex required to maintain low nucleosome occupancy during the memory phase (Brzezinka *et al.*, 2016). In agreement, the expression of HS memory genes in *fgt1*, *brm*, and *chr11 chr17* decreased more quickly and the mutants displayed lower survival upon recurrent HS (Brzezinka *et al.*, 2016). Both FGT1 and BRM are also functional under non-stress conditions; therefore, the question remains of how the FGT1–BRM complex is recruited to HS memory genes. In humans, the SWI/SNF remodeller BRG1 is recruited to HS-responsive genes by HSF1 (Sullivan *et al.*, 2001). Hence, a similar mechanism may be active in plants.

Lower nucleosome occupancy may be a widespread feature of memory genes after stress is perceived (Brzezinka *et al.*, 2016; Park *et al.*, 2018; Zeng *et al.*, 2019). For instance, *A. thaliana* plants defective in the chromatin remodeller PICKLE (PKL) are less 'primable' by cold than the wild type (Yang *et al.*, 2019). Although no differences between *pkl-1* and the wild type were observed in plants subjected to a single freezing stress, mutants that had been previously primed by exposure to mild cold stress exhibited lower survival (Yang *et al.*, 2019). This observation suggests that PKL acts in cold stress memory responses, although the molecular mechanisms are still not fully understood (Fig. 2C). PKL belongs to the subfamily CHD3 and it is required for the deposition and maintenance of the repressive chromatin mark H3K27me3 (Zhang *et al.*, 2008; Ho *et al.*, 2013; Carter *et al.*, 2018). As discussed above, this histone modification is known to play a key role in prolonged cold stress memory during vernalization (Finnegan *et al.*, 2007) and it was recently suggested to be involved in short-term cold stress memory as well (Vyse *et al.*, 2020). Whether PKL also acts in cold stress priming through the regulation of H3K27me3 remains to be elucidated.

## Effect of chromatin spatial organization

Chromatin inside the nucleus often occupies defined regions that are associated with pools of regulatory proteins and exhibit specific transcriptional profiles. At a finer scale, several local and long-distance chromatin loops that bring together genes and *cis*-regulatory elements have been identified in different



organisms, forming another layer of transcription regulation (reviewed in Gibcus and Dekker, 2013).

Current knowledge on how plant chromatin 3D organization impacts abiotic stress responses is still scarce, with only a few studies reporting changes upon exposure to adverse conditions. Using fluorescence *in situ* hybridization (FISH), Pecinka *et al.* (2010) found that upon prolonged HS nucleosome occupancy was reduced and heterochromatic chromocentres were strongly dispersed. While the former recovered quickly after return to ambient temperatures, overall heterochromatin de-condensation prevailed for up to 1 week, suggesting a possible role in stress memory (Pecinka *et al.*, 2010). Similarly, rice chromosomes de-condensed after exposure to cold, although this was not accompanied by global changes in chromatin structural organization (Liu *et al.*, 2017). Moreover, cold-induced repression of *FLC* involves loci clustering in the nucleus, which is positively correlated with the duration of exposure to cold (Rosa *et al.*, 2013), suggesting that vernalization requires chromatin spatial re-organization.

Local chromatin interaction domains (gene loops) have also been correlated with transcriptional changes and memory, as they allow the faster recycling of RNA Pol II at specific loci (Tan-Wong *et al.*, 2009). For instance, in yeast, gene loops induced by changes in the supplied carbon source were shown to be positively correlated with a stronger reinduction upon a recurrent stress (Laine *et al.*, 2009; Tan-Wong *et al.*, 2009). This process probably involves the recruitment of specific chromatin regulators, as reinduction of the *GAL10* gene was reduced in a mutant for the chromatin remodeller Snf2 (Laine *et al.*, 2009). Interestingly, transcriptional memory was also dependent on the association of these loops with nuclear pore proteins, reinforcing the idea that subnuclear localization is important for regulation of gene expression (Tan-Wong *et al.*, 2009). On the other hand, in *Drosophila*, HS led to dramatic changes in the 3D organization of the nucleus due to the increased number of interactions between different topologically associated domains (TADs), which correlated with a weakening of the domain borders (Li *et al.*, 2015). TADs are secondary interaction domains within higher order chromatin domains that are well conserved between cell types and different species (Dixon *et al.*, 2012).

Plant chromatin 3D structure seems to differ from that of other organisms (Fig. 3). For instance, in contrast to metazoans, no canonical TADs were identified in *A. thaliana*, which may be linked to the absence of orthologues of metazoan CTCF insulator proteins (Feng *et al.*, 2014; Wang *et al.*, 2015). Alternatively, it could be a consequence of the compact genome, as TAD-like domains have been observed in plants with larger genomes (Dong *et al.*, 2017; Liu *et al.*, 2017), probably reflecting a lower gene density (Doğan and Liu, 2018). However, local chromatin loops formed by the interaction of 5' and 3' ends of highly expressed genes have been observed in *A. thaliana* (Liu *et al.*, 2016). For *FLC*, silencing by vernalization correlated with the disruption of a gene loop that encompasses the whole locus (Crevillén *et al.*, 2013). Disruption of the *FLC* loop additionally required the activity of CHC1 (Fig. 3B), a subunit of SWI/SNF chromatin-remodelling complexes (Jégu *et al.*, 2014), suggesting a role for these proteins in the regulation

of chromatin 3D structure. Recently, BORDER (BRD) proteins were found to be associated with gene loop formation at several *A. thaliana* loci by regulating RNA Pol II pausing/recycling and thus preventing transcriptional read-through to neighbouring genes (Yu *et al.*, 2019). BRD proteins were shown to contribute to the rapid induction of several light-responsive genes (Yu *et al.*, 2019), showing that local chromatin interaction domains act in the regulation of plant responses to the environment.

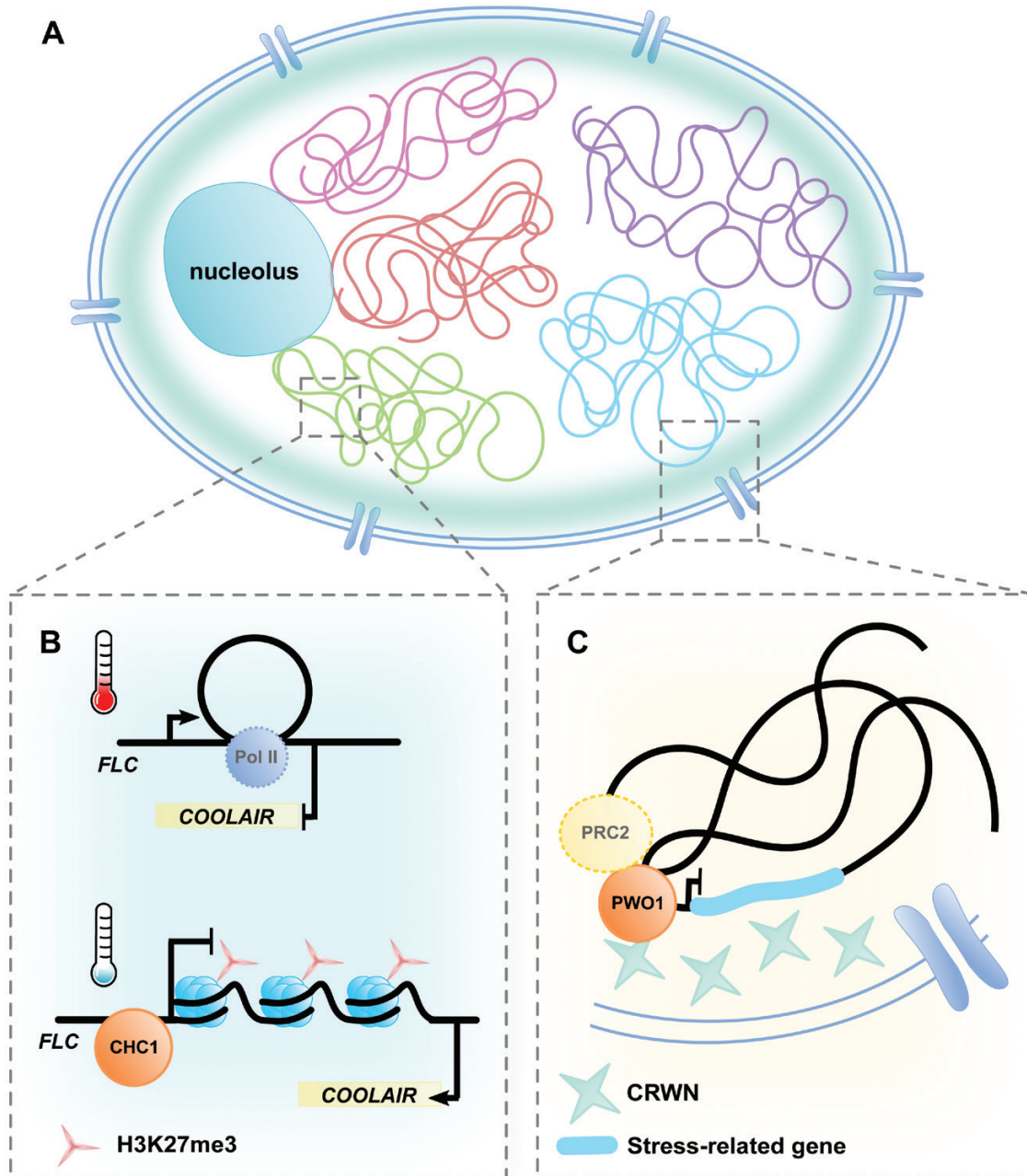
Additional studies indirectly suggest a role for chromatin 3D organization in responses to abiotic stress. PWWP INTERACTOR OF POLYCOMBS1 (PWO1), which recruits PRC2 to specific nuclear foci (Hohenstatt *et al.*, 2018), interacts physically and genetically with CROWDED NUCLEI (CRWN) family proteins (Mikulski *et al.*, 2019), which may be functional orthologues of nuclear lamina proteins (Wang *et al.*, 2013). In *A. thaliana*, chromatin interactions with the nuclear periphery have been linked to an accumulation of repressive chromatin features, including H3K27me<sub>3</sub>, at protein-coding genes and transposable elements (Bi *et al.*, 2017), which is in agreement with a possible recruitment of PRC2 to these locations. Gene Ontology analysis revealed an enrichment for stress-induced genes amongst those up-regulated in both *pwo1* and *crwn1/2* mutants (Mikulski *et al.*, 2019), suggesting that localization at the nuclear periphery might be involved in repressing stress-inducible genes under non-stress conditions (Fig. 3C). In yeast, the recruitment of genes to the nuclear periphery was associated with transcriptional memory and a faster re-induction following repression (reviewed in Brickner, 2009). Additionally, tethering at the subnuclear location and faster re-induction depended on the incorporation of the histone variant H2A.Z during previous active transcription (Brickner *et al.*, 2007). In *A. thaliana*, H2A.Z is known to be involved in plant responses to environmental cues (see above); however, evidence for its involvement in abiotic stress memory in plants is still lacking.

## Conclusions and perspectives

It is becoming increasingly clear that chromatin regulation plays an important part in modulating plant responses to environmental stresses. Changes in chromatin structure and composition have been associated with storage of information of a previous condition. Such marking may allow plants to save energy not only by responding faster and/or more strongly to recurrent stresses, but also allowing temporary shut-down of defence mechanisms without compromising survival (Hilker *et al.*, 2016). From the available data, some transcriptional memory features emerge that are common to more than one stress type. These include the accumulation of H3K4me and possibly RNA Pol II at memory loci, as well as reduced nucleosome occupancy (Fig. 2A, B). However, each stress memory type also has specific elements (Fig. 2).

Our review has focused on abiotic stress memory at the somatic level, which is usually limited to a few days or weeks. An important unresolved question is how the duration of the memory phase is regulated. Despite the fitness advantages of priming, one study suggests it can be detrimental under





**Fig. 3.** Chromatin 3D organization can have an impact on abiotic stress responses. (A) Chromosomes are packed inside the nucleus in a non-random way, and in metazoans have been shown to interact with different nuclear domains, such as the lamina in the periphery and the nucleolus. In plants, no such large-scale domains have been identified, but local chromatin interactions seem to be important for regulation of gene expression. (B) A gene loop at the *FLC* locus is associated with active transcription, possibly by facilitating the recycling of RNA Pol II. Upon prolonged exposure to cold, this loop is disrupted in a CHC1-dependent manner, allowing for the transcription of the lncRNA COOLAIR, thus triggering the cold-induced silencing of *FLC*. (C) The PRC2 interactor PWO1 also interacts with CRWN proteins, which may be functional orthologues of nuclear lamina proteins. Both PWO1 and CRWN were shown to target an overlapping subset of stress-related genes. Tethering to the nuclear periphery has been associated with gene repression and faster reactivation, suggesting that PWO1 and CRWN could have a role in abiotic stress responses and perhaps transcriptional memory. This probably involves the recruitment of PRC2 to the nuclear periphery. However, the role of these proteins in transcriptional memory remains to be elucidated. Dashed circles represent regulators whose direct involvement in abiotic stress responses remains to be validated.

non-stress conditions (van Hulst *et al.*, 2006), indicating that, in the absence of a recurrent stress, it might be advantageous to limit the duration of the memory phase. Two scenarios are therefore conceivable: either this duration is limited by the biochemical stability of the induced changes, and thus memory would be ended in a passive way; or, alternatively, it may be actively terminated through the activity of chromatin

regulators with opposing functions. A few works favour the latter, although a simultaneous occurrence of both scenarios cannot be discarded. Recently, Huang *et al.* (2019) reported the identification of the H3K4 demethylase JUMONJI 17 (JMJ17) as a negative regulator of dehydration stress responses in *A. thaliana*. Additionally, the H3K27 histone demethylase EARLY FLOWERING (ELF6) is known to be required for

the reactivation of *FLC* in reproductive tissues at the onset of a new generation (Crevillén *et al.*, 2014). Whether these or similar mechanisms also take place at memory genes during the memory phase requires further investigation.

Additional questions have been raised concerning the effect of plant age in priming responses and whether tissues respond differently to environmental conditions. HS transcriptional memory in different parts of *A. thaliana* seedlings was similar across tissues (Liu *et al.*, 2018). In contrast, HS-triggered heterochromatin de-condensation occurred only in differentiated cells (Pecinka *et al.*, 2010). Moreover, these results raise the question of if/how priming responses are mitotically transmitted from stress-exposed tissues to the newly formed ones, as well as general mitotic heritability.

Stress priming and memory have a great potential when it comes to crop improvement towards increased tolerance to environmental conditions. Therefore, understanding how these phenomena are regulated at the molecular level and what is the outcome of the interplay between the different regulatory mechanisms is of utmost importance and urgency. We believe recent advances in microscopy techniques, single cell and single molecule analysis, and genome editing strategies will strongly contribute to finding answers to the above-mentioned questions.

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