CHAPTER 16

Molecular mechanisms regulating priming and stress memory

Aybars Koç[a], Dimitrije Markovic[b,c], Velemir Ninkovic[d], German Martinez[a]
[a]Department of Plant Biology, Uppsala BioCenter, Swedish University of Agricultural Sciences and Linnean Center for Plant Biology, Uppsala, Sweden
[b]Department of Crop Production Ecology, Swedish University of Agricultural Sciences, Uppsala, Sweden
[c]University of Banja Luka, Faculty of Agriculture, Banja Luka, Bosnia and Herzegovina
[d]Department of Ecology, Swedish University of Agricultural Sciences, Uppsala, Sweden

16.1 Introduction

During their life cycle, plants constantly monitor environmental signals and tailor their developmental program to continuously adapt to them. Most environments are dynamic and consist of many variables that can be predictable or fluctuate. Eventually, plants experience environmental conditions that surpass their genetic program. These situations are defined as stress, which can be transient or persistent. Transient stresses can vary in their severity and only persistent stresses are predictable, opening a window for plant adaptation over subsequent generations. Plants exposed to stress can reprogram their development allowing the distribution of resources to activate specific adaption responses. This re-distribution of resources affects tremendously the development of the plant and, in the field, it is translated into yield losses that threaten agricultural production.

Exposure of plants to a mild stress condition enhances the acclimation to a subsequent exposure to the stress through the acquisition of memory. This phenomenon, known as priming, serves as a stress memory, which can persist even to future generations. This memory of priming is not a common response to stress and is poorly characterized and understood. Nevertheless, the involvement of several regulatory pathways as RNA decay and, especially, epigenetics is well accepted.

In this review, we will focus on the known molecular and mechanistic aspects that regulate the priming response. We will also review their potential regulation during stress. Furthermore, we will review the known examples of transgenerational epigenetic inheritance in plants and discuss the mechanistic knowledge about its transmission that could mediate transgenerational priming and epigenetic memory.

16.2 Mechanisms regulating priming and stress memory

As exposed above, priming of stress response is defined as an enhanced response to a stress by a plant that has been previously exposed to a mild or temporary type of the acute

Priming-Mediated Stress and Cross-Stress Tolerance in Crop Plants
https://doi.org/10.1016/B978-0-12-817892-8.00016-7

stress.[1] Importantly, the primed state does not affect the individual at the phenotypical level and neither induces changes in the DNA sequence. This points to a stress memory that might involve the conservation of the response to stress by transcriptional, translational, or epigenetic means. The stress memory has a duration that varies from days to weeks but that could also be transmitted transgenerationally.

Changes in the transcriptional response have been associated with the memory of stress. These responses involve the activation or repression of transcripts, transcriptional feedback loops, or paused RNA polymerase II (Pol II) induced by the initial mild stress.[2–4] Examples of this type of regulation exist in yeast, where the interaction of the nuclear pore protein complex with the INO1 gene leads to an altered chromatin structure and binding of a preinitiation form of RNA Polymerase II to its promoter that bypasses the need of new transcription rounds.[3] In Arabidopsis, priming with benzo(1,2,3)thiadiazole-7-carbothioic acid *S*-methyl ester (termed benzothiadiazole) induces the accumulation inactive proteins and transcripts from the mitogen-activated protein kinase 3 (MPK3) and MPK6 genes,[5] an example that will be explained in detail below.

Together with changes at the transcriptional level, changes in the conformation or accumulation defense proteins induced by the initial stress have also been associated with stress memory.[6–9] For example, as anticipated above, priming Arabidopsis with benzothiadiazole induces the accumulation of inactive proteins and transcripts from the MPK3 and MPK6 genes.[5] Infection of primed plants with *Pseudomonas syringae* pv. tomato strain DC3000 induced the activation of more MPK3 and MPK6 proteins than in unprimed plants. Furthermore, priming with benzothiadiazole increases the level of the leucine-rich repeat receptor kinase (LRR-RK) FLS2, which is involved in the recognition of the bacterial microbe-associated molecular patterns flagellin epitope flg22.[10] The recognition of flg22 by FLS2 increases an MPK signaling pathway that includes MPK3/6, which indicates how these two reports might be influencing the same pathway. This also sheds light into the broad-spectrum conferred by priming.[11]

Simultaneously with these two mechanisms, epigenetic regulation of priming has been proposed as a general pathway that might control the accessibility of defense-related genes for enhanced transcription after priming.[1,12] Indeed, an epigenetic control of priming will explain its transgenerational component. In the next sections of this chapter we will focus in explaining the known examples of interaction between stress and epigenetic regulation, how these mechanisms might control priming, and the transgenerational stress memory.

16.3 Interplay between epigenetics and the stress response

16.3.1 Epigenetic machinery in plants: DNA methylation, histone modifications, and their interplay

Developmental processes in plants (as the stress response) rely on a wide range of genetic reprogramming, which is managed by different transcriptional regulatory mechanisms.

One of those mechanisms is the epigenetic regulation of transcription. As in most eukaryotes, in plants two main players mediate epigenetic regulation: DNA methylation and histone modifications (Fig. 16.1). These marks have an ample presence on transposons and other repetitive genes[13] and can eventually influence gene expression. The first of these two epigenetic marks, DNA methylation, involves the covalent modification of the residue cytosine of the DNA by the addition of a methyl group. In plants, three different modes of methylation can be encountered: symmetrical CG and CHG (H represents A, T, or C nucleotides) and asymmetrical CHH patterns.[13] In *Arabidopsis thaliana* the global representation in the genome of each of these contexts of methylation are: 24% CG methylation, 6.7% CHG methylation, and 1.7% CHH methylation.[14] These marks are heavily concentrated on TEs, where their values increase drastically to more than 80% CG, 20%–60% CHG, and up to 20% CHH methylation.[15] The location of this epigenetic mark shows differences between plants but, as a general rule, in plants with smaller genomes like Arabidopsis, these marks are found in pericentromic regions, whereas in plants with larger genomes, like maize, these marks are located throughout the chromosome arms.[15]

Mechanistically, incorporation of cytosine methylation is mediated through the action of small RNAs (sRNAs) in a pathway referred to as RNA-directed DNA methylation (RdDM).[16] There are alternate versions of this pathway, but the canonical version begins when the heterochromatic regions of the genome gets transcribed by the RNA polymerase IV (Pol IV), which as a results synthesizes short single-stranded RNAs (ssRNAs) that are around 40 nucleotides in length. These ssRNAs are then converted into double stranded RNA through the action of RNA DIRECTED RNA POLYMERASE 2 (RDR2), which are then cleaved by DICER-LIKE 3 (DCL3)[13] to produce 24-nucleotide sRNAs and exported to the cytoplasm.[17] There, they are loaded into ARGONAUTE (AGO) proteins, primarily AGO4 but possibly AGO6 or AGO9,[16,17] which re-import them to the nucleus. There, these complexes regulate the targeting of newly formed transcripts of Pol V[17] by recruiting DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2), which methylates cytosine residues in every possible pattern (CG, CHG, and CHH) in the targeted area[17] (Fig. 16.1A). In the alternative pathway of RdDM, which is referred to as RDR6-RdDM, Pol II transcription and RDR6 amplification are used in order to produce a long double stranded RNA that is cleaved by DCL4 to produce sRNAs that are 21/22 nucleotides long. These sRNAs are then loaded into AGO6 to mediate cytosine methylation of the TEs through initiation of active transcription.[18] There is also a third variation of RdDM pathway that was revealed to use RDR6 and DCL3 to silence the newly formed copies of the retrotransposon *Evadé*.[19]

Once cytosine methylation is established, a number of regulators act in order to maintain DNA methylation during replication. In plants, several DNA methyltransferases are known to maintain this for every pattern of methylation.[15] METHYLTRANSFERASE 1 (MET1), maintains CG methylation in plants through recognition of hemi-methylated

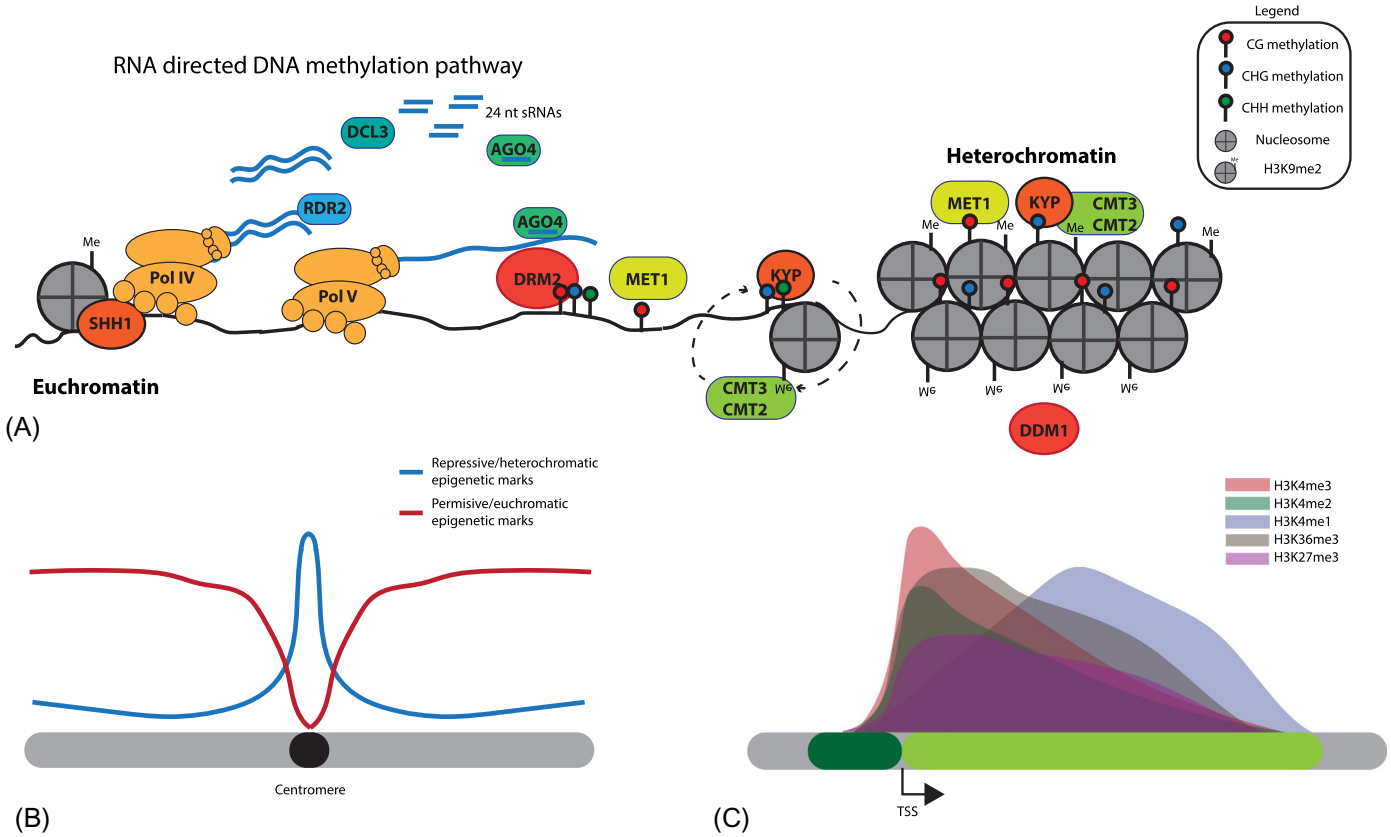

Fig. 16.1 The epigenetic machinery in plants. (A) Establishment and maintenance of heterochromatin. RNA polymerase IV produces a transcript processed by RDR2 and DCL3 that produces 24 nts sRNAs that are loaded in AGO4. The sRNA-AGO4 complex interacts with a transcript produced by the RNA polymerase V, which brings DRM2 and introduces DNA methylation. DNA methylation is then maintained by MET1 in the CG context and by CMT3 and CMT2 in the CHG and CHH contexts, respectively. CHG methylation attracts KYP, which induces the methylation of H3K9. Heterochromatic regions are then maintained by DDM1, which allows the accessibility of methyltransferases to the heterochromatic DNA. (B) Representation of the genome-wide distribution of repressive/heterochromatic (H3K9me2) and active/euchromatic histone marks (H3K4me1/2/3, H3K36me3, but also the repressive histone mark H3K27me3) in a linear representation of a chromosome. Centromeric region is marked in *black*. (C) Depiction of the distribution of different histone marks in genic regions showing their enrichment in the 5′UTR or the gene body.

CG sites after DNA replication, which results in the methylation of the daughter strand.[16] Additionally, two chromomethylases (CMTs), CMT2 and CMT3, can bind to the histone mark dimethylation of the lysine 9 of histone 3 (H3K9me2) to maintain CHG methylation,[20] while the maintenance of CHH methylation relies on DRM2 through the action of the RdDM pathway. In addition, maintenance by CMT2 depends on DECREASE IN METHYLATION (DDM1), a chromatin remodeler that facilitates the interaction between CMT2 and its target, H1-containing heterochromatin. In addition, DRD1, a part of the RdDM pathway, is also required for the maintenance of CHH methylation in short TEs and the terminal regions of long TEs.[15,16] It must be noted that DNA methylation can be a reversible process and can be erased by DNA demethylation. This process can occur either passively, from an absence of DNA methyltransferase activity, or an absence of a methyl donor, as well as actively, through an enzymatic activity to remove the methyl group. In Arabidopsis, four DNA glycolases that function for this purpose can be found: REPRESSOR OF SILENCING (ROS1), TRANSCRIPTIONAL ACTIVATOR DEMETER (DME), DEMETER-LIKE (DML2), and DML3.[16]

Together with DNA methylation, histone marks are relatively well known and their effects have been studied in detail in plants. Histone proteins H2A, H2B, H3, and H4 are integral parts of the nucleosome, the fundamental subunit of chromatin.[21] The tails on the N-termini of these histones are exposed to many covalent modifications, such as methylation, acetylation, phosphorylation, ubiquitination ADP-ribosylation, biotinylation, and sumoylation.[22] These modifications can regulate various attributes of the nucleosome such as its density or receptiveness to transcription machinery[21] (Fig. 16.1B). One of the best-studied modifications is methylation, which is incorporated through the activity of histone lysine methyltransferases (HKMTs).[22] In Arabidopsis, histone methylation occurs primarily (around 75%) on lysine 4 of histone H3 (H3K4) and lysine 36 of histone H3 (H3K36), which are correlated with active genes,[23] as well as lysine 9 of histone H3 (H3K9) and lysine 27 of histone H3 (H3K27), which are correlated with silenced regions.[24,25] In general, H3K9me1 and H3K9me2 are found in chromocenters, while H3K9me2 is mostly present in TEs and repetitive sequences.[26] H3K9me3, on the other hand, can be found in euchromatin.[27] A summary of the distribution of histone marks over genic regions is shown in Fig. 16.1C.

Some histone modifications can function in a combinatorial way to institute additional chromatin states for gene expression regulation.[28] However, an analysis made on 12 different marks in Arabidopsis, which impacts about 90% of its genome, has revealed that the combinatorial activity of histone marks are only limited to a small number of combinations.[28] It must be noted also that, like DNA methylation, modifications of histone proteins are reversible, such as via the hydroxylation activity of Jumonji C (JmjC) containing proteins and amine oxidation activity of lysine-specific demethylase1 (LSD1) histone demethylase families.[22,29]

Both DNA methylation and histone modification are involved in gene repression during plant development. The dependence of these pathways on one another and how this crosstalk is mediated by biochemical interactions between histone methyltransferases and DNA methylases have been extensively studied.[30] The first identified H3K9 methyltransferase in plants was KRYPTONITE (KYP),[31] also known as SU(VAR)3-9 homolog 4 (SUVH4).[32] Similar to SUVH6, KYP carries out H3K9 methylation to nearby histones through its SET domain.[31] This is executed after the proteins are recruited to target methylated CHG, which they bind through their N-terminal YDG/SRA domains.[22] SUVH2, that binds primarily to methylated CG, and SUVH9, that mainly binds to methylated CHH, have been revealed to be required for RdDM.[33] In addition, these epigenetic marks have been shown to act in a reinforcing loop model, as removal of H3K9 methylation results in loss of non-CG methylation and vice-versa.[34] It was also revealed that both of these distinct epigenetic marks can be the initial epigenetic event that begins the gene silencing process.[35] In summary, this loop model is required to maintain heterochromatin by regulating the silencing of TEs during most stages of plant development.[36]

16.3.2 Epigenetic modifications induced by stress

Several stresses (both biotic and abiotic) are known to interfere with the epigenetic regulation of the genome both at the DNA methylation and chromatin levels.[37] Viruses and viroids are, so far, the only known examples of stresses that can interact directly with the components of the epigenetic pathways. For example, geminiviruses produce silencing suppressor proteins that directly interfere with the host genome DNA methylation and also reduce the expression of MET1 and CMT3, which explains the known reactivation of TEs during their infection.[38,39] Also, RNA viruses like Cucumber mosaic virus produce a viral silencing suppressor that sequesters the sRNAs produced by the RdDM pathway, which consequently affects the level of methylation of its target genes.[40] Viroids are also know to interact directly with a histone deacetylase, HDA6, in order to hijack the DNA methylation machinery.[41] Other pathogens are also known to decrease the levels of DNA methylation. For example, *P. syringae* pv. *tomato* strain DC3000 (*Pst* DC3000) induces demethylation at genomic repeats,[42] which might be responsible of the transcriptional reactivation of a defense gene located physically close to a TE.[43] Indeed, components of the RdDM pathway have an enhanced defense response to *Pst* DC3000[42–46] but also to other pathogens like *Hyaloperonospora arabidopsis* isolate WACO9,[47] *Agrobacterium tumefaciens*,[48] or *Fusarium oxysporum*.[49] On the other hand, resistance against necrotrophic fungi is reduced in RdDM mutants.[45] Together with biotic stresses, abiotic stresses like drought, salinity, low humidity, or heat are known to reduce the levels of DNA methylation and activate the expression of TEs.[50–53] In general, for almost all the stresses studied to date, the general response to stress involves a decrease of DNA methylation.

Together with DNA methylation, reprogramming the histone landscape is another common response to stress. Stresses like heat, *Pst* DC3000, or viroid infection are known to alter the organization of the chromocenters of somatic or reproductive cells,[46,54–57] which might visually represent broader changes in the histone composition of the nucleosome.[58] Certainly, histone acetylation, histone methylation, and histone ubiquitination play a role in the regulation of the stress response. Histone deacetylases (HDAC) and histone acetyltransferases (HAT) have a complex regulation of plant defense and stress responses. For example, HDAC mediated by HDA19, HDA6, and SRT2 activity negatively regulate the defense response against *Alternaria brassicicola* and/or *Pst* DC3000.[59–61] Interestingly HDAC activity mediated by HDA19 mediates the removal of the H3 and H4 acetylation marks present in several defense genes.[60,62] Another HDAC, the MAPK-activated HD2B, positively regulates immunity (in contrast with the previous examples). During stress, HD2B is phosphorylated by MPK3 and transported from the nucleolus to the nucleus, where it removes H3K9Ac from the promoters of several defense genes, fine-tuning their expression.[63] HATs, like the Arabidopsis HAC1, are crucial for the switch of histone marks needed for the transcriptional activation of several loci.[64] Drought and salinity stresses also induce H3K9Ac of several drought and salinity-related genes and is reduced during rehydration,[65] in an HAD6 mutant[66] or an HDA9 mutant,[67] respectively.

Analogous to acetylation, histone methylation also plays an important role in the regulation of plant defense through two families of enzymes with opposite functions: histone methyltransferases (HMTs) and histone demethylases (HDMs), which can regulate positively or negatively stress response. The Arabidopsis H3K9me1/2 demethylase JMJ27, H3K4 methyltransferase ATX1, H3K36me2/3 methyltransferase SDG8, the H3K36me3 methyltransferase SDG25, and the rice H3K27me3 and H3K4 demethylases JMJ705 and JMJ704 are all positive regulators of immunity.[68–72] H3K4me3 has been associated with the responses to dehydration and salinity. Its levels are dynamic during dehydration stress and mark the body of genes that respond to this stress,[73,74] and mutants in JMJ15 (a H3K4 demethylase) have a downregulation of salinity stress-related genes.[75] H3K27me3 has also been widely associated with the response to stress. The levels of this histone mark decrease upon hyperosmotic priming in Arabidopsis roots[76] and the levels of this mark decrease upon heat or cold stress on target genes.[77,78]

Genome-wide analysis of genes targeted by the PRC1 complex indicates that many stress response-associated genes are actually targeted by H3K27me3.[79] Together with acetylation and methylation, ubiquitination has been identified as required for resistance to pathogens. For example, HUB1 positively regulated resistance to fungal pathogens, both in Arabidopsis and tomato.[80,81] Furthermore, the interaction between different histone marks has been addressed for several target genes, showing the complexity of this regulatory mechanism. The simultaneous presence of H3K4me3 and H3K9/K14Ac was correlated with response to submergence in rice.[82] Also the enrichment of

H3K4me3, H3K9Ac, H3K23Ac, and H3K27Ac was found during dehydration,[83] an enrichment that is followed by loss of H3K4me3 and H3K9Ac during rehydration.[65] These two marks increase also in selected genes during heat stress, together with H3K4me2 and, interestingly, while H3K9ac decreases rapidly after stress, H3K4me2/3 levels are sustained.[84] This pattern of enrichment in H3K4me2/3 together with H3K9/14ac has also been observed in the promoter of several immunity genes,[64] pointing to a conservation of this histone landscape during stress response.[12] Together with this complex activity, chromatin remodelers and histone variants have also been involved in the control of the stress response. For example, BRM and DDM1 have been involved in the regulation of abscisic acid responses during drought stress response and R gene regulation, respectively.[85–88] Furthermore, histone variants also play a role during stress. SWR1 and H1.3 have been related to the regulation of defense genes and the response to drought stress.[89]

As highlighted by the examples mentioned here, the role of histone modifications during stress is not as straightforward as that of DNA methylation. Their analysis needs a careful individual evaluation that impedes making generalizations about their role in stress response. This probably highlights the high complexity and intertwined layers of crosstalk between the different histone modification enzymes.[90] Interestingly, nucleotide-binding site leucine-rich repeat genes (NBS-LRR) accumulate in clusters in heterochromatic regions of genomes closely associated with TEs characterized by the presence of DNA methylation and repressive histone marks.[91] In support of this relationship, the *bal* epiallele (located in the *RPP5* cluster of NBS-LRR genes) generated in *ddm1* mutants[92] and the upregulation of the *RMG1* defense gene under *Pst* DC3000 infection[43] emerge as two illustrative examples of the interaction between epigenetic regulation and control of defense responses.

16.3.3 Interplay between priming and epigenetic regulation

As mentioned above, epigenetic regulation is one of the mechanisms regulating priming or stress memory.[11] In the examples provided above, epigenetic modifications induced by stress are most of the time transient and overlap with the presence of the stress. However, stresses that induce a stress memory or priming induce epigenetic modifications that exceed the presence of the initial priming stress.

From all the histone marks that respond to stress, histone methylation (more concretely H3K4me2 and H3K4me3) has been closely associated with stress memory. Indeed, there are several examples that show the relationship of priming with the enrichment in H3K4me2/3. Plants primed with benzothiadiazole showed increased levels of H3K4me2/3.[93] H3K4me3 is also enriched in the promoter and first exon of several genes associated with immunity to *Pst* DC3000 after priming with different abiotic stresses and it requires the function of the histone acetyltransferase HAC1.[64] Enrichment in

H3K4me3 has also been observed for genes that experience a priming pattern.[74] Comparison of stress-primed and nonprimed genes showed that the former experience a maintenance of H3K4me3 together with stalled Pol II during stress recovery that lead to increased transcription during the stress phase.[74] Increased presence of H3K4me2/3 has also been shown for heat-inducible genes after priming.[84] This study also showed that heat stress memory and H3K4me2/3 accumulation depend on a transcription factor, HSFA2.[84] Another transcription factor, HY5, has been associated with H3K4me3-dehydration stress memory of the P5CS1 gene.[94] Together with H3K4me2/3, other histone marks have been linked to priming. For example, analysis of genome-wide histone mark profiling after salt priming in roots showed that H3K27me3 was the only dynamic mark.[76] Together with histone methylation, nucleosome occupancy has been shown to play a role in the maintenance or establishment of priming. The helicase FGT1, which interacts with BRM, binds to heat-memory genes, decreasing the nucleosome occupancy on those, and is required for heat stress memory.[95] The histone chaperone CAF-1 has also been implicated with priming. CAF-1 mutants show constitutive priming response. Analysis of its function showed that CAF-1 suppresses H3K4me3 incorporation in defense genes preventing priming.[96]

In summary, stress memory seems to be correlated with an enrichment and maintenance of H3K4 methylation in certain stress-responsive genes (Fig. 16.2A). Together with this, nucleosome occupancy regulates the acquisition of memory for genes. The interaction between all these different players remains to be discovered but it is certainly an active subject of research that is expected to give interesting results in the next years.

16.4 Transgenerational memory of stress

16.4.1 Examples of transgenerational inheritance: Epialleles

Epialleles are forms of a gene that have differential epigenetic marks (and not DNA sequence) that lead to a differential level of expression of that gene causing, most of the time, a heritable phenotype.[15] A very illustrative example is the epiallele, found in the *Lcyc* locus of *Linaria vulgaris*, which radically changes the symmetry of the flower from bilateral to radial.[97] The changes in expression of *Lcyc* are associated with the presence of DNA methylation, which is inherited transgenerationally.[97] Other examples of epialleles in plants include the *CNR* locus in tomato,[98] the paramutation phenomenon in maize,[99–101] the *Epi-dwarf* allele in rice, the *g* and *VTE3* loci in melon, the regulation of vitamin E content in tomato,[15] or the well-studied cases of *FWA* and *QQS* genes in Arabidopsis.[102,103] Some of these epialleles involve the presence of repeats, DNA methylation, and sRNAs.[101,104] Analysis of the variability of DNA methylation in nature using different Arabidopsis ecotypes indicates that cytosine methylation is highly variable.[105,106] These methylation cytosines belong mostly to the CHH context and are frequently found in their unmethylated form on TEs.[105] These changes seem, moreover, to

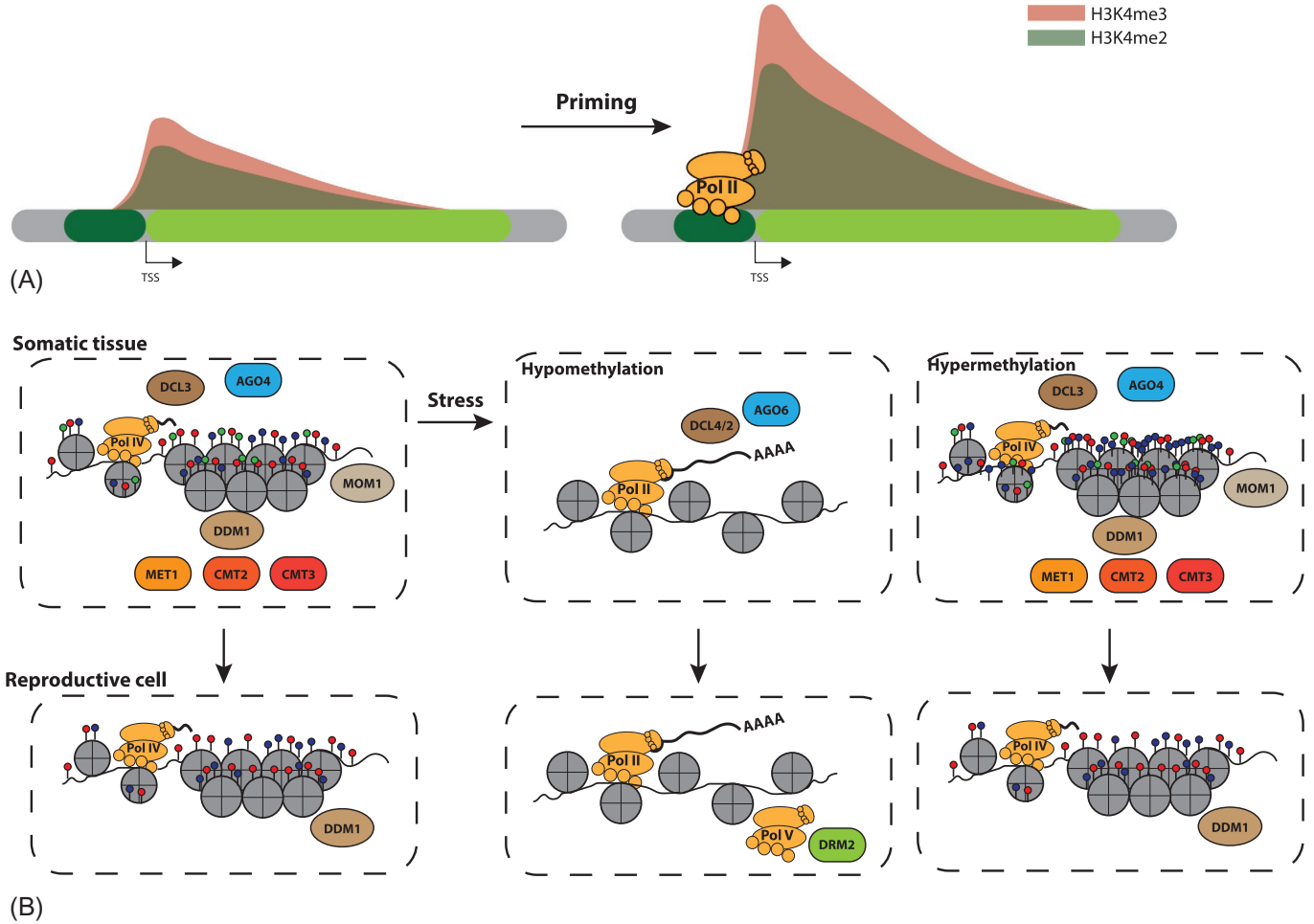

Fig. 16.2 Epigenetic regulation of priming and memory of stress. (A) Priming induces enrichment in H3K4me2/3 and stalled RNA polymerase II in the regulatory regions and bodies of genes with stress memory. (B) Potential epigenetic mechanisms involved in transgenerational epigenetic inheritance. The epigenetic status of the somatic tissues is maintained during reproduction by the activity of Pol IV, DDM1, and MOM1. Stress can induce two different epigenetic statuses: hypomethylation, which is in principle easily inherited from both paternal and maternal genomes, and hypermethylation, which would only be inherited from the maternal gamete.

be correlated with variation at the DNA sequence level.[105] The inheritance of epialleles has also been addressed experimentally through the use of Arabidopsis mutants.[107,108] In these experiments, *met1* and *ddm1* were used as parents for crosses with wild type plants to create recombinant inbred lines (termed epiRILs). These epiRIL lines have genomes with a mosaic of methylation pattern that shows stable inheritance over several generations. In general, methylation differences accounted mostly for TEs, which also suffer a progressive re-methylation mediated by the RdDM pathway.[109] Interestingly, met1-induced epiRIL lines showed broader changes due to the misregulation of ROS1 and other epigenetically regulated genes.[109] Briefly, transgenerational inheritance of epigenetically induced alleles is supported by these numerous examples taking place in nature.

16.4.2 Inheritance of stress-induced epigenetic changes

Naturally and experimentally induced epialleles can be inherited transgenerationally and even be stable for hundreds of years.[97] This inheritance of epigenetic regulation has led the field to question if environmentally or stress-induced epigenetic changes can be inherited transgenerationally, and if this represents a memory of the stress conditions experienced by the plant in previous generations. As reviewed, both abiotic and biotic stresses induce epigenetic changes in the genome.[37,110] Dehydration,[73] salinity,[66] heat,[84] viroidal,[111,112] viral,[38] and bacterial infections[43] cause the relaxation of the epigenetic control of stress-responsible genes and repetitive regions in the genome that can lead, generally, to short-term memory that is not inherited by the subsequent generation. It has been proposed that, like epialleles, some of these epigenetic changes could be transmitted through the reproductive phase and inherited by the next generation.[37,113] The inheritance of these phenotypes is technically challenging and has become controversial due to reduced reproducibility of results and duration of the transgenerational effects.[114–116] Nevertheless, an epigenetic memory is known to exist because TE silencing is inherited transgenerationally,[117] but also environmental cues like vernalization can be inherited transgenerationally in H3K27 demethylase mutants.[118]

One of the first reports showing transgenerational inheritance of a resistance phenotype in plants showed that treatment of parental plants with UV-C or flg22 induced an increase of somatic homologous recombination.[119] Heat stress affects posttranscriptional gene silencing (PTGS) and induces siRNA-mediated epigenetic changes that are transgenerationally inherited.[120] Salt stress causes hypermethylation in the CHG and CHH contexts of TEs in the proximity of genes involved in the response to this stress.[50] These methylation changes are transgenerational only through the female gamete, due to the efficient demethylation that takes place in the paternal gamete.[50] A mechanism that must be taken into account and that can explain transgenerational inheritance of stress response is the potential transposition of TEs and the genome rearrangements associated with them. One such example is the heat stress-dependent reactivation of the *ONSEN* retrotransposon in

Arabidopsis.[121] The retrotransposon *ONSEN* contains a heat stress-response transcription factor binding-site in its promoter region.[122] Under heat stress *ONSEN* reactivates and reintegrates in the genome transmitting heat stress-responsiveness to the genes physically close to the new *ONSEN* transposition events.[123]

This mechanism has been observed, too, for abscisic acid insensitivity, which has been recently associated with the transposition of a TE.[52] A forward genetic screen in Arabidopsis looking for factors involved in the transmission of stress-induced transcriptional changes identified DDM1 and MOM1 as inhibitors of the transmission of those changes. The majority of affected transcripts derived from TEs, indicating that indeed the transmission of TE epigenetic states would be responsible for the transmission of the stress memory.[124] A deeper analysis of the molecular characteristics of transgenerational epialleles identified several properties associated with their transmissibility, such as low-copy number loci or enrichment in CG dinucleotides.[125] Altogether, the inheritance of stress-induced epigenetic changes is still a matter of debate that requires further efforts and deeper investigation of its extent and the mechanisms involved in the process.

16.4.3 Transgenerational memory of stress

Inheritance of primed states has been shown for some biotic stresses. For example, the immune response to the infection by *Pst* DC3000 is inherited by the next generation.[47] This response is also mimicked by the triple mutant *drm1 drm2 cmt3*, which has low levels of DNA methylation; this points to the changes in DNA methylation induced by the pathogen as the cause for the transgenerational resistance.[47] Priming with the chemical reagent BABA induces enhanced resistance to *P. syringae* in the next generation.[126] In addition, herbivore insects and biotrophic pathogens can induce an enhanced defense state in the next generation.[127–129]

Mechanistically, little is known about how this transgenerational memory could work. Analysis of the stress memory of resistance to *Pst* DC3000 indicated that PolV and ROS1 are needed for transgenerational acquired resistance, pointing to DNA methylation as the main regulatory mechanism.[128] A profound subsequent analysis revealed that these two factors (PolV and ROS1) are responsible for the indirect regulation of 49% of pathogen-responsive genes, since only 15% of these genes were associated with TEs.[128] Further analysis of the genome-wide epigenetic changes taking place during three generations of plants exposed to an initial stress showed alterations in the third generation, but not in the initial generation exposed originally to stress.[130] Most of the changes took place over gene bodies in the CG context,[130] a mark that is not completely understood in plants. The inheritance of transgenerational resistance is limited in the triple mutant *dcl2 dcl3 dcl4* in the case of herbivores[127] and associated with DNA methylation regulated by PolV and ROS1 or DRM1 DRM2 and CMT3 in the case of biotrophic pathogens.[45,47,128,129] The involvement of inherited histone marks has not

been studied in depth yet, but it is believed that they are completely reprogrammed during gametogenesis.[131] In summary, current evidences point to DNA methylation or changes in the RNA silencing mechanisms (linked to DNA methylation in plants) as the transmitters to the next generation of epigenetic states induced by stress.

In summary, several mechanisms have been implicated in the transgenerational transmission of priming or memory stress but the overall mechanism is still undefined. In general, it seems improbable that there is a transgenerational inheritance of the H3K4me2/3 states that are implicated with priming in somatic tissues, and it would rather seem that transgenerational priming relays on DNA methylation or associated sRNAs (Fig. 16.2B). From that perspective, and with the knowledge that we have from natural epialleles, transgenerational inheritance of epigenetic mechanisms would rely mostly on TEs or genes in close association with them. Additionally, the intrinsic characteristics of the TE as genomic location, copy number, or CG dinucleotide enrichment will determine the extent of the epigenetic memory.

16.5 Conclusion and perspective

In the light of climate change, epigenetic variation could contribute to both short-term and the longer-term adaptive capacity in plants and thus provide them with the ability to overcome variable environment conditions. Together with this, the influence of priming and the transgenerational memory of stress in plants grown in communities, where they encounter competition with other plants of the same or different species, may be an essential factor in mediating ecological interactions. In field conditions, their offspring would benefit from enhanced resistance via transgenerational inheritance, especially if they encounter the same stress factors as their parents. Integration of transgenerational defense priming into agricultural pest management then can have a great potential to provide novel and sustainable solutions.

References

1. Lamke J, Baurle I. Epigenetic and chromatin-based mechanisms in environmental stress adaptation and stress memory in plants. *Genome Biol* 2017;**18**(1):124.
2. Ptashne M. Transcription: a mechanism for short-term memory. *Curr Biol* 2008;**18**(1):R25–7.
3. Light WH, Brickner JH. Nuclear pore proteins regulate chromatin structure and transcriptional memory by a conserved mechanism. *Nucleus* 2013;**4**(5):357–60.
4. D'Urso A, Brickner JH. Mechanisms of epigenetic memory. *Trends Genet* 2014;**30**(6):230–6.
5. Beckers GJ, Jaskiewicz M, Liu Y, Underwood WR, He SY, Zhang S, et al. Mitogen-activated protein kinases 3 and 6 are required for full priming of stress responses in *Arabidopsis thaliana*. *Plant Cell* 2009;**21**(3):944–53.
6. Chakrabortee S, Byers JS, Jones S, Garcia DM, Bhullar B, Chang A, et al. Intrinsically disordered proteins drive emergence and inheritance of biological traits. *Cell* 2016;**167**(2):369–81. e12.
7. Chen CW, Panzeri D, Yeh YH, Kadota Y, Huang PY, Tao CN, et al. The Arabidopsis malectin-like leucine-rich repeat receptor-like kinase IOS1 associates with the pattern recognition receptors FLS2 and EFR and is critical for priming of pattern-triggered immunity. *Plant Cell* 2014;**26**(7):3201–19.

8. Shoresh M, Gal-On A, Leibman D, Chet I. Characterization of a mitogen-activated protein kinase gene from cucumber required for Trichoderma-conferred plant resistance. *Plant Physiol* 2006; **142**(3):1169–79.
9. Zacharioudakis I, Gligoris T, Tzamarias D. A yeast catabolic enzyme controls transcriptional memory. *Curr Biol* 2007;**17**(23):2041–6.
10. Tateda C, Zhang Z, Shrestha J, Jelenska J, Chinchilla D, Greenberg JT. Salicylic acid regulates Arabidopsis microbial pattern receptor kinase levels and signaling. *Plant Cell* 2014;**26**(10):4171–87.
11. Conrath U, Beckers GJ, Langenbach CJ, Jaskiewicz MR. Priming for enhanced defense. *Annu Rev Phytopathol* 2015;**53**:97–119.
12. Asensi-Fabado MA, Amtmann A, Perrella G. Plant responses to abiotic stress: the chromatin context of transcriptional regulation. *Biochim Biophys Acta Gene Regul Mech* 2017;**1860**(1):106–22.
13. Law JA, Jacobsen SE. Establishing, maintaining and modifying DNA methylation patterns in plants and animals. *Nat Rev Genet* 2010;**11**(3):204–20.
14. Cokus SJ, Feng S, Zhang X, Chen Z, Merriman B, Haudenschild CD, et al. Shotgun bisulphite sequencing of the Arabidopsis genome reveals DNA methylation patterning. *Nature* 2008; **452**(7184):215–9.
15. Quadrana L, Colot V. Plant transgenerational epigenetics. *Annu Rev Genet* 2016;**50**:467–91.
16. Zhang H, Lang Z, Zhu JK. Dynamics and function of DNA methylation in plants. *Nat Rev Mol Cell Biol* 2018;**19**(8):489–506.
17. Matzke MA, Mosher RA. RNA-directed DNA methylation: an epigenetic pathway of increasing complexity. *Nat Rev Genet* 2014;**15**(6):394–408.
18. Cuerda-Gil D, Slotkin RK. Non-canonical RNA-directed DNA methylation. *Nat Plants* 2016; **2**(11):16163.
19. Mari-Ordonez A, Marchais A, Etcheverry M, Martin A, Colot V, Voinnet O. Reconstructing de novo silencing of an active plant retrotransposon. *Nat Genet* 2013;**45**(9):1029–39.
20. Stroud H, Do T, Du J, Zhong X, Feng S, Johnson L, et al. Non-CG methylation patterns shape the epigenetic landscape in Arabidopsis. *Nat Struct Mol Biol* 2014;**21**(1):64–72.
21. Strahl BD, Allis CD. The language of covalent histone modifications. *Nature* 2000;**403**(6765):41–5.
22. Liu C, Lu F, Cui X, Cao X. Histone methylation in higher plants. *Annu Rev Plant Biol* 2010;**61**:395–420.
23. Zhang X, Bernatavichute YV, Cokus S, Pellegrini M, Jacobsen SE. Genome-wide analysis of mono-, di- and trimethylation of histone H3 lysine 4 in *Arabidopsis thaliana*. *Genome Biol* 2009;**10**(6):R62.
24. Berger SL. The complex language of chromatin regulation during transcription. *Nature* 2007; **447**(7143):407–12.
25. Zhang X, Clarenz O, Cokus S, Bernatavichute YV, Pellegrini M, Goodrich J, et al. Whole-genome analysis of histone H3 lysine 27 trimethylation in Arabidopsis. *PLoS Biol* 2007;**5**(5):e129.
26. Fuchs J, Demidov D, Houben A, Schubert I. Chromosomal histone modification patterns—from conservation to diversity. *Trends Plant Sci* 2006;**11**(4):199–208.
27. Mathieu O, Probst AV, Paszkowski J. Distinct regulation of histone H3 methylation at lysines 27 and 9 by CpG methylation in Arabidopsis. *EMBO J* 2005;**24**(15):2783–91.
28. Roudier F, Ahmed I, Berard C, Sarazin A, Mary-Huard T, Cortijo S, et al. Integrative epigenomic mapping defines four main chromatin states in Arabidopsis. *EMBO J* 2011;**30**(10):1928–38.
29. Kooistra SM, Helin K. Molecular mechanisms and potential functions of histone demethylases. *Nat Rev Mol Cell Biol* 2012;**13**(5):297–311.
30. Cedar H, Bergman Y. Linking DNA methylation and histone modification: patterns and paradigms. *Nat Rev Genet* 2009;**10**(5):295–304.
31. Jackson JP, Lindroth AM, Cao X, Jacobsen SE. Control of CpNpG DNA methylation by the KRYPTONITE histone H3 methyltransferase. *Nature* 2002;**416**(6880):556–60.
32. Malagnac F, Bartee L, Bender J. An Arabidopsis SET domain protein required for maintenance but not establishment of DNA methylation. *EMBO J* 2002;**21**(24):6842–52.
33. Johnson LM, Law JA, Khattar A, Henderson IR, Jacobsen SE. SRA-domain proteins required for DRM2-mediated de novo DNA methylation. *PLoS Genet* 2008;**4**(11):e1000280.
34. Du J, Johnson LM, Jacobsen SE, Patel DJ. DNA methylation pathways and their crosstalk with histone methylation. *Nat Rev Mol Cell Biol* 2015;**16**(9):519–32.

35. Vaissiere T, Sawan C, Herceg Z. Epigenetic interplay between histone modifications and DNA methylation in gene silencing. *Mutat Res* 2008;**659**(1–2):40–8.
36. Martinez G, Slotkin RK. Developmental relaxation of transposable element silencing in plants: functional or byproduct? *Curr Opin Plant Biol* 2012;**15**(5):496–502.
37. Annacondia ML, Mageroy MH, Martinez G. Stress response regulation by epigenetic mechanisms: changing of the guards. *Physiol Plant* 2018;**162**(2):239–50.
38. Raja P, Sanville BC, Buchmann RC, Bisaro DM. Viral genome methylation as an epigenetic defense against geminiviruses. *J Virol* 2008;**82**(18):8997–9007.
39. Rodriguez-Negrete E, Lozano-Duran R, Piedra-Aguilera A, Cruzado L, Bejarano ER, Castillo AG. Geminivirus Rep protein interferes with the plant DNA methylation machinery and suppresses transcriptional gene silencing. *New Phytol* 2013;**199**(2):464–75.
40. Hamera S, Song X, Su L, Chen X, Fang R. Cucumber mosaic virus suppressor 2b binds to AGO4-related small RNAs and impairs AGO4 activities. *Plant J* 2012;**69**(1):104–15.
41. Castellano M, Pallas V, Gomez G. A pathogenic long noncoding RNA redesigns the epigenetic landscape of the infected cells by subverting host Histone Deacetylase 6 activity. *New Phytol* 2016; **211**(4):1311–22.
42. Dowen RH, Pelizzola M, Schmitz RJ, Lister R, Dowen JM, Nery JR, et al. Widespread dynamic DNA methylation in response to biotic stress. *Proc Natl Acad Sci U S A* 2012;**109**(32):E2183–91.
43. Yu A, Lepere G, Jay F, Wang J, Bapaume L, Wang Y, et al. Dynamics and biological relevance of DNA demethylation in Arabidopsis antibacterial defense. *Proc Natl Acad Sci U S A* 2013;**110**(6):2389–94.
44. Agorio A, Vera P. ARGONAUTE4 is required for resistance to *Pseudomonas syringae* in Arabidopsis. *Plant Cell* 2007;**19**(11):3778–90.
45. Lopez A, Ramirez V, Garcia-Andrade J, Flors V, Vera P. The RNA silencing enzyme RNA polymerase v is required for plant immunity. *PLoS Genet* 2011;**7**(12):e1002434.
46. Pavet V, Quintero C, Cecchini NM, Rosa AL, Alvarez ME. Arabidopsis displays centromeric DNA hypomethylation and cytological alterations of heterochromatin upon attack by *Pseudomonas syringae*. *Mol Plant Microbe Interact* 2006;**19**(6):577–87.
47. Luna E, Bruce TJ, Roberts MR, Flors V, Ton J. Next-generation systemic acquired resistance. *Plant Physiol* 2012;**158**(2):844–53.
48. Gohlke J, Scholz CJ, Kneitz S, Weber D, Fuchs J, Hedrich R, et al. DNA methylation mediated control of gene expression is critical for development of crown gall tumors. *PLoS Genet* 2013;**9**(2): e1003267.
49. Le TN, Schumann U, Smith NA, Tiwari S, Au PC, Zhu QH, et al. DNA demethylases target promoter transposable elements to positively regulate stress responsive genes in Arabidopsis. *Genome Biol* 2014; **15**(9):458.
50. Wibowo A, Becker C, Marconi G, Durr J, Price J, Hagmann J, Papareddy R, Putra H, Kageyama J, Becker J, Weigel D, Gutierrez-Marcos J. Hyperosmotic stress memory in Arabidopsis is mediated by distinct epigenetically labile sites in the genome and is restricted in the male germline by DNA glycosylase activity. *eLife* 2016;**5**:e13546. https://doi.org/10.7554/eLife.13546.
51. Colaneri AC, Jones AM. Genome-wide quantitative identification of DNA differentially methylated sites in Arabidopsis seedlings growing at different water potential. *PLoS One* 2013;**8**(4):e59878.
52. Ito H, Kim JM, Matsunaga W, Saze H, Matsui A, Endo TA, et al. A stress-activated transposon in Arabidopsis induces transgenerational abscisic acid insensitivity. *Sci Rep* 2016;**6**:23181.
53. Tricker PJ, Gibbings JG, Rodriguez Lopez CM, Hadley P, Wilkinson MJ. Low relative humidity triggers RNA-directed de novo DNA methylation and suppression of genes controlling stomatal development. *J Exp Bot* 2012;**63**(10):3799–813.
54. Pecinka A, Dinh HQ, Baubec T, Rosa M, Lettner N, Mittelsten SO. Epigenetic regulation of repetitive elements is attenuated by prolonged heat stress in Arabidopsis. *Plant Cell* 2010;**22**(9):3118–29.
55. Santos AP, Ferreira L, Maroco J, Oliveira MM. Abiotic stress and induced DNA hypomethylation cause interphase chromatin structural changes in rice rDNA loci. *Cytogenet Genome Res* 2011; **132**(4):297–303.
56. Tomas D, Brazao J, Viegas W, Silva M. Differential effects of high-temperature stress on nuclear topology and transcription of repetitive noncoding and coding rye sequences. *Cytogenet Genome Res* 2013; **139**(2):119–27.

57. Castellano M, Martinez G, Marques MC, Moreno-Romero J, Kohler C, Pallas V, et al. Changes in the DNA methylation pattern of the host male gametophyte of viroid-infected cucumber plants. *J Exp Bot* 2016;**67**(19):5857–68.
58. Gutzat R, Mittelsten SO. Epigenetic responses to stress: triple defense? *Curr Opin Plant Biol* 2012; **15**(5):568–73.
59. Zhou CH, Zhang L, Duan J, Miki B, Wu KQ. HISTONE DEACETYLASE19 is involved in jasmonic acid and ethylene signaling of pathogen response in Arabidopsis. *Plant Cell* 2005;**17**(4):1196–204.
60. Choi SM, Song HR, Han SK, Han M, Kim CY, Park J, et al. HDA19 is required for the repression of salicylic acid biosynthesis and salicylic acid-mediated defense responses in Arabidopsis. *Plant J* 2012; **71**(1):135–46.
61. Wu K, Zhang L, Zhou C, Yu CW, Chaikam V. HDA6 is required for jasmonate response, senescence and flowering in Arabidopsis. *J Exp Bot* 2008;**59**(2):225–34.
62. Mengel A, Ageeva A, Georgii E, Bernhardt J, Wu KQ, Durner J, et al. Nitric oxide modulates histone acetylation at stress genes by inhibition of histone deacetylases. *Plant Physiol* 2017;**173**(2):1434–52.
63. Latrasse D, Jegu T, Li HC, de Zelicourt A, Raynaud C, Legras S, et al. MAPK-triggered chromatin reprogramming by histone deacetylase in plant innate immunity. *Genome Biol* 2017;**18**:131.
64. Singh P, Yekondi S, Chen PW, Tsai CH, Yu CW, Wu KQ, et al. Environmental history modulates Arabidopsis pattern-triggered immunity in a HISTONE ACETYLTRANSFERASE1-dependent manner. *Plant Cell* 2014;**26**(6):2676–88.
65. Kim JM, To TK, Ishida J, Matsui A, Kimura H, Seki M. Transition of chromatin status during the process of recovery from drought stress in *Arabidopsis thaliana*. *Plant Cell Physiol* 2012; **53**(5):847–56.
66. Chen LT, Luo M, Wang YY, Wu KQ. Involvement of Arabidopsis histone deacetylase HDA6 in ABA and salt stress response. *J Exp Bot* 2010;**61**(12):3345–53.
67. Zheng Y, Ding Y, Sun X, Xie SS, Wang D, Liu XY, et al. Histone deacetylase HDA9 negatively regulates salt and drought stress responsiveness in Arabidopsis. *J Exp Bot* 2016;**67**(6):1703–13.
68. Dutta A, Choudhary P, Caruana J, Raina R. JMJ27, an Arabidopsis H3K9 histone demethylase, modulates defense against *Pseudomonas syringae* and flowering time. *Plant J* 2017;**91**(6):1015–28.
69. Li TT, Chen XS, Zhong XC, Zhao Y, Liu XY, Zhou SL, et al. Jumonji C domain protein JMJ705-mediated removal of histone H3 lysine 27 trimethylation is involved in defense-related gene activation in rice. *Plant Cell* 2013;**25**(11):4725–36.
70. Alvarez-Venegas R, Avramova Z. Methylation patterns of histone H3 Lys 4, Lys 9 and Lys 27 in transcriptionally active and inactive Arabidopsis genes and in atx1 mutants. *Nucleic Acids Res* 2005; **33**(16):5199–207.
71. Hou YX, Wang LY, Wang L, Liu LM, Li L, Sun L, et al. JMJ704 positively regulates rice defense response against *Xanthomonas oryzae* pv. *oryzae* infection via reducing H3K4me2/3 associated with negative disease resistance regulators. *BMC Plant Biol* 2015;**15**:286.
72. Lee S, Fu FY, Xu SM, Lee SY, Yun DJ, Mengiste T. Global regulation of plant immunity by histone lysine methyl transferases. *Plant Cell* 2016;**28**(7):1640–61.
73. van Dijk K, Ding Y, Malkaram S, Riethoven JJM, Liu R, Yang JY, et al. Dynamic changes in genome-wide histone H3 lysine 4 methylation patterns in response to dehydration stress in *Arabidopsis thaliana*. *BMC Plant Biol* 2010;**10**:238.
74. Ding Y, Fromm M, Avramova Z. Multiple exposures to drought 'train' transcriptional responses in Arabidopsis. *Nat Commun* 2012;**3**:740. https://doi.org/10.1038/ncomms1732.
75. Shen Y, Silva NCE, Audonnet L, Servet C, Wei W, Zhou DX. Oyer-expression of histone H3K4 demethylase gene JMJ15 enhances salt tolerance in Arabidopsis. *Front Plant Sci* 2014;**5**:290. https://doi.org/10.3389/fpls.2014.00290.
76. Sani E, Herzyk P, Perrella G, Colot V, Amtmann A. Hyperosmotic priming of Arabidopsis seedlings establishes a long-term somatic memory accompanied by specific changes of the epigenome. *Genome Biol* 2013;**14**(6):R59. https://doi.org/10.1186/gb-2013-14-6-r59.
77. Gan ES, Xu YF, Wong JY, Goh JG, Sun B, Wee WY, et al. Jumonji demethylases moderate precocious flowering at elevated temperature via regulation of FLC in Arabidopsis. *Nat Commun* 2014;**5**.
78. Kwon CS, Lee D, Choi G, Chung WI. Histone occupancy-dependent and -independent removal of H3K27 trimethylation at cold-responsive genes in Arabidopsis. *Plant J* 2009;**60**(1):112–21.

79. Molitor AM, Latrasse D, Zytnicki M, Andrey P, Houba-Herin N, Hachet M, et al. The Arabidopsis hnRNP-Q protein LIF2 and the PRC1 subunit LHP1 function in concert to regulate the transcription of stress-responsive genes. *Plant Cell* 2016;**28**(9):2197–211.
80. Dhawan R, Luo HL, Foerster AM, AbuQamar S, Du HN, Briggs SD, et al. HISTONE MONOUBIQUITINATION1 interacts with a subunit of the mediator complex and regulates defense against necrotrophic fungal pathogens in Arabidopsis. *Plant Cell* 2009;**21**(3):1000–19.
81. Zhang YF, Li DY, Zhang HJ, Hong YB, Huang L, Liu SX, et al. Tomato histone H2B monoubiquitination enzymes SlHUB1 and SlHUB2 contribute to disease resistance against *Botrytis cinerea* through modulating the balance between SA- and JA/ET-mediated signaling pathways. *BMC Plant Biol* 2015;**15**:252. https://doi.org/10.1186/s12870-015-0614-2.
82. Tsuji H, Saika H, Tsutsumi N, Hirai A, Nakazono M. Dynamic and reversible changes in histone H3-Lys4 methylation and H3 acetylation occurring at submergence-inducible genes in rice. *Plant Cell Physiol* 2006;**47**(7):995–1003.
83. Kim JM, To TK, Ishida J, Morosawa T, Kawashima M, Matsui A, et al. Alterations of lysine modifications on the histone H3 N-tail under drought stress conditions in *Arabidopsis thaliana*. *Plant Cell Physiol* 2008;**49**(10):1580–8.
84. Lamke J, Brzezinka K, Altmann S, Baurle I. A hit-and-run heat shock factor governs sustained histone methylation and transcriptional stress memory. *EMBO J* 2016;**35**(2):162–75.
85. Bezhani S, Winter C, Hershman S, Wagner JD, Kennedy JF, Kwon CS, et al. Unique, shared, and redundant roles for the Arabidopsis SWI/SNF chromatin remodeling ATPases BRAHMA and SPLAYED. *Plant Cell* 2007;**19**(2):403–16.
86. Yi H, Richards EJ. A cluster of disease resistance genes in Arabidopsis is coordinately regulated by transcriptional activation and RNA silencing. *Plant Cell* 2007;**19**(9):2929–39.
87. Han SK, Sang Y, Rodrigues A, Wu MF, Rodriguez PL, Wagner D, et al. The SWI2/SNF2 chromatin remodeling ATPase BRAHMA represses abscisic acid responses in the absence of the stress stimulus in Arabidopsis. *Plant Cell* 2012;**24**(12):4892–906.
88. Saez A, Rodrigues A, Santiago J, Rubio S, Rodriguez PL. HAB1-SWI3B interaction reveals a link between abscisic acid signaling and putative SWI/SNF chromatin-remodeling complexes in Arabidopsis. *Plant Cell* 2008;**20**(11):2972–88.
89. Rutowicz K, Puzio M, Halibart-Puzio J, Lirski M, Kotlinski M, Kroten MA, et al. A specialized histone H1 variant is required for adaptive responses to complex abiotic stress and related DNA methylation in Arabidopsis. *Plant Physiol* 2015;**169**(3):2080–101.
90. Ramirez-Prado JS, Piquerez SJM, Bendahmane A, Hirt H, Raynaud C, Benhamed M. Modify the histone to win the battle: chromatin dynamics in plant-pathogen interactions. *Front Plant Sci* 2018;**9**:355. https://doi.org/10.3389/fpls.2018.00355.
91. Meyers BC, Kozik A, Griego A, Kuang H, Michelmore RW. Genome-wide analysis of NBS-LRR-encoding genes in Arabidopsis. *Plant Cell* 2003;**15**(4):809–34.
92. Yi H, Richards EJ. Gene duplication and hypermutation of the pathogen Resistance gene SNC1 in the Arabidopsis bal variant. *Genetics* 2009;**183**(4):1227–34.
93. Jaskiewicz M, Conrath U, Peterhansel C. Chromatin modification acts as a memory for systemic acquired resistance in the plant stress response. *EMBO Rep* 2011;**12**(1):50–5.
94. Feng XJ, Li JR, Qi SL, Lin QF, Jin JB, Hua XJ. Light affects salt stress-induced transcriptional memory of P5CS1 in Arabidopsis. *Proc Natl Acad Sci U S A* 2016;**113**(51):E8335–43.
95. Brzezinka K, Altmann S, Czesnick H, Nicolas P, Gorka M, Benke E, et al. Arabidopsis FORGETTER1 mediates stress-induced chromatin memory through nucleosome remodeling. *Elife* 2016;**5**:e17061. https://doi.org/10.7554/eLife.17061.
96. Mozgova I, Wildhaber T, Liu Q, Abou-Mansour E, L'Haridon F, Metraux JP, et al. Chromatin assembly factor CAF-1 represses priming of plant defence response genes. *Nat Plants* 2015;**1**:15127.
97. Cubas P, Vincent C, Coen E. An epigenetic mutation responsible for natural variation in floral symmetry. *Nature* 1999;**401**(6749):157–61.
98. Manning K, Tor M, Poole M, Hong Y, Thompson AJ, King GJ, et al. A naturally occurring epigenetic mutation in a gene encoding an SBP-box transcription factor inhibits tomato fruit ripening. *Nat Genet* 2006;**38**(8):948–52.

99. Brink RA. A genetic change associated with the R locus in maize which is directed and potentially reversible. *Genetics* 1956;**41**(6):872–89.
100. Coe EH. A regular and continuing conversion-type phenomenon at the B-locus in maize. *Proc Natl Acad Sci U S A* 1959;**45**(6):828–32.
101. Gabriel JM, Hollick JB. Paramutation in maize and related behaviors in metazoans. *Semin Cell Dev Biol* 2015;**44**:11–21.
102. Weigel D, Colot V. Epialleles in plant evolution. *Genome Biol* 2012;**13**(10):249. https://doi.org/10.1186/gb-2012-13-10-249.
103. Silveira AB, Trontin C, Cortijo S, Barau J, Del Bem LEV, Loudet O, et al. Extensive natural epigenetic variation at a de novo originated gene. *PLoS Genet* 2013;**9**(4):e1003437. https://doi.org/10.1371/journal.pgen.1003437.
104. Giacopelli BJ, Hollick JB. Trans-homolog interactions facilitating paramutation in maize. *Plant Physiol* 2015;**168**(4):1226–36.
105. Schmitz RJ, Schultz MD, Urich MA, Nery JR, Pelizzola M, Libiger O, et al. Patterns of population epigenomic diversity. *Nature* 2013;**495**(7440):193–8.
106. Kawakatsu T, Huang SSC, Jupe F, Sasaki E, Schmitz RJ, Urich MA, et al. Epigenomic diversity in a global collection of *Arabidopsis thaliana* accessions. *Cell* 2016;**166**(2):492–505.
107. Johannes F, Porcher E, Teixeira FK, Saliba-Colombani V, Simon M, Agier N, et al. Assessing the impact of transgenerational epigenetic variation on complex traits. *PLoS Genet* 2009;**5**(6):e1000530. https://doi.org/10.1371/journal.pgen.1000530.
108. Reinders J, Wulff BBH, Mirouze M, Mari-Ordonez A, Dapp M, Rozhon W, et al. Compromised stability of DNA methylation and transposon immobilization in mosaic Arabidopsis epigenomes. *Gene Dev* 2009;**23**(8):939–50.
109. Colome-Tatche M, Cortijo S, Wardenaar R, Morgado L, Lahouze B, Sarazin A, et al. Features of the Arabidopsis recombination landscape resulting from the combined loss of sequence variation and DNA methylation. *Proc Natl Acad Sci U S A* 2012;**109**(40):16240–5.
110. Alvarez ME, Nota F, Cambiagno DA. Epigenetic control of plant immunity. *Mol Plant Pathol* 2010;**11**(4):563–76.
111. Martinez G, Castellano M, Tortosa M, Pallas V, Gomez G. A pathogenic non-coding RNA induces changes in dynamic DNA methylation of ribosomal RNA genes in host plants. *Nucleic Acids Res* 2014;**42**(3):1553–62.
112. Castellano M, Martinez G, Pallas V, Gomez G. Alterations in host DNA methylation in response to constitutive expression of Hop stunt viroid RNA in *Nicotiana benthamiana* plants. *Plant Pathol* 2015;**64**:1247–57.
113. Ito H. Chapter 12—Plant models of transgenerational epigenetic inheritance. In: Tollefsbol T, editor. *Transgenerational epigenetics*. Academic Press; 2014. p. 147–61. ISBN 9780124059443. https://doi.org/10.1016/B978-0-12-405944-3.00012-X.
114. Pecinka A, Scheid OM. Stress-induced chromatin changes: a critical view on their heritability. *Plant Cell Physiol* 2012;**53**(5):801–8.
115. Iwasaki M, Paszkowski J. Epigenetic memory in plants. *EMBO J* 2014;**33**(18):1987–98.
116. Pecinka A, Rosa M, Schikora A, Berlinger M, Hirt H, Luschnig C, et al. Transgenerational stress memory is not a general response in Arabidopsis. *PLOS One* 2009;**4**(4):e5202.
117. Slotkin RK, Martienssen R. Transposable elements and the epigenetic regulation of the genome. *Nat Rev Genet* 2007;**8**(4):272–85.
118. Crevillen P, Yang HC, Cui X, Greeff C, Trick M, Qiu Q, et al. Epigenetic reprogramming that prevents transgenerational inheritance of the vernalized state. *Nature* 2014;**515**(7528):587.
119. Molinier J, Ries G, Zipfel C, Hohn B. Transgeneration memory of stress in plants. *Nature* 2006;**442**(7106):1046–9.
120. Zhong SH, Liu JZ, Jin H, Lin L, Li Q, Chen Y, et al. Warm temperatures induce transgenerational epigenetic release of RNA silencing by inhibiting siRNA biogenesis in Arabidopsis. *Proc Natl Acad Sci U S A* 2013;**110**(22):9171–6.
121. Ito H, Gaubert H, Bucher E, Mirouze M, Vaillant I, Paszkowski J. An siRNA pathway prevents transgenerational retrotransposition in plants subjected to stress. *Nature* 2011;**472**(7341):115–9.

122. Cavrak VV, Lettner N, Jamge S, Kosarewicz A, Bayer LM, Mittelsten SO. How a retrotransposon exploits the plant's heat stress response for its activation. *PLoS Genet* 2014;**10**(1):e1004115.
123. Ito H, Gaubert H, Bucher E, Mirouze M, Vaillant I, Paszkowski J. An siRNA pathway prevents transgenerational retrotransposition in plants subjected to stress. *Nature* 2011;**472**(7341):115-U51.
124. Iwasaki M, Paszkowski J. Identification of genes preventing transgenerational transmission of stress-induced epigenetic states. *Proc Natl Acad Sci U S A* 2014;**111**(23):8547–52.
125. Catoni M, Griffiths J, Becker C, Zabet NR, Bayon C, Dapp M, et al. DNA sequence properties that predict susceptibility to epiallelic switching. *EMBO J* 2017;**36**(5):617–28.
126. Slaughter A, Daniel X, Flors V, Luna E, Hohn B, Mauch-Mani B. Descendants of primed Arabidopsis plants exhibit resistance to biotic stress. *Plant Physiol* 2012;**158**(2):835–43.
127. Rasmann S, De Vos M, Casteel CL, Tian DL, Halitschke R, Sun JY, et al. Herbivory in the previous generation primes plants for enhanced insect resistance. *Plant Physiol* 2012;**158**(2):854–63.
128. Lopez Sanchez A, Stassen JH, Furci L, Smith LM, Ton J. The role of DNA (de)methylation in immune responsiveness of Arabidopsis. *Plant J* 2016;**88**(3):361–74.
129. Luna E, Ton J. The epigenetic machinery controlling transgenerational systemic acquired resistance. *Plant Signal Behav* 2012;**7**(6):615–8.
130. Stassen JHM, Lopez A, Jain R, Pascual-Pardo D, Luna E, Smith LM, et al. The relationship between transgenerational acquired resistance and global DNA methylation in Arabidopsis. *Sci Rep* 2018;**8**, Article number 14761.
131. Ingouff M, Rademacher S, Holec S, Soljlc L, Xin N, Readshaw A, et al. Zygotic resetting of the HISTONE 3 variant repertoire participates in epigenetic reprogramming in Arabidopsis. *Curr Biol* 2010;**20**(23):2137–43.