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Review

Plant responses to abiotic stress: The chromatin context of transcriptional regulation

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ABSTRACT

The ability of plants to cope with abiotic environmental stresses such as drought, salinity, heat, cold or flooding relies on flexible mechanisms for re-programming gene expression. Over recent years it has become apparent that transcriptional regulation needs to be understood within its structural context. Chromatin, the assembly of DNA with histone proteins, generates a local higher-order structure that impacts on the accessibility and effectiveness of the transcriptional machinery, as well as providing a hub for multiple protein interactions. Several studies have shown that chromatin features such as histone variants and post-translational histone modifications are altered by environmental stress, and they could therefore be primary stress targets that initiate transcriptional stress responses. Alternatively, they could act downstream of stress-induced transcription factors as an integral part of transcriptional activity. A few experimental studies have addressed this 'chicken-and-egg' problem in plants and other systems, but to date the causal relationship between dynamic chromatin changes and transcriptional responses under stress is still unclear. In this review we have collated the existing information on concurrent epigenetic and transcriptional responses of plants to abiotic stress, and we have assessed the evidence using a simple theoretical framework of causality scenarios.

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1. Introduction

Plants experience an ever changing environment, ranging from fast fluctuations of light and humidity caused by clouds, wind or rain, to larger diurnal and seasonal changes in temperature, light, rainfall and nutrient availability. In some environments plants have to deal with extreme conditions of permanent or frequent nature, whereas in other environments serious stress only occurs sporadically and therefore does not provide evolutionary pressure for permanent adaptations. Nevertheless plants need to have a safety net in place to deal with occasional stress events. Flexibility is an essential requirement for surviving stress at a sedentary life style. Plants maintain this flexibility by operating a signal-response network that allows them to rapidly re-programme their development, physiology and metabolism in response to environmental stress [1,2]. The ability of plants to perceive and integrate an enormous amount of environmental information and to respond to any given situation in an *ad hoc* manner has often led to comparisons with intelligent behaviour of animals, although in the absence of a central brain, the regulatory circuits that generate adaptive responses in plants differ considerably from those in animals [3]. What is common to adaptive responses in all life forms is that they depend to a large extent on dynamic changes in gene expression.

Transcriptional responses of plants to environmental stress factors have been investigated extensively over the last decades, from genome-wide transcript profiling under multiple stress combinations to the unravelling of specific signalling pathways and the identification of individual regulatory proteins and their targets. The research has generated a large body of detailed information on how plants respond to abiotic stresses such as cold, heat, drought, salinity or flooding [4–9]. The knowledge gained has already been used to improve crop resilience, e.g. through stress-inducible up-regulation of transgenes encoding enzymes that produce stress protectants or their regulators [10]. Over recent years scientists have become increasingly aware of the fact that transcriptional regulation cannot be fully understood unless we consider the structural context in which it occurs. DNA is assembled with histone proteins to form chromatin, which enables a higher order structure. Chromatin provides a means to stabilise and condense DNA but it is much more than a packaging device; it is dynamic and can be altered by developmental or environmental stimuli [11–16]. It is often assumed that environmentally induced changes in chromatin status control, or at least modify, transcriptional responses

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but this notion is still built on relatively spare evidence. In this review we have tried to collate and to assess the existing information that links epigenetic processes with transcriptional responses of plants to abiotic stress.

1.1. Chromatin structure – setting the scene

DNA is wrapped around protein units called nucleosomes. Each nucleosome is an octamer composed of two copies of histones H2A, H2B, H3, and H4, which associates with approximately 146 bp of DNA [17]. H1 is associated with the linker DNA between nucleosomes (30–100 bp), and causes further compaction [18,19]. While this overall arrangement is ubiquitous its exact composition and structure can change, both locally and temporally [20]. The chromatin status determines the accessibility and effectiveness of the transcriptional machinery (polymerases and regulatory proteins), and therefore chromatin remodelling is a potential means to control gene expression. The basic molecular processes underpinning chromatin dynamics are (1) the exchange of histone variants, (2) DNA-methylation and (3) histone modifications. The fact that these processes impact on gene expression, and hence on the phenotype of a plant, without altering the genetic code, has led to their general association with the term 'epigenetics', although some scientists argue that this term should be reserved to heritable phenomena.

1.1.1. Histone variants

Each histone type is represented by a number of variants with small differences in amino acid sequence and structure. Histone variants differ in their affinity for DNA and for histone binding proteins, and therefore replacement of one histone variant by another could alter compaction status and recruitment of regulatory protein complexes. The H3 variants H3.1 and H3.3 of *Arabidopsis* differ only in four amino acids [21], yet they are associated with different parts of the genome [22]. While H3.1 correlates with silenced genomic regions, H3.3 preferentially occurs in regions of active gene transcription and rapid nucleosome turnover [23–25]. Replacement of H3.1 by H3.3 accompanies important processes such as developmental re-reprogramming [26]. Similarly, the H2A variant H2AZ replaces H2AX in genome regions with active transcription [27]. Another H2A variant, H2AW, functions in the silencing of heterochromatic sequences [28,29]. The *Arabidopsis* genome also contains three genes encoding variants of the linker histone H1 [30]. H1.1 and H1.2 are most likely products of gene duplication and exist in a stable pool occupying preferentially heterochromatic regions. By contrast, H1.3 is more divergent and has a faster turnover; it shows specific expression in guard cells, and can be induced in other tissues by abiotic stress [31–35]. Stress-dependent deposition of histone variants provides a potential means to link environmental signals to downstream transcriptional responses. Current evidence supporting this paradigm will be reviewed below.

1.1.2. DNA-methylation

DNA-methylation (5-methylcytosine in various sequence contexts) is particularly prominent in the centromeric and pericentromeric regions of the chromosomes that are rich in transposable elements (TEs). Accumulation of DNA-methylation in all cytosine contexts results in highly condensed chromatin (heterochromatin), which prevents transcription thereby silencing TEs [36,37]. The mechanism of silencing through DNA-methylation, involving small RNAs and histone modifications such as H3K9me2 has been investigated in great detail and is reviewed elsewhere [38–42]. Removal of linker histones seems to be required to allow access for the DNA-methylation machinery [30,43].

In the laboratory, certain stress treatments, e.g. prolonged or repeated high temperature, can release silencing of transgenes or TEs, and in some case of neighbouring genes [44]. Vice versa, transcriptional regulation in response to low-phosphate stress of rice has been reported to cause transient hypermethylation of TEs in the vicinity of the stress-induced genes [45]. Furthermore, some DNA-demethylases target TE sequences within the promoters of stress-regulated genes [46]. The question whether stress-induced changes in DNA-methylation status could be heritable and generate a trans-generational memory of stress experience has been a matter of intense research, but remains controversial. In order to progress into the next generation stress-induced changes of DNA-methylation status would need to 'slip' through a very effective resetting process in the germ line [47–49]. Inheritance of re-activated TEs or transgenes into the next generation is therefore a very rare event, although it can be observed in mutants with defects in the processes underpinning resetting, for example the generation of siRNAs [50–52]. Importantly, however, if changes in DNA-methylation patterns are artificially introduced, e.g. through mutations in genes that maintain DNA-methylation, these can be inherited over many generations, even if the original mutant allele is outcrossed. This has allowed the generation of stable epi-RILs and new phenotypic variation [53,54].

The vast majority of transcriptional responses to environmental stress will occur outside the heterochromatic regions in the transcriptionally competent euchromatin, which harbours most genes (Fig. 1). Euchromatin has generally a low level of DNA methylation, although CG DNA methylation occurs within gene bodies of 13.5% *Arabidopsis* genes, and might be an important feature of highly expressed, constitutively active genes [55,56].

1.1.3. Histone modifications

Euchromatin is less compact than heterochromatin and accessible to the transcriptional machinery including polymerases and transcription factors. It is therefore primarily at this level of chromatin organisation that short-term regulation of gene expression occurs. Signalling pathways involving plant hormones such as abscisic acid (ABA), ethylene, jasmonate or brassinosteroids, connect environmental stress perception with activation of transcription factors, which in turn bind to the promoter regions of their target genes and either induce or repress them. This process occurs within the local chromatin context, which potentially provides an additional level of control.

The important dynamic features of euchromatin are post-translational modifications of the histones. The so-called 'histone code' is complex [57,58]; it includes a range of chemical modifications (methylation, acetylation, phosphorylation, ubiquitination) of different residues (mostly lysines and arginines in the N-terminal histone tails) at various levels (e.g. mono-, di- and tri-methylation) and in multiple combinations (e.g. the same residue can be both methylated and phosphorylated) [59–64]. In this review we will employ the usual terminology to label histone modifications, e.g. H3K4me3 standing for histone H3 tri-methylated in lysine 4. Considerable effort has been made to monitor histone modifications in individual genes and genome-wide, and to correlate them with each other and with downstream processes such as transcription, DNA repair and chromatin condensation. Therefore, the majority of studies investigating chromatin processes in relation to transcriptional stress responses have focussed on histone modifications. Before describing these studies in more detail, we will discuss possible causal relationships between signals, chromatin, transcription and responses in order to establish a conceptual framework for assessing and interpreting the empirical evidence.

1.2. Chromatin modifications and transcription - causal scenarios

Considering the importance of chromatin structure for transcriptional competence and transcriptional regulation it is clear that changes in this structure will have effects on processes that require transcriptional re-programming. It is therefore not surprising that mutants that are impaired in crucial processes underpinning chromatin structure will be affected in developmental transitions, such as germination and flowering, or in responses to environmental stresses. However, the

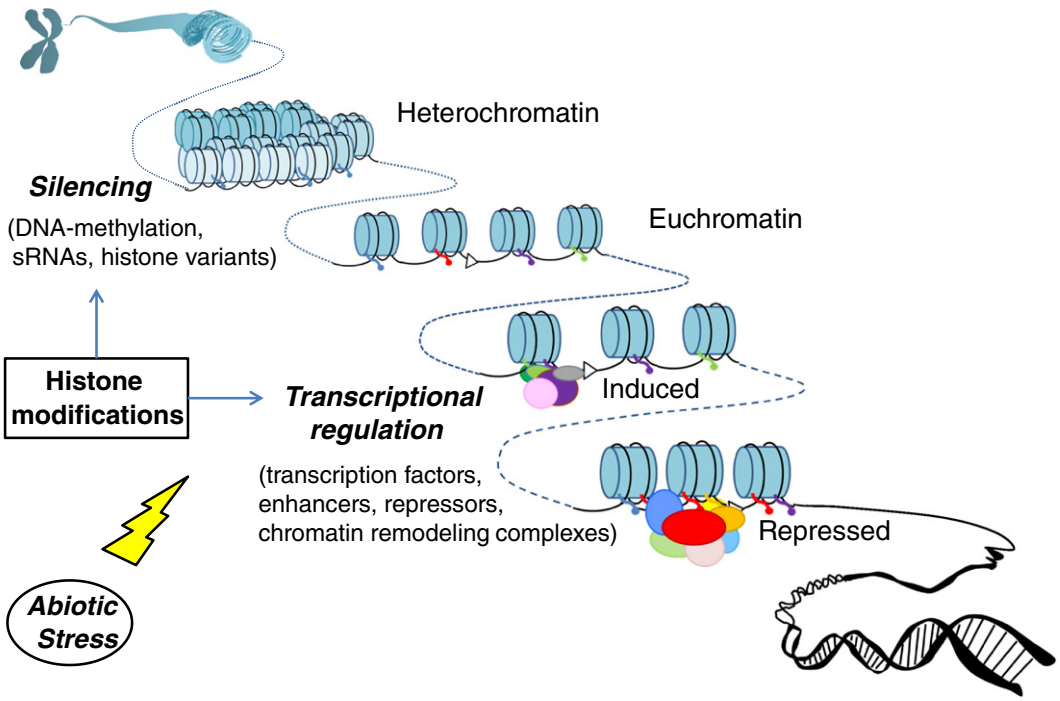

Fig. 1. Levels of gene expression control in the chromatin. Chromatin, the association of DNA (black line) with nucleosomes made from histone proteins (pale blue), facilitates tight packaging of the genetic material in chromosomes. Chromatin structure determines whether or not a gene is transcribed and at what rate. Genetic information in the highly condensed heterochromatin is silenced. Genes in the less condensed euchromatin are transcriptionally competent, 'poised' to be transcribed by RNA-polymerases. Transcription factors and other regulatory proteins (multiple colours) that bind to the upstream promoter regions (triangles) can activate (induce) or inhibit (repress) gene expression. Multi-protein complexes containing histone-modifying enzymes also associate with the DNA to attach or remove chemical modifications on histone tails (differently coloured extrusions from the nucleosomes). Chromatin-remodelling complexes also associate with the chromatin to exchange histone variants and/or alter nucleosome spacing. How abiotic stress signals regulate gene expression within the chromatin context is a topic of active research.

fact that a particular chromatin-modifying enzyme is required for transcriptional changes does not necessarily mean that it is actively involved in bringing about such changes. For example, if production of a compatible osmolyte requires transcription of a biosynthetic enzyme, it is possible that knockout of a deacetylase, which represses the particular gene leads to enhanced osmotic stress tolerance of the mutant. However, we cannot conclude that the plant uses a similar tactic during regulation. To ascertain the latter we would need to measure a change in the histone acetylation status of the gene and link it *causally* to both, the upstream regulation of the deacetylase by the environmental stimulus and the downstream regulation of the gene in question. To date many studies have reported stress-tolerant/sensitive phenotypes of mutants defective in chromatin-related genes, but establishing causalities has proven more difficult, especially because many mutants have already developmental phenotypes in unstressed conditions, which may affect their performance under stress.

Similarly, correlative observations do not prove a causal relationship. The notion of 'active' and 'repressive' marks is often used to argue that stress-induced change in a certain histone modification will lead to a transcriptional change, yet this terminology is purely based on genome-wide correlations. Plotting genome-wide histone modifications of chromatin in *Arabidopsis* roots against transcript levels in the same tissues confirmed indeed a positive correlation between transcript levels and H3K4me3 (an 'active' mark) and a negative correlation between transcript levels and H3K27me3 (a 'repressive' mark) [65], as shown before for other tissues. However, a few properties of the curves are notable. Firstly, in order to reveal the correlations, histone modification and transcript levels had to be averaged over several hundreds of genes, meaning that the relationship does not hold for individual genes, and is therefore not diagnostic. It is possible that correlation at single-gene level could be improved if the resolution was increased with respect to both, individual cell types and exact location of the histone modifications within the gene sequence, but this remains to be proven. Secondly, the curves are only linear in the lower part. They flatten with increasing values for transcript levels, indicating weak correlation for genes with moderate or high expression levels. Thus up-regulation of a gene that is already highly expressed is unlikely to be accompanied by a change in histone modification, and *vice versa*. Even more important in the context of stress-induced responses, is the fact that the correlations were established under steady-state conditions. There is no reason why the correlations should no longer hold once the plant has adapted to a long-term condition that differs from the control, e.g. lower water availability or higher temperature. It is therefore not surprising that studies monitoring histone modifications and transcript levels in plants that have experienced a stress condition for a prolonged period of time find similar correlations. Thus, if the 'stress-induced changes' are simply defined as the differences between the two steady states, 'changes' in chromatin marks and 'changes' in transcription will again be correlated. By contrast, when histone modifications and transcript levels were recorded immediately after the stress treatment, e.g. over the first 24 h after salt application [30], every gene tested differed in their kinetic profiles of transcript level and histone modification, and most of the changes did not follow the pattern predicted form the steady state correlations. Clearly, at our current state of knowledge, the notion of 'active' or 'repressive' mark is not sufficient for identifying causal relationships between stress-induced changes of histone modifications and stress-induced changes of transcript levels.

Theoretically, chromatin modifications could be causally linked to transcriptional responses in a number of ways, as schematically shown in Fig. 2. In the first scenario (1) the chromatin features are not themselves altered by the stress but their association with a particular gene before the stress may determine whether a stress-induced regulatory protein can exert its function or it may modulate its

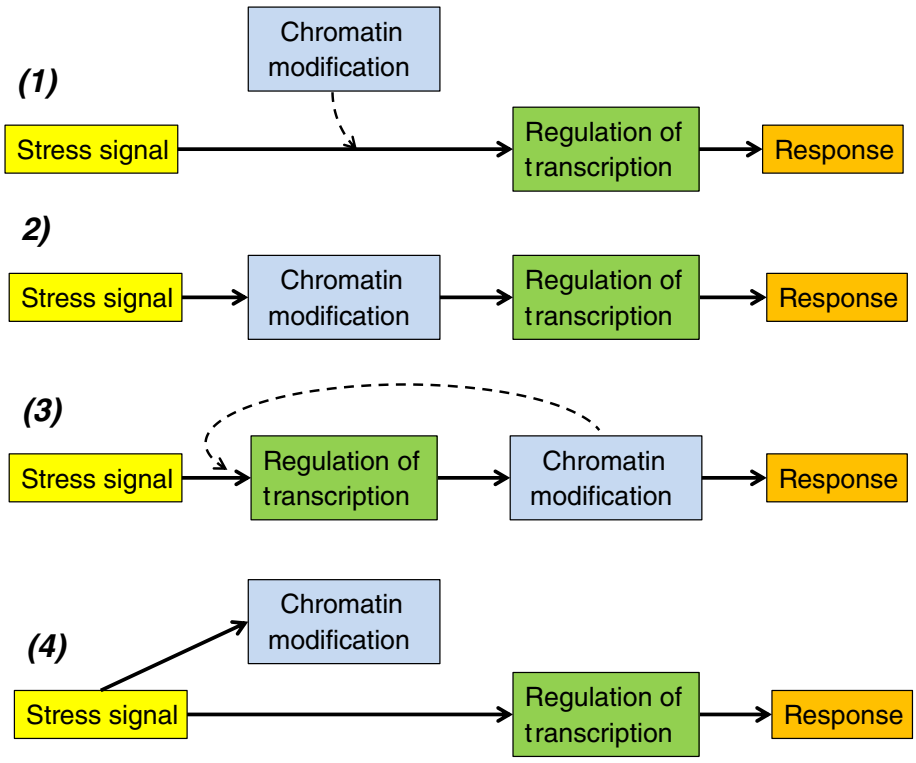

Fig. 2. Causality scenarios for the role of chromatin modifications in transcriptional stress responses. In the first scenario (1) chromatin marks are not themselves altered by the stress but their association with the gene before the stress may determine whether a stress-induced regulatory protein can exert its function, or may modulate the strength of the response. In the second case (2) the mark is the primary target of the stress signal and its change causes downstream transcriptional regulation of the genes associated with the particular mark. The third scenario (3) describes a situation where a change of chromatin is in fact part of the transcriptional regulation, acting downstream of a stress-inducible regulator. For example a transcription factor may recruit a histone modifying enzyme which then enhances or represses transcription. In the last case (4), the stress alters both, chromatin marks and gene transcription, but the two responses occur independently and the former is not necessary for the latter. The individual elements of the causal pathways may enhance or inhibit each other in feedback loops (e.g. (3) dotted line), and they may connect one scenario to another for different stresses or modifications. For detailed discussion see text.

efficiency. An obvious, yet unproven case is a cell-type specific response where the action of a transcription factor depends on whether the target gene is transcriptionally competent in this cell-type or not. It is similarly plausible that this scenario enables responsiveness to depend on the physiological state of the plant at the time of stress experience. To prove this scenario, it would be important to compare the responsiveness of a particular gene in different cell types or physiological states, and to relate any differences to cell-type/state specific chromatin modifications. In the second scenario (2), the chromatin is in fact the primary target of the stress signal. Changes of chromatin modifications would then cause (and be necessary) for downstream transcriptional regulation of the genes associated with the particular mark. This scenario is often implied when scientists report changes in histone modification profiles upon stress together with changes in gene expression. However, to prove this case, one would need to prevent the change in the histone mark, for example through knockout of the respective histone-modifying enzyme, and show that the transcriptional response no longer occurs. Optimally, impairment of the enzyme should be limited to the stress situation, for example through RNAi under the control of a stress-inducible promoter. The third scenario (3) describes a situation in which the primary target of the stress signal is a transcription factor and a change of chromatin properties is then part of the transcriptional regulation. For example, repressive transcription factors can recruit co-repressor proteins that are integral components of histone deacetylation complexes. Subsequent deacetylation of the histones associated with the target gene would then restrict access of the transcriptional machinery. To prove this case, binding regions of repressor or co-repressor could be altered, and this should prevent the stress-dependent down-regulation of the gene. Novel gene editing techniques offer an opportunity to carry out such experiments without the need to over-express the mutant proteins. In the last scenario (4), the stress alters chromatin features and transcription, but the two responses occur independently. To prove independence one needs to show that each change can be eliminated without altering the other. For example, one should test whether knockout mutants for the transcription factor or the histone-modifying enzyme still produce a stress-induced change in the histone mark or the transcript, respectively.

In reality, the above listed experimental strategies to prove a particular causal relationship are difficult if not impossible, the main reason being redundancy of gene functions underpinning chromatin modifications and transcriptional regulation. For example, histone-modifying enzymes are encoded by many genes with overlapping expression patterns. Biochemically they are rather promiscuous, obtaining their specificity primarily through association with other proteins that guide them to the target histone (histone-binding proteins) and to the target DNA (e.g. co-repressors). Similarly, histone variant replacement and nucleosome re-positioning is mediated by multi-protein complexes. Very few of these complexes have been characterised for their native composition in plants, and they can be expected to alter their contingent of protein partners depending on cell-type, developmental stage and environment. Thus, in most cases the specific interaction modules of modifiers and regulators that underpin a particular transcriptional response remain to be identified.

The distinction into the different scenarios is also simplistic, because the individual cases are likely to be interrelated both in space and in time. For example, histone-binding proteins in histone deacetylation complexes often have reading functions, meaning that they only bind to histones that have particular modifications (e.g. SHL1 and ING1/2 specifically bind to H3K4me3 [66,67]). A repressor can only recruit the histone deacetylation complex if the target histone has the particular modification. This connects scenario 3 to scenario 1 where the action of the repressor depends on the histone modification status prior to

the stress. Furthermore, changes of histone modifications and transcription are likely to differ in their dynamics [30]. Histone marks are relatively stable and can be transmitted through mitosis, they therefore can outlast transcriptional activity. This situation could link the outcome of scenarios 2 or 3 to scenario 1 if the stress is repeated, thereby providing a basis for priming and acclimation. Within a shorter time frame, the histone modifications occurring in scenarios 2 or 3 could inhibit or enhance transcription of the same gene (*cis*) or of other genes (*trans*). For example, negative feedback in *cis* could be a means to generate transient transcriptional responses, as are often observed after a sudden onset of stress.

Despite its obvious over-simplification, a distinction of possible causal relationships as depicted in Fig. 2 is helpful when assessing the existing evidence. In the following sections we will review studies that have monitored chromatin modifications and gene expression changes in response to abiotic stress treatments, and we will try to summarise them in causal models if possible.

2. Experimental evidence

2.1. Stress-dependent deposition of histone variants

The role of H2A variants in gene transcription and stress responses was investigated in *Arabidopsis* mutants defective for H2A.Z or for components of the SWR1 complex that deposits H2A.Z [68,69]. Loss of function of SWR1-complex components led to reduced sensitivity to pathogens and constitutively high transcript levels of pathogen-inducible genes [69]. Mutants for H2A.Z and SWR1-proteins were also found to be less sensitive to temperature changes [70]. When grown at cool temperatures (12–17 °C) the mutant plants pheno-copied wildtype plants grown at 27 °C and they displayed a constitutive high-temperature transcriptome. A genome-wide analysis of H2A.Z and transcript levels revealed that deposition of H2A.Z within gene bodies correlated not just with lower transcript levels but also with high variation of transcript levels across tissues and environmental conditions [56]. In combination with the reported anti-correlation between H2A.Z and DNA methylation, this suggests that gene-body methylation may be a means to evict H2A.Z in order to constitutively maintain high expression levels. The obvious follow-on question is whether environmental stimuli actively alter H2A.Z disposition. Comparing H2A.Z profiles along temperature-responsive genes between *Arabidopsis* plants exposed to 17 °C or 27 °C revealed higher levels of H2A.Z at the low temperature [70]. While this indicates temperature-dependent H2A.Z deposition the relation to the transcriptional response is unclear since the shift in H2A.Z level occurred irrespective of whether the genes were up-, down-, or unregulated by the temperature change. In the absence of a conclusive causal link the evidence available to date favours a model shown in Fig. 3A, in which the H2A.Z status prior to the stress determines stress responsiveness of individual genes, which is reminiscent of scenario 1 in Fig. 2.

H1 variants in plants fall into two groups; the ubiquitously and stably expressed major variants and stress-inducible minor variants. The latter include H1.3 in *Arabidopsis*, H1-C/D in tobacco and wild tomato, and H1-S in tomato. Drought-inducibility was reported in all species tested, but mutant analysis revealed no obvious functions, apart from

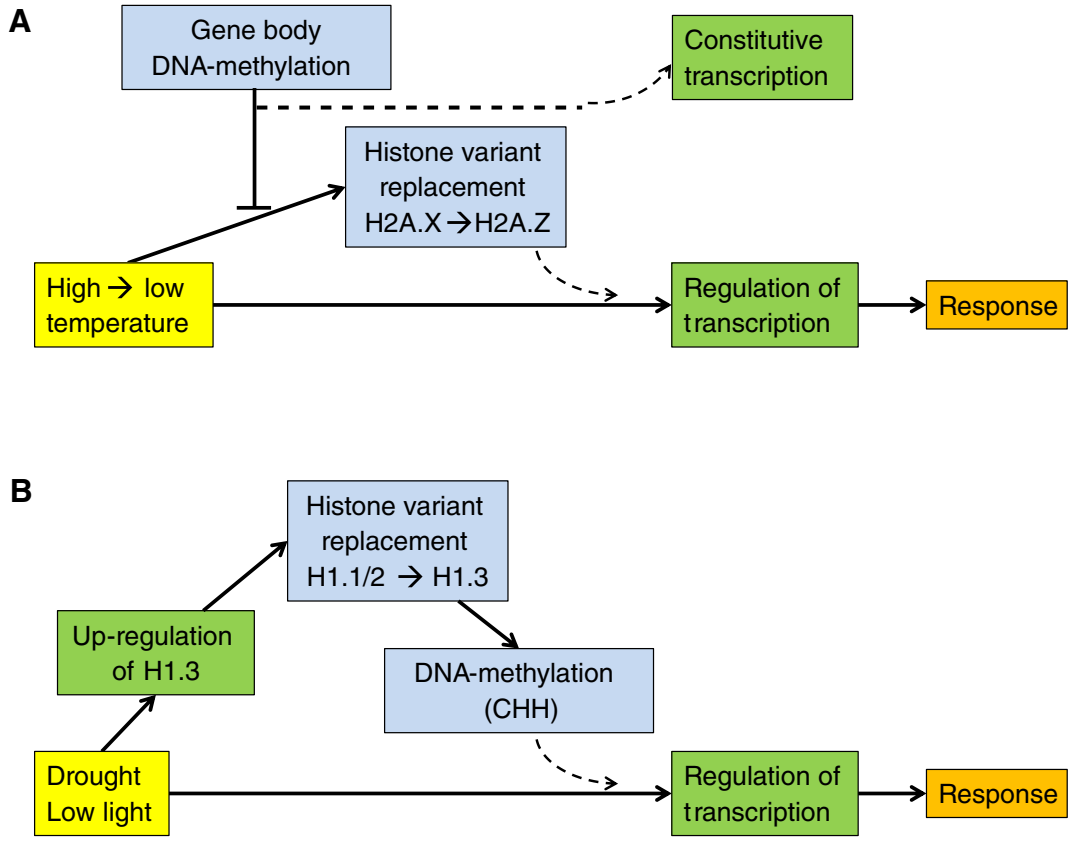

Fig. 3. Role of histone variants replacement in stress responses. **A:** Histone 2 variants: The combined evidence available to date favours a model, in which the H2A.Z status determines whether a gene can be transcriptionally regulated or not. H2A.Z deposition is enhanced in the cold and increases the plant's sensitivity to the temperature change. Gene-body methylation may be a means to evict H2A.Z in order to maintain high expression levels of constitutively expressed genes. The exact molecular processes that mediate between H2A.Z deposition and transcriptional responses remain to be established. **B:** Histone 1 variants: Experimental research suggests a model in which the canonical H1 variants (H1.1, H1.2) prevent access of the DNA-methylation machinery to the DNA under normal conditions, but are replaced by the more mobile, smaller H1.3 variant under stress, thereby causing DNA hyper-methylation in CHH context. The observation that H1.3-mediated DNA-methylation is shifted towards expressed genes indicates a potential effect of variant replacement on gene expression, but the exact mechanistic link between stress-induced hyper-methylation, transcriptional regulation and physiological responses remains to be elucidated. For details and references see main text.

tomato H1-S which was shown to maintain water status during drought stress [71–76]. Only recently, the function of *Arabidopsis* H1.3 was analysed in more detail [33]. It was found that in unstressed conditions H1.3 was specifically expressed in guard cells. *h1.3* mutants displayed decreased stomatal density in young leaves, reduced CO_2 assimilation rate per plant and altered expression of genes with known function in guard cell development. These differences did not impact on plant growth under normal conditions or under drought in high light. However, when drought was combined with low light the *h1.3* plants had lower leaf number and weight [33]. Indeed, H1.3 was strongly induced in all tissues by low light, with a synergistic effect to the previously shown induction by drought. The authors also determined histone mobility through Fluorescence Recovery After Photobleaching (FRAP) in plants expressing GFP-fusions of the different H1 variants [33]. The measurements revealed that H1.3 has considerably higher mobility in the chromatin than the main variants H1.1. and H1.2, suggesting that under stress it could outcompete them. In accordance with this notion, an increase of DNA methylation (particularly in CHH context) upon combined low-light/drought stress was dependent on a functional H1.3. As summarised in Fig. 3B, the evidence to date favours a model in which H1.1/2 variants protect the DNA under normal conditions, but are replaced by the more mobile H1.3 under stress. This allows access of the DNA methylation machinery and hypermethylation. Comparison of DNA-methylation patterns between *h1*-variant mutants showed that H1.3-mediated DNA-methylation is slightly shifted from TE targets towards expressed genes [33]. While this observation indicates a potential effect of variant replacement on gene expression, the exact mechanistic link between stress-induced hypermethylation, transcriptional regulation and physiological responses remains to be established.

2.2. Chromatin re-modelling complexes as direct targets of drought stress signals

SWI/SNF-type ATP-dependent chromatin re-modelling complexes are evolutionarily conserved multi-protein machineries which control DNA accessibility and chromatin structure [77,78]. These complexes enable histone variant replacement and nucleosome re-positioning, and have also been shown to alter histone-DNA interaction during stress response [78–80].

A suite of studies investigating mutants defective for protein components of SWI/SNF-type complexes in *Arabidopsis* have established a mechanistic link between water stress and transcriptional responses through chromatin remodelling. Under water stress (e.g. drought, salt) plants produce the hormone ABA, which binds to ABA-receptors and enables them to recruit PP2C-A phosphatases. This releases inhibition of SnRK2-type kinases, which in turn phosphorylate and activate ABA-Response Element (ABRE) transcription factors [1,81]. There is now convincing evidence that BRAHMA (BRM), the ATPase component of SWI2/SNF2, is a key target of the ABA-dependent de-/phosphorylation switch operated by PP2C-A and SnRKs [80,82]. BRM resides on target loci of ABA signalling (e.g. ABI5) and represses them. ChIP showed that BRM occupancy is independent of ABA, but phosphomimetic mutants revealed that BRM needs to be de-phosphorylated to be active and to repress the target gene [82]. Furthermore, BRM directly interacts with the clade-A PP2Cs HAB1 and PP2CA, as well as with the SnRKs 2.2,2.3 and 2.6/OST1 [82]. The current model is that in the absence of ABA, the PP2Cs maintain an active, de-phosphorylated state of BRM thereby preventing expression of ABA-response genes. Upon an ABA-signal, PP2Cs are removed and BRM can be phosphorylated by SnRKs, which leads to its inactivation and releases the repression of the ABA-inducible gene [82]. As summarised in Fig. 4, the evidence obtained so far positions BRM between the environmental signal and the transcriptional response and therefore reflects the causal scenario (2) in Fig. 2. The exact mode by which BRM represses the target loci remains to be determined, but may involve nucleosome repositioning [80].

Knockout *brm* mutants share an ABA-hypersensitive germination phenotype with *swi3c* mutants supporting the notion that SWI3C is a subunit of in the same complex [77,83]. However, the opposite phenotype was reported for *swi3b* mutants defective for another SWI3 homolog [82]. *swi3b* seeds were less sensitive to ABA during germination and showed a reduced expression of the ABA responsive genes, RAB18 and RD29B. As BRM, SWI3B was also found to directly interact with HAB1 [79].One possibility is that SWI3B competes with BRM for HAB1 binding thereby de-phosphorylating BRM. Another possibility is that SWI3B is associated with a different complex with distinct function to the BRM/SWI3C complex [77,84].

2.3. Histone acetylation marks and transcriptional regulation under abiotic stress

Histone acetylation reduces charge interactions between histones and DNA whereas deacetylation increases them, and these changes facilitate or impede transcription respectively [85–91]. Histone acetylation/de-acetylation is catalysed by histone acetyltransferases (HATs) and histone deacetylases (HDAs). Many of the genes encoding these enzymes have been identified in plants such as *Arabidopsis*, tomato, maize, rice, barley and grapevine, as well as *Brassica* and *Brachypodium* [85,92–97]. Analysis of histone modification sites by mass spectrometry and biochemical assays [60,98] has indicated a high conservation between plants and other organisms for the position and the post-translational modification of individual sites. Among the different lysine residues found to be reversibly acetylated within the H3 and H4 tails, several have been reported to respond to abiotic stress either at a single-gene or at whole-genome level. A number of studies that have investigated the effects of abiotic stress on both histone acetylation and transcript levels are listed in Table 1, and are summarised in the following text.

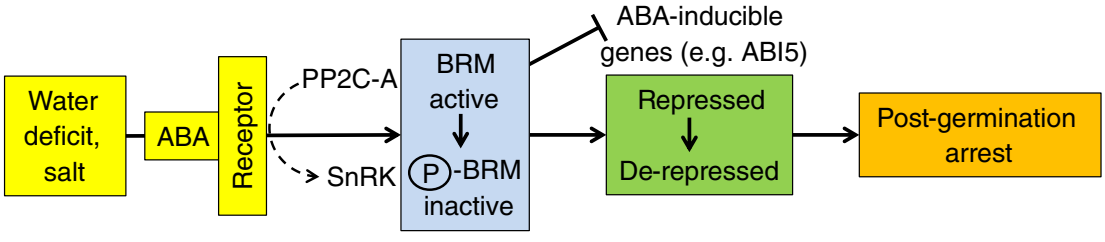

Fig 4. Role of chromatin remodelling in stress responses. BRAHMA (BRM), the ATPase of a SWI2/SNF2 chromatin remodelling complex resides on ABA-regulated loci and inhibits transcription. BRM is a direct target of the ABA-perception module and positions the chromatin modification between the environmental signal and the transcriptional response (causal scenario (2) in Fig. 2). Evidence gathered so far suggests the following model: In the absence of ABA, PP2C-A phosphatases maintain an active, de-phosphorylated state of BRM thereby preventing expression of ABA-response genes. Upon an ABA signal, ABA-receptors bind PP2Cs. PP2Cs are removed from BRM, and BRM is phosphorylated by SnRK kinases, which leads to its inactivation. Inactivation of BRM releases the repression of the ABA-inducible genes. The exact mode by which BRM represses the target loci remains to be determined, but may involve nucleosome repositioning. For details and references see main text.

2.3.1. Histone de-/acetylation at stress-responsive genes of Arabidopsis

In response to a dehydration treatment lasting from 1 to 5 h, known drought-responsive genes such as *RD29A*, *RD29B*, *RD20* and *RAP2.4* were found to be differentially acetylated at K9, K14, K23 and K27 of histone 3 in *A. thaliana* [99]. Higher levels of histone acetylation correlated with an increase in gene transcription within 2–5 h after the treatment. The levels of H3K9Ac in *RD20* and *RD29A* were also monitored over a time course of several hours after recovery from drought stress [100]. H3K9Ac, which was increased during drought, was quickly reduced after rehydration. In addition to the typical drought stress markers *RD29A/B*, which have unknown function, acetylation levels of H3K9/K14 were also monitored for genes encoding proteins of known function, including the transcription factor *DREB2A*, the protein phosphatases *ABI1* and *ABI2*, and the potassium channels *KAT1* and *KAT2* [101,102]. *ABI1* and *ABI2* were induced by ABA and NaCl, whereas transcript levels of *KAT1* and *KAT2* only increased in response to ABA. In ChIP experiments a salt-induced increase of H3K9/K14 acetylation was found for *ABI2* and *RD29B* at the first exon, while a decrease was recorded at the promoter region of *ABI2*, and no change was found for *ABI1*, *KAT1* and *KAT2*. These studies showed that stress alters H3K9/K14Ac levels of some genes, but they did not reveal if and how local differences may impact on transcriptional stress responses.

2.3.2. Stress-related phenotypes of histone deacetylase mutants

A more mechanistic insight into the role of histone de-/acetylation can be expected from mutant analysis. Analysis of *hda6* mutants, defective for histone deacetylase HDA6 [102], revealed higher H3K9/K14ac levels than in wildtype in control condition for some loci, but there was no clear correlation with the transcript levels. More importantly, salt-induced hyper-acetylation of *DREB2A* and *RD29A* was lost in *hda6* mutants and transcriptional up-regulation was attenuated, suggesting that HDA6 is required for both responses. Knockout of the HDA6-interacting putative deacetylase HD2C in *Arabidopsis* also led to an increase of H3K9/K14 acetylation levels, for example in *ABI1* and *ABI2* [103]. In accordance with a requirement of ABI1/2 for ABA-sensing [104], *hd2c* mutants displayed a hypersensitive response to ABA or NaCl during germination [103]. Conversely, plants overexpressing HD2C were found to be less sensitive to ABA or NaCl during germination [105]. The findings indicate a potential mechanistic link between histone deacetylation and ABA signalling, whereby histone acetylation levels of important ABA-signaling components determine the set point of ABA sensitivity. One would expect then that knockout of the deacetylases no longer increases ABA sensitivity in an *abi1/2* background, and this needs to be tested in the future. Furthermore, the transcriptional responses of ABA-responsive downstream genes should be assessed in *hda/abi* double mutants to interrogate causal relationships between histone acetylation and transcriptional responses.

Recently, histone deacetylase 9 (HDA9) was reported to repress stress-responsive genes [106]. Transcriptome analysis of *hda9* mutants revealed increased expression of genes involved in plant responses to water deprivation. Furthermore ChIP analysis of plants subjected to salt or drought stresses showed H3K9 hyperacetylation at 14 selected genes in *hda9* mutants compared to wildtype [106]. Surprisingly, at phenotypic level, *hda9* seedlings showed less sensitivity to salt and PEG during germination than wildtype. They had longer roots and higher germination rates, and hence the opposite phenotype of other histone deacetylation mutants (see above). The findings exemplify the fact that transcriptional repression by histone deacetylases can have different phenotypic consequences depending on the specific set of target genes.

2.3.3. Protein partners of histone de-/acetylases

Histone deacetylases form complexes with multiple other proteins which have been biochemically characterised in yeast [107]. Alongside co-repressors and histone-binding proteins, several proteins of unknown function co-eluted with the yeast RPD3 deacetylase, one of them being RXT3. An *Arabidopsis* homolog of RXT3 named Histone Deacetylase Complex 1 (HDC1) was found to be able to directly interact with the histone deacetylases HDA6 and HDA19 and to affect stress sensitivity of seedlings [108]. Similar to *hda6* and *hda19* mutants [109], the *hdc1* knockout mutant seedlings displayed hypersensitivity to ABA and NaCl [108]. Overexpression of *HDC1* resulted in ABA/salt hyposensitivity. No phenotypes have been reported for plants overexpressing the HDAs in *A. thaliana*, indicating that HDC1 is a rate-limiting component of HDAC complexes. In accordance with this notion, loss of *hdc1* led to an increase of H3K9/K14ac at the total protein level, which was reversed after complementation with genomic *HDC1*. At single-gene level, genes encoding ABA biosynthetic enzymes (*ABA1*), drought-repressed proteins (*DR4*) and ABA receptors (*PYL4*) were hyper-acetylated in *hdc1-1* and hypo-acetylated in HDC1 overexpressing lines, respectively, and their transcript levels followed the expected pattern with overall higher or lower transcript levels, respectively. The results identify HDC1 as an important factor controlling the apparent activity of HDAs and fine-tuning histone acetylation during stress responses. In a follow-up study it was found that HDC1 not only directly binds to HDAs and H3-binding proteins but also to H1 variants, suggesting a novel role for linker histones in transcriptional gene repression under abiotic stress [66].

In an independent study, HDC1 was confirmed as member of a native protein complex in *A. thaliana* containing HDA19 [110] and the H3-binding protein MSI1 [111]. ABA responsive genes such as *RD29B*, *ANACO19* and *COR15A*, as well as ABA receptors *PYL4*, *PYL5* and *PYL6*, showed higher transcript levels in *msi1*, *hda19* and *msi1/hda19* knockout plants than in wildtype. At the chromatin level, *PYL* genes displayed increased H3K9 acetylation around the transcriptional start site, and ChIP experiments indicated that MSI1 was able to physically associate with the *PYL* gene sequences around the same positions. It is likely that the interaction is mediated by other proteins in the complex, in particular co-repressors, but these remain to be identified. Based on their homology to yeast co-repressors, SIN3-like proteins that co-eluted with HDA19 and MSI1 [110] are good candidates. In fact, *At*SIN3 had previously been shown to interact with HDA19 and with the ethylene responsive repressive transcription factor ERF7 [112].

HATs catalyse histone acetylation thereby potentially facilitating gene transcription. The *A. thaliana* HAT GCN5 forms a complex with the transcriptional co-activators ADA and SAGA [113]. Loss of function mutants *ada2b* and *sfg29* show reduced salt sensitivity and lower expression of known salt-responsive genes, including *RAB18*, *COR6.6*, *RD29B* [114]. ChIP-PCR sampling of H3K9/K14 and H4K5/K8/K12/K16 acetylation levels at promoter regions indicated that knockout of ADA2b affects all of these marks at *RAB18* and *COR6.6*, but only H3K9/K14Ac at *RD29B* [114]. This suggests that the residues targeted by HATs depend on local sequence and chromatin environment.

Overall, there is strong evidence that HDAs and HATs are an integral part of transcriptional regulation, as depicted in Fig. 5A. They are recruited to the DNA through co-activators/repressors and further modulated in their apparent activity by additional factors within multi-protein complexes. Their relative activities determine acetylation levels and responsiveness of the genes (and the plant) to abiotic stresses such as salt and drought. However, much more research is required to understand whether plants (1) actively make use of this system to adjust the set point of stress sensitivity, e.g. after priming, or in response to multiple stresses, and (2) dynamically re-assemble HAT/HDA complexes to switch between different sets of target genes.

2.3.4. Stress-responsive histone acetylation marks in crops

In addition to experiments carried out with the model plant *A. thaliana* several studies of histone acetylation/deacetylation in response to stress were performed on crops. In maize, salt treatment of roots in hydroponics caused a global increase of H3K9 and H4K5 acetylation and transcriptional up-regulation of expansins and other cell wall-related genes. Among these, *ZmEXPB2* and *ZmXET1* had increased

Table 1
List of selected studies that have analysed histone modifications and gene expression under abiotic stress. The table includes the species and genotype, the specific histone modifications monitored, the stress treatment applied, the duration of the treatment and time points analysed, and the techniques used to measure the chromatin marks (ChIP-sequencing, ChIP-qPCR, Western blot) and gene expression (RNA-sequencing or microarray, RT-qPCR).

Species, genotype	Chromatin marks tested	Stress	Time	Genes tested	ChIP-seq	ChIP-qPCR	RNA-seq/microarray	RT-qPCR	Western blot	Ref
A. thaliana Col-0	H3K9ac, H3K14ac, H3K23ac, H3K27ac, H3K4me3	Drought	1, 2, 5 h	*RD29A*, *RD29B*, *RD20*, *RAP2.4*		X		X		[99]
A. thaliana Col-0	H3K9ac, H3K4me3	Drought	4 h; rehydration for 1–5 h (time course)	*RD20*, *RD29A*, *AtGOLS2*, *ProDH*		X		X		[100]
A. thaliana axe1-5 Col-0, *CS24039(HDA6 RNAi)* Ws	H3K9K14ac, H3K4me3, H3K9me2	ABA, NaCl	5 days	*ABI1*, *ABI2*, *RD29A*, *RD29B*, *KAT1*, *KAT2*, *DREB2A*		X		X		[102]
A. thaliana axe1-5, *hd2c-1*, *hd2c-3* Col-0	H3K9K14ac, H3K9me2	ABA, NaCl	5 days	*ABI1*, *ABI2*, *ERF4*		X		X	X	[103]
A. thaliana 35S::HD2C-GFP Col-0		ABA, NaCl, Mannitol	5–20 days	*RD29B*, *RAB18*, *ABI2*, *ADH1*, *KAT1*, *KAT2*, *SKOR*				X		[105]
A. thaliana hda9-1, *hda9-2* Col-0	H3K9ac	NaCl, KCl, Mannitol	6–78 h	Genome-wide		X	X			[106]
A. thaliana hdc1-1, *35::HDC1*, *Ubi10::HDC1* Col-0	H3K9K14ac	NaCl	24 h	*ABA1*, *RD29B*, *PYL4*, *DR4*, *ABA3*, *RD29A*, *AFP3*, *RAB18*		X		X	X	[108]
A. thaliana hda19-1 Ws		ABA, NaCl	5 days	*ABI1*, *ABI2*, *RD29B*, *KAT1*, *KAT2*				X		[109]
A. thaliana hda19, *msi1–as* Col-0	H3K9ac	ABA, NaCl	4–10 h (ABA); 0–70 h (NaCl)	*RD29B*, *ANACO19*, *COR15A*, *PYL4*, *PYL5*, *PYL6*		X		X		[111]
A. thaliana ada2b-1, *gcn5-1* Ws		Cold	21 h to 2 days (time course)	Genome-wide			X			[113]
A. thaliana ada2b-1, *gcn5-1*, *ada2a-2*, *sgf29a-1* Ws	H3K9K14ac, H4ac (K5, K8, K12, K16)	NaCl	3–12 h, 5 days (germination)	*RAB18*, *COR47*, *COR78*, *COR6.6*, *RD29B*, *COR15*		X		X		[114]
Zea mays	H3K9ac, H4K4ac	NaCl	7 days	*ZmExPA1*, *ZmEXPA3*, *ZmEXPA5*, *ZmEXPB1*, *ZmEXPB2*, *ZmEXPB4*, *ZmXET1*		X		X	X	[115]
Hordeum vulgare		ABA, SA, JA	6–24 h	*HvHDAC2-1*, *HvHDAC2-2*				X		[116]
Oryza sativa	H3K18ac, H3K27ac, H4K5ac, H3K9ac	Drought	0–33 h (time course)	*OsHAC703*, *OsHAG703*, *OsHAM701*, *OsHAF701*				X	X	[117]
Oryza sativa		ABA, NaCl	5–14 days	*OsGA20ox2*, *OsGA20ox3*, *OsGA3ox1*				X		[118]

(continued on next page)

Table 1 (*continued*)

Species, genotype	Chromatin marks tested	Stress	Time	Genes tested	ChIP-seq	ChIP-qPCR	RNA-seq/microarray	RT-qPCR	Western blot	Ref
ZmUbi10::HDA705										
A. thaliana axe1-5 Col-0, *sil1* Ler		Cold	3 days acclimation, 3 h freezing	Genome-wide			X			[120]
Zea mays	H3K9ac, H4K5ac, H4K4ac	Cold	15 min freezing (time course)	*ZmDREB1*, *ZmICE1*, *ZmCOR413*		X		X	X	[121]
Zea mays	H3K9ac	Cold	3–6 weeks	Genome-wide	X					[122]
Oryza sativa	H3K9ac, H3K9K14ac, H3K27ac	Cold	2–16 h (time course)	*OsDREB1*		X				[123]
A. thaliana Col-0	H3K4me3, H3K4me2, H3K4me1	Drought	4–6 days (to RWC* 65%)	Genome-wide	X		X			[129]
Oryza sativa ssp. *japonica* cv. ZH11	H3K4me3	Drought	To RWC 50%	Genome-wide	X		X			[130]
A. thaliana atx1, *35S::ATX1 atx1* Ws	H3K4me3	Drought	12 days	*NCED3*, *RD29A*, *RD29B*		X		X		[131]
A. thaliana atx1 Ws, *areb1areb2abf3*	H3K4me3	Dehydration	2 h + 22 h recovery, 4 cycles	*RD29A*, *COR15A*, *RD29B*, *RAB18*		X		X		[132]
A. thaliana jmj15-1, *jmj15-2*, *jmj15-3*, *JMJ15::GUS*, *35S::JMJ15-HA* Col-0	H3K4me3, H3K4me2, H3K4me1	Salt	1 h	*RD29A*, *RD29B*, *RD22*, *COR15A*, *COR47*, *P5CS1*, *P5CS2*			X	X		[133]
A. thaliana Col-0	H3K27me3	Salt	24 h	Genome-wide	X	X	X	X		[65]
A. thaliana flc-3, *jmj32-1*, *jmj30-1*, *jmj30-2*, *jmj30-2jmj32-1*, *35S::JMJ30-HA*, *35S::JMJ32-HA* Col-0	H3K27me3	Heat	8 days	*FLC*		X	X	X	X	[125]
A. thaliana Col-0	H3K27me3	Cold	6 days; 2/1/1/days stress/recovery/stress	*COR15A*, *ATGOLS3*		X		X		[136]
Oryza sativa cv. Nipponbare	H3K4me3, H3K4me2, H3K9/14ac	Submergence	24 h	*OsADH1*, *OsPDC1*		X		X		[137]
A. thaliana hsfa2-1, *pHSFA2::HSFA2-YFP* Col-0	H3K4me3, H3K4me2, H3K9ac	Heat	1–3 h acclimation, repeated.	*APX2*, *HSP18.2*, *HSP22.0*, *HSP70*		X		X		[140]
A. thaliana sid2-1, *npr1-1*, *ein2-1*, *coi1-16*, *hac1-1* Col-0/Col-6	H3K4me3/2, H3K9/14ac	Heat, cold, salt, *P. syringae*	1.5 h per day (for up to 7 days)	*WRKY53*, *FRK1*, *NHL10*		X		X		[141]

*RWC: relative water content.

H3K9ac at the promoter regions [115]. Two histone deacetylases *HvHDAC2-1* and *HvHDAC2-2*, were isolated from barley and found to transcriptionally respond to ABA, SA and JA [116]. In rice plants exposed to drought stress, the expression of four histone acetyltransferases (*OsHAC703*, *OsHAG703*, *OsHAF701* and *OsHAM701*) was found to be significantly increased. The transcriptional response was matched by higher H3K9/K18/K27 and H4K5 acetylation at the total protein level [117]. Overexpression of the rice histone deacetylase *HDA705* decreased seed germination in response to ABA or salt, thus reflecting phenotypes of *Arabidopsis* mutants related to HDA6 and HDA19. In this case, the lower germination rate was attributed to decreased transcript levels of the GA biosynthetic *genes OsGA20ox2*, *OsGA20ox3*, *OsGA3ox1* [118]. In general, causal relationship between histone deacetylation, transcript level and physiological responses remain to be proven, however, the observed transcriptional regulation of the HDAs are interesting. In our tentative model (Fig. 5A), induction of HDAs in response to stress would de-sensitize the plant, leading either to transient responses to the initial stress or to a lower response upon stress re-occurrence.

In addition to drought and salt, low temperature is one of the major environmental stresses that cause agricultural yield loss. Plants are able to increase their freezing tolerance after exposure to short and/or moderate chilling. Cold acclimation involves re-programming of gene expression [119], and histone de-/acetylation has been proposed to play a major role in this process [120]. In maize, short treatments with cold temperatures decreased histone acetylation at positions H3K9, H4K5 and H4K4 at the total protein level [121]. The effect was reverted when the plants were returned to control temperature. *ZmDREB1* is the major transcription factor induced by cold, together with its target gene *ZmCOR13*. After treatment with the histone deacetylase inhibitor trichostatin A (TSA), *ZmDREB1* was no longer induced by cold, suggesting that ZmDREB1 induction requires histone deacetylation, although not necessarily in the same gene. Another cold-induced transcription factor, *ZmICE1* was not affected by TSA. Analysis of the H3K9, H4K5 and H4-tetra acetylation in the *DREB1* promoter regions indicated that after cold acclimation *DREB1* DNA sequences that are usually bound by *ICE1* were hyper-acetylated while adjacent regions which are not involved in ICE1 binding were not. Upon cold treatment with TSA, all regions were hyper-acetylated compared to control conditions. These results indicate a positive regulatory role of histone deacetylation on *DREB1* induction during cold-acclimation, which is somewhat counter-intuitive given the assumed repressive action of histone deacetylation. It is possible that the observed local differences hyper/hypo-acetylation explain this effect. A subsequent study assessed the genome-wide effect of cold on H3K9 acetylation in maize [122].

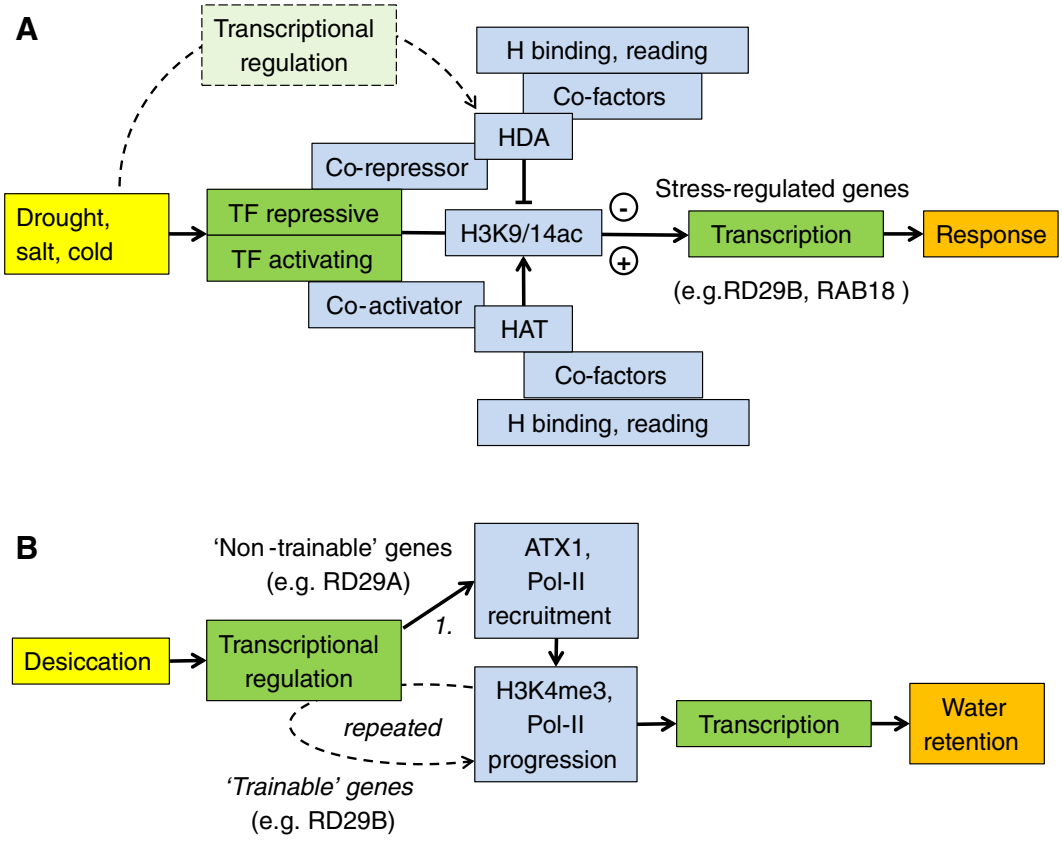

Fig. 5. Role of histone modifications in stress responses. **A:** Histone de-/acetylation: Histone acetyl-transferases (HATs) and deacetylases (HDAs) are an integral part of transcriptional regulation. The current state of knowledge suggests a model in which the enzymes are recruited to the DNA by stress-regulated transcription factors (TFs) through co-activators and co-repressors, and further modulated in their apparent activity by additional factors within multi-protein complexes (for further details on individual proteins see main text). The relative activity of HATs and HDAs determines histone acetylation levels at the target loci and transcriptional activity, with downstream effects on plant responses. However, specific pairs of TFs and co-activators/repressors, as well as the exact composition of native multi-protein complexes, need to be identified to unravel precise causal relationships between histone de-/acetylation, transcript levels and physiological responses. Transcriptional induction of HDAs in response to stress, as observed in some crop species could provide a means to terminate transcriptional responses or to desensitize the plant to repeated stress. Histone-binding proteins in HAT and HDA complexes have 'reading' function thereby guiding the enzymes to certain histone marks such as H3K4me3. **B:** Histone de-/methylation: Experiments involving repeated exposure of seedlings to desiccation followed by recovery periods have led to a model for short-term stress memory based on establishment and maintenance of H3K4me3 marks. In this model, chromatin processes such as protein recruitment and histone methylation are associated with different phases of transcription, namely initiation and elongation. In some genes, so called 'trainable' or 'memory' genes, H3K4me3 deposited during the first stress response is retained for some time after stress relief, and Pol-II is stalled at the initiation complex. This formation then facilitates transcript elongation when the stress re-occurs, leading to hyper-induction of the genes. The physiological effect is improved water retention during the subsequent stress events. The factors that determine whether a particular stress-induced gene has a transcriptional memory or not remain to be further characterised. For details and references see main text.

ChIP-seq experiments showed that H3K9Ac was enriched in genic regions compared to intergenic regions, but the relative enrichment was significantly decreased after cold treatment. In particular, cold stress led to an increase of H3K9 acetylation and activation of tandem repeats [122]. Whether H3K9 acetylation is indeed the direct cause for the release of silencing, or reflects other changes within the heterochromatin, is not clear.

In rice, *DREB1* is also cold-induced. ChIP analysis revealed an increase of H3K9 acetylation at the promoter and at upstream regions (up to 600 bp from the TSS site) of *OsDREB1* upon cold treatment [123]. Furthermore, different regions within the *OsDREB1* promoter showed changes that were specific for a particular mark. For example, an increase of H3K14 acetylation was associated with the TATA box, whereas a region further upstream showed hyperacetylation of H3K27. The authors suggested that increased acetylation of histone residues of *DREB1* regulatory regions after cold treatment may underlie the cold induction of this gene, and that deacetylation may be required to maintain the gene in an off-state at higher temperatures. The findings in maize and rice still need to be reconciled, and further experimentation in both species is needed to underpin causal relationships between cold stimulus, chromatin changes and transcriptional responses.

2.4. Histone methylation marks and transcriptional regulation under abiotic stress

Methylation of histone tails takes place not only at different amino acids (lysine and arginine), but also at different atoms resulting in the addition of one, two or three methyl groups (mono-, di- or trimethylation). Methylation marks are established by histone methyltransferases and can be dynamically removed by demethylases, which are specific for a particular lysine or arginine residue [67,124,125]. Histone methylation in plants is associated with active or repressed genes depending on the particular mark. H3K4me3, H3K9me3 and H3K36me3 correlate with active transcription [59,126], while genes associated with H3K27me3 have often low transcript levels [127]. H3K9me2 and H3K27me1 are features of silent transposons and other repeats, showing interplay with methylated DNA [59,128]. H3K4me3 is the most studied methylation mark in abiotic stress conditions. Studies that have investigated a potential link between histone methylation and gene expression under abiotic stress are listed in Table 1 and reviewed in the following sections.

2.4.1 Genome-wide comparison of transcript and H3K4me3 levels under drought

A genome-wide study of mono-, di- and trimethylation of H3K4 in *Arabidopsis* plants exposed to soil dehydration found that H3K4me3 displayed the most significant changes, and that the differences positively correlated with differences of transcript levels when genes were grouped according to their expression levels [129]. Changes of H3K4me3 were steeper for genes showing the largest expression changes, and dehydration-induced genes showed a broader distribution of the mark over the gene body. In contrast, a genome-wide study in rice [130] found that only 13% of the genes that showed changes of H3K4me3 upon drought were also differentially expressed. Strikingly, while the mark increased genome-wide, most genes undergoing a change of both transcript and H3K4me3 levels showed down-regulation and a decrease of the mark. These genes had high expression levels in control conditions and were mainly involved in photosynthesis and glycolysis. The genes that showed an increase of H3K4me3 and transcriptional up-regulation under drought had low expression levels in control conditions, and were mostly involved in terpenoid biosynthesis. In both studies the drought stress imposed was moderate and changes were assessed several days after stress-onset. Therefore the observed changes describe differences between two steady states rather than initial stress responses, and it is difficult to separate causal from symptomatic differences.

2.4.2. H3K4me3 in individual genes; stress training and memory

Besides the genome-wide analyses, several studies focused on the response of H3K4 methylation to abiotic stress in a particular group of genes. For example, increased transcript levels of *RD29A*/*B* as well as *NCED3* (which encodes the enzyme catalysing the limiting step of ABA biosynthesis) upon soil dehydration were found to be accompanied by an increase of H3K4me3 [131]. Both the histone modification and the transcriptional changes were abolished or diminished in *atx1* mutant, defective in the methyltransferase ATX1, indicating a causal relationship between histone methylation and the change of gene expression. However, plants were analysed after 12 days of dehydration and therefore will have undergone adaptive changes in growth, development and metabolism that may be reflected in the observed profiles. Indeed, both wildtype and *atx1* mutants showed visible symptoms after 9 days of stress already. The symptoms were more pronounced in the mutant, since it had more open stomata than the wildtype (both in control and under drought stress).

More rapid changes of H3K4me3 and gene expression were tested in *Arabidopsis* seedlings exposed to repetitive 24-hour cycles, including 2 h of air-dehydration and 22 h of recovery under normal humidity [132]. Depending on their response pattern genes were grouped into 'non-trainable' genes (*RD29A* and *COR15A*) and 'trainable' genes (*RD29B* and *RAB18*). The former showed a similar up-regulation after each stress treatment whereas the latter showed increased up-regulation upon repeated stress. For both gene groups transcript levels returned to control levels during each recovery period, but the dynamics of H3K4me3 differed. In the non-trainable genes H3K4me3 was enriched to a similar degree upon each stress treatment and returned to control levels during recovery. In contrast, in 'trainable' genes the increase of H3K4me3 was stronger in repeated stress treatments, and the mark was retained during recovery, together with stalled Pol-II. H3K4me3 therefore behaved as a 'memory' mark that influenced gene expression during a subsequent stress exposure. Importantly, *RD29B* and *RAB18* were still trainable in *atx1* mutants, but transcript levels were much lower than in wildtype plants. H3K4me3 levels still increased after each stress treatment in *atx1*, but to a lower extent than in wildtype. Similarly, a triple knockout of key ABA-regulated transcription factors (ABREs) reduced transcriptional induction after stress treatments, but the trainable genes were still super-induced in this mutant. Thus, the transcriptional memory relied on additional factors other than ABA, ABREs or ATX1. As summarised in Fig. 5B, the experiments suggest a model, in which H3K4 trimethylation is an inherent part of transcription of stress-induced genes. In some genes, part of the transcriptional machinery and the chromatin mark can be retained for a limited period after the stress is relieved, and subsequently facilitate transcription when the stress re-occurs, leading to improved water retention in the leaves. The factors that determine whether a particular stress-induced gene has a transcriptional memory or not remain to be further characterised.

In two gain-of-function mutants of JMJ15, a H3K4 demethylase, most of the genes that were differentially expressed compared to the wild type in control conditions were downregulated. Down-regulated genes in the *jmj15* mutants corresponded to genes that had an enrichment in the H3K4me2/3 double mark in a WT dataset, in agreement with the expected correlation between the removal of the H3K4me3 'active' mark and gene repression. Down-regulated genes in the *jmj15* mutants were mainly stress-related genes [133]. However, selected stress-responsive genes (*RD29A*, *RD29B*, *RD22*, *COR15A*, *COR47*, *P5CS1* and *P5CS2*) were up-regulated after salt treatment to a higher extent in the mutants compared to the wild type, suggesting that these genes might not be direct targets of the JMJ15 demethylases. Unfortunately, the levels of H3K4 methylation marks on these genes were not

measured to ascertain their relationship with gene expression in stress conditions.

2.4.3. Role of H3K27me3 in abiotic stress responses

H3K27me3 is best known for its role in the progressive repression of Flowering Locus C (*FLC*) during vernalization [134,135]. Its relationship with gene expression under abiotic stress is less clear. A short priming treatment with moderate salt caused genome-wide changes of H3K27me3 alongside other histone marks in *Arabidopsis* roots [65]. A decrease of H3K27me3, specifically at island edges ('etching'), was found to be the most notable response to the priming treatment. For some genes, changes of H3K27me3 were accompanied by transcriptional changes during the first hours of the priming treatment, but outlasted the transient transcriptional responses for 10 days after recovery in control conditions. Furthermore, a few genes carrying a long-lasting decrease (*HKT1*, *PIP2E*) or increase (*GH3.1*, *GH3.3*) of H3K27me3 in primed plants showed enhanced or attenuated up-regulation, respectively, in response to a second, stronger salt treatment. However, a genome-wide analysis of the relationship between changes of histone marks and gene expression in individual genes revealed a lack of correlation [65]. Most genes undergoing changes either in H3K4me3 or H3K27me3 were not differentially expressed after the priming treatment, and only 50% of genes with overlapping changes in a histone mark and gene expression followed the expected correlation. However, when genes were ranked according to their expression levels and averaged over 200-gene shifting windows, the expected correlations between gene expression and the levels of each histone mark were found both for primed and for non-primed plants. A more detailed time-course analysis of several genes over the first 24 h after the priming treatment showed that the kinetic profiles of transcript levels and H3K27me3 were very variable. This might explain the weak correlations when considering only one time point after a stress stimulus.

Other studies monitoring H3K27me3 and transcript levels under abiotic stress have concentrated on individual genes. *FLC* was the target of a heat stress study [125]. H3K27me3 decreased over the gene body while *FLC* expression increased in plants grown at 29 °C compared to plants grown at 22 °C, resulting in early flowering. A causal relationship between the histone mark and the regulation of *FLC* gene expression upon heat was derived from the analysis of a double mutant defective in JMJ30 and JMJ32, two demethylases responsible for the removal of the mark. In the *jmj30 jmj32* mutant, H3K27me3 failed to decrease to wildtype levels and *FLC* was no longer up-regulated when the plants were exposed to high temperature [125]. H3K27me3 levels also decreased upon cold exposure along the promoter and gene body of two cold-induced genes, *COR15A* and *ATGOLS3* [136]. The transcript levels of these genes returned quickly back to control levels in control temperature after cold stress, indicating that altered H3K27me3 did not influence transcript de-repression upon stress release. By contrast, decreased levels of the histone mark were maintained for up to 3 days, supporting a potential stress-memory function of H3K27me3 de-methylation [65]. However, in this study, the transcriptional responses were not altered when cold stress was repeated.

2.5. Combinations and relative dynamics of histone acetylation and methylation marks

The relationship between gene expression and a combination of different histone marks under abiotic stress has been addressed for individual stress-inducible genes. In most occasions, several 'activating' marks converging in the same locus were analysed, such as H3K4me3 in combination with H3K9ac.

H3K4me3, H3K4me2, H3K9me2 and H3K9/K14ac were analysed in *OsADH1* and *OsPDC1* after submergence of rice [137]. Up-regulation of these genes was accompanied by a decrease of di-methylation and an increase of tri-methylation of H3K4, as well as an increase of H3K9/K14 acetylation. All histone marks returned to their initial levels after 48 h of recovery. Treatment with the histone deacetylase inhibitor TSA increased both, H3K9/K14ac and transcript levels, but whether TSA also altered the histone methylation marks was not investigated.

A progressive enrichment of H3K4me3, H3K9ac, H3K23ac and H3K27ac in the coding regions of *RD20*, *RAP2.4* and *RD29B* was monitored over 5 h of dehydration, correlating with an up-regulation of the transcripts [99]. Interestingly, RNA Pol-II accumulation occurred before the increase of H3K4me3. This suggested a role for this histone mark in transcript elongation rather than initiation, which was subsequently proven [138,139]. The kinetics of H3K4me3 and H3K9ac during rehydration were analysed using the same experimental setup [100]. A decrease of transcript levels correlated with the removal of the histone marks in the drought-inducible genes *RD20*, *RD29A* and *AtGOLS2*. Yet, the dynamics of H3K4me3 and H3K9ac removal were different. While H3K4me3 decreased in a progressive manner over 5 h of recovery and at a similar pace as transcriptional repression of the genes, H3K9ac levels were already decreased after 1 h.

The dynamics of H3K4me3, H3K4me2 and H3K9ac during stress recovery have also been studied for heat stress [140]. In selected genes (e.g. *APX2*, *HSP22.0*) acclimation to heat stress was found to be accompanied by an increase of H3K9ac and H3K4me3, followed by a late increase in H3K4me2. During a recovery period of 52 h H3K9ac decreased again whereas high levels of H3K4me3 and H3K4me2 were sustained. Since *APX2* and *HSP22.0* gene expression was over-induced during a second heat stress treatment, H3K4me3 (and H3K4me2) fulfilled the criteria of 'memory' mark (Fig. 5B) [140]. Interestingly, binding of the transcription factor HSFA2 to the memory loci was required for both, maintenance of the marks and transcriptional hyper-induction. The combined evidence indicates that histone de-/acetylation is very fast, whereas histone de-/methylation is a slower process and methylation marks can outlast transcriptional responses, thereby potentially harbouring a short-term memory of experienced stress.

2.6 Histone marks at the cross road between biotic and abiotic stress

An enrichment of H3K4me3, H3K4me2 and H3K9/14ac was observed at the promoter and the first exon of several pattern-triggered immunity genes (*WRKY53*, *FRK1* and *NHL10*) when plants were repetitively primed with different mild abiotic stress treatments (i.e. heat, cold or salt) [141]. Increased acetylation levels were maintained up to 5 days after the last stress. Interestingly, transcription of these genes was only up-regulated upon pathogen attack (*Pseudomonas syringae*), but to a higher extent if plants had previously experienced the repetitive abiotic stress. The histone acetyltransferase mutant *hac1* failed to show increased H3K9/K14ac and H3K4me2/3 levels upon repetitive abiotic (heat) stress and pathogen-induced transcription. The observations indicated a requirement of histone acetylation for transcriptional activation, and an interdependency of different histone modifications. Importantly, the study demonstrated that crosstalk between abiotic and biotic stress signals involves the chromatin level. It showed that an abiotic stress signal can alter histone marks even if the respective genes are not responsive to this type of stress, and that such changes may subsequently alter the transcriptional response to a biotic stress signal.

3. Conclusions

3.1. Abiotic stress alters histone marks

The evidence collected so far leaves no doubt that changes of chromatin features, particularly histone modifications, occur after abiotic stress treatments, and that many of these changes are associated with genes that are transcriptionally regulated by the stress. However, at this stage most studies have focussed on a few known stress-induced genes. To assess whether changes of histone modifications during stress are indeed geared towards stress-regulated genes, more genome-wide

analyses are needed, particularly for early time points after stress onset. The evidence to date suggests that transcriptional responses to stress can occur without accompanying changes in histone modifications, although it could be argued that not all possible modifications have been tested. Conversely, there are also many genes that display altered histone modifications after stress treatment without showing a change in transcription, although it could be argued that fast transient responses of transcripts may have been missed. Either way, most measurements of chromatin modifications and transcripts after stress have not delivered sufficient information to draw firm conclusions about causal relationships between stress signal, chromatin modifications and transcriptional response. To obtain a better understanding it will be important in the future to move away from monitoring any stress-responsive genes, and instead focus on genes that have a proven function as early and essential hubs in the signalling network.

3.2. Histone modifying enzymes participate in transcription

The knowledge obtained through genetics is also limited. Experiments with mutants have clearly shown that histone modifying enzymes are required for abiotic stress responses, both at transcriptional and at phenotypic level, but these findings do not necessarily imply that the enzymes are the primary targets of the stress signalling pathway or that histone modifications cause the phenotype. Transcriptional regulation of HDAs as observed in some crop species is intriguing and provides a possible point of entry for the stress signal; however, this link still needs to be further explored. Most histone modifying enzymes contain several protein-binding motifs and have important functions in protein recruitment in addition to their catalytic functions. For example, it was shown that a catalytically-defective mutant version of the histone methyl transferase ATX1 was still sufficient (and necessary) for establishment of the Pol-II recruiting pre-initiation complex at gene promoters, suggesting that initiation of transcription does not require H3K4me3 [138]. However, catalytic function of ATX1 (and hence trimethylation of H3K4) was required for Pol-II progression and transcript elongation. If we extend this model to stress responses (Fig. 5B), it is plausible that the binding of a stress-induced transcription factor to the promoter of the stress-inducible gene does not require a change of histone modification, but that subsequent active transcription involves a change of histone modification. This model is a hybrid between scenarios 2 and 3 in Fig. 2. Similarly, it is likely that DNA-binding repressive transcription factors are the direct targets of stress-signaling pathways, and subsequently exert inhibition of transcription by recruiting histone-deacetylases through interaction with co-repressors (Fig. 5A). Removal of acetyl groups from histones could then tighten histone-DNA interaction and prevent Pol-II progression along the gene. However, this model still requires experimental proof, the main limitation currently being the lack of knowledge on individual repressor/co-repressor modules.

3.3. Histone modifying complexes integrate transcription factor binding with histone reading

While stress effects upon the transcriptional activity are likely to be initiated by transcription factors, recognition of the pre-existing chromatin status is likely to be an integral part of the histone-modifying complexes since they often contain modification-specific histone-binding proteins ('readers'). Thus, multi-protein complexes assembled around histone-modifying enzymes establish a double-lock with a given chromatin region. On the one hand, the complex will bind to the target DNA through co-activator/repressor proteins if a compatible transcription factor is present. On the other hand, the complex will interact with the histones in this region if their modifications are compatible with the histone binding protein in the complex. Once this double lock has been established, further alterations of the histones can occur and participate in the activation or inhibition of the gene. Transcriptional stress responses would then be conditional not only on stress-activated transcription factors but also on pre-existing histone marks. To test this model, the exact composition of native complexes in different tissues and stress situations needs to be resolved. Recent successful pull-down of a native complex containing HDA19 [110] and the H3-binding protein MSI1 [111] is encouraging. Subsets of histone-binding proteins, histone-modifying enzymes and transcription factors are likely to differ for different genes and to dynamically reassemble in response to different stress signals. We therefore need informative tagged lines and good biochemical tools to monitor such rearrangement. The same applies to chromatin remodelling complexes [77,78].

3.4. Histone reading could explain cell type-specific responses, transient responses and priming effects.

If the input from histone modifications in scenario (1) was determined by the developmental program of a given cell-line this could explain cell-specific transcriptional responses to abiotic stress [9,142]. Cell-type specific changes of histone modifications under stress have yet to be addressed experimentally. New collections of *Arabidopsis* lines with cell-type specific nuclear envelope-tags [143] provide excellent opportunities for comparing stress-induced changes of histone-modifications and gene transcription between different cell types. Integrated histone-reading function of histone modifying complexes also provides a possible basis for feedback within the transcriptional stress response (dotted line in scenario 3), as exemplified for ATX1 above [138,139]. Negative feedback could be exerted if an activating transcription factor recruits a histone deacetylation complex, which represses the initial response leading to a transient response. Mechanistic proof of this situation is still elusive, but there is evidence that HDA complexes contain histone-binding proteins that recognize active marks such as H3K4me3, and some of them participate in both HDA and PcG complexes [66,110,111]. Finally, long-lasting changes of histone marks generated during initial stress exposure generate a potential molecular memory that could underpin stress priming and acclimation. In this case the input from histone modifications in scenario (1) is the output from altered histone modifications in scenario (3) or (4). The evidence to date suggests that changes in acetylation marks are short-lived and do not outlast transcript changes [100] [140], while changes of H3K4 methylation can be maintained for a few days [132] [140], and changes of H3K27me3 can outlast transcriptional changes for at least 10 days after stress relief [65]. Histone methylation therefore provides a possible means for a stress memory. While there is good evidence that H3K4me3 is indeed involved in enhancement of transcriptional responses over repeated dehydration treatments in 24-h cycles [132] (Fig. 5B), a mechanistic link between priming-induced changes of H3K27me3 and altered transcriptional profiles upon stress re-occurrence after longer recovery periods still awaits proof [65].

3.5. Independently generated histone marks could provide a basis for cross-priming

An interesting deviation from priming through repeated exposure to the same stress is cross priming. It has been reported that one type of stress (e.g. abiotic) can lead a change of histone modification without a change in gene transcription, which subsequently causes super-induction of the gene by another type of stress (e.g. biotic [141]). This implied that the response-modifying histone modification in scenario 1 could be the result of a direct effect of the first stress on histone modifications (upper arm of scenario 4). To strengthen this hypothesis, it still needs to be confirmed that the apparent lack of transcriptional response to the initial stress was not due to insufficient resolution (e.g. missing transient fast responses) or to secondary repression.

3.6. Chromatin remodelling complexes are direct targets of stress-signals

Although there is little evidence for scenario 2 as far as histone modifications are concerned, other components of the chromatin-modifying machinery have been identified as direct targets of stress-signaling pathways (Fig. 3B). For example, the BRAHMA ATPase entity of a SWI/SNF chromatin-remodelling complex physically interacts with, and is directly regulated by early components of the ABA-signalling pathway [82]. Interestingly, mutants defective in BRAHMA or other components of the chromatin re-modelling complex, display ABA-hypersensitivity of post-germination growth, a phenotype shared with histone deacetylation mutants [79]. A potential mechanistic link between histone de-/acetylation and chromatin remodelling should therefore be investigated in the future.

3.7. Open questions

Many open questions remain to be solved before we can mechanistically embed transcriptional stress responses in the chromatin context. Some of these are listed here:

- Time resolution: What are the exact kinetics of changes in histone modifications and transcripts immediately after stress signal perception?
- Nucleotide resolution: Does the correlation between chromatin and transcript levels become more predictive if the exact location of the mark at the DNA is taken into account?
- Cell-type specific responses: Is there a tighter relationship between histone modifications and transcript changes if they are measured in individual cell types? Does the cell type determine transcriptional regulation through its specific chromatin status?
- Specificity of protein interactions: Which transcription factors interact with which co-activators or co-repressors in a given stress situation and cell-type?
- What is the exact composition of native chromatin modifying complexes in different tissues, developmental stages and stress situations? How do complexes assemble and dis-assemble?
- Which steps of transcriptional regulation during stress rely on protein recruitment alone, and which rely on alteration of histone marks?
- Is there cross-talk between histone modifying enzymes with each other and with silencing pathways under stress?
- How exactly are histone-modifying enzymes linked to the upstream stress-signalling pathways; directly, through transcriptional regulators, or both?

3.8. Future prospects

Understanding the causal relationship between environmental stress, chromatin status and transcriptional responses is essential if we want to 'genetically' or 'epigenetically' engineer crop varieties for improved stress tolerance. Because chromatin processes rely on a plethora of protein interactions as well as catalytic functions, genome editing techniques provide exciting new prospects to manipulate individual functionalities of this regulatory context. We are only just starting to get a handle on the dynamic properties of chromatin. The question how chromatin modifying processes are connected with transcriptional stress responses and integrated into signalling networks, has led us into an exciting new direction of research; environmental epigenetics. The open questions outlined here need to be solved urgently and demand a move from purely descriptive monitoring of changes towards hypothesis-driven mechanistic studies. Cutting-edge molecular biology approaches to monitor cell-type specific chromatin processes or to modify specific functional motifs within proteins, will need to be combined with traditional biochemical approaches to characterise the composition and precise catalytic properties of chromatin modifying complexes. The latter is the more painstaking side of chromatin research, but it is unlikely that real progress can be made unless we have quantitative data on the relative rate constants of the individual biochemical reactions that generate and modify the epigenetic code. The long-term goal is the generation of predictive network models that are able to bring together the molecular and the biochemical aspects of transcriptional regulation in plants that experience environmental stress. Achieving this level of understanding would bring about a gearshift in crop improvement strategies.

Transparency document

The Transparency document associated with this article can be found in the online version.

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