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Review

Epigenetic control of plant immunity

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SUMMARY

In eukaryotic genomes, gene expression and DNA recombination are affected by structural chromatin traits. Chromatin structure is shaped by the activity of enzymes that either introduce covalent modifications in DNA and histone proteins or use energy from ATP to disrupt histone–DNA interactions. The genomic 'marks' that are generated by covalent modifications of histones and DNA, or by the deposition of histone variants, are susceptible to being altered in response to stress. Recent evidence has suggested that proteins generating these epigenetic marks play crucial roles in the defence against pathogens. Histone deacetylases are involved in the activation of jasmonic acid- and ethylene-sensitive defence mechanisms. ATP-dependent chromatin remodellers mediate the constitutive repression of the salicylic acid-dependent pathway, whereas histone methylation at the *WRKY70* gene promoter affects the activation of this pathway. Interestingly, bacterial-infected tissues show a net reduction in DNA methylation, which may affect the disease resistance genes responsible for the surveillance against pathogens. As some epigenetic marks can be erased or maintained and transmitted to offspring, epigenetic mechanisms may provide plasticity for the dynamic control of emerging pathogens without the generation of genomic lesions.

INTRODUCTION

Long-standing, intimate associations between plants and microbial pathogens have forced the incessant selection of antagonistic capabilities on each of these respective organisms. As a consequence, sophisticated mechanisms of the promotion of plant defence and pathogen virulence have developed. Plants counteract pathogens by means of an innate immune system that relies on cell autonomous responses and multiple defence layers. This involves the detection of pathogen-associated molecular patterns (PAMPs) and the stimulation of basal defences defined as 'PAMP-triggered immunity' (PTI) (Ausubel, 2005; Zipfel, 2008), as well as the recognition of pathogen-derived effectors by intracellular resistance proteins (R) and the activation of 'effector-triggered immunity' (ETI) (Bent and Mackey, 2007; Jones and Dangl, 2006). Most R proteins that provide the basis for ETI and disease resistance carry nucleotide binding site-leucine-rich repeat (NBS-LRR) domains. The *NBS-LRR* gene family is one of the largest in plants and contains polymorphic and rapidly evolving genes that are often arranged in clusters. One process that leads to the reshuffling and evolution of *NBS-LRR* genes involves mispairing and recombination between transposon elements (TEs) and sequence repeats, which are abundant in these clusters (Baumgarten *et al*., 2003; McHale *et al*., 2006; Meyers *et al*., 2003). However, the mechanisms underlying enhanced recombination at these loci have not been established.

The stimulation of PTI and ETI involves extensive reprogramming of plant transcription. In order for changes in gene expression to contribute to selective pathogen resistance, specific defence circuits must become activated immediately after infection (Bent and Mackey, 2007; Jones and Dangl, 2006; Tsuda *et al*., 2009). The signals for resistance to biotrophic pathogens occur mainly through the salicylic acid (SA)-dependent pathway and usually lead to hypersensitive cell death, whereas defences against necrotrophs are mainly stimulated by the jasmonic acid/ethylene (JA/ET) pathway. These two defence programmes maintain antagonistic or synergistic interactions (Bari and Jones, 2009; Koornneef and Pieterse, 2008; Vlot *et al*., 2009). Global changes in gene expression that are stimulated through the SA and JA pathways have been characterized in detail (Tsuda *et al*., 2009). More recently, studies have begun to analyse how chromatin structure affects the expression of defence genes.

The chromatin compaction level influences several genomic functions. High-order chromatin organization involves different levels of DNA packing. At the basic level, 147 bp of DNA are wrapped in a 1.7 turn around an octamer of core histones (two subunits of H2A, H2B, H3 and H4), forming the structural and functional chromatin unit termed the nucleosome. Neighbouring nucleosomes are separated by stretches of 10–50 bp of unwrapped DNA that is associated with the linker histone H1,

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which is primarily responsible for the condensation of the 30-nm DNA fibre. The packing of DNA into fibres occludes the access of proteins to components that regulate transcription, DNA repair, replication and recombination. Therefore, in order for these components to be exposed, chromatin relaxation is required. Chromatin unfolding involves the action of ATP-dependent remodelling complexes (Jerzmanowski, 2007; de la Serna *et al*., 2006), covalent modification of histone proteins (Berger, 2007; Kouzarides, 2007; Pfluger and Wagner, 2007; Zhang *et al*., 2007b), deposition of histone variants (Draker and Cheung, 2009; Guillemette and Gaudreau, 2006; March-Diaz and Reyes, 2009; Zlatanova and Thakar, 2008) or DNA methylation changes (Gehring and Henikoff, 2007; Zilberman, 2008). In addition, noncoding small RNAs (smRNAs) are responsible for directing heterochromatin formation at specific genomic sequences (Chan, 2008).

In this work, we summarize the data that sustain the existence of epigenetic control of plant immunity. We focus on selected studies, mainly from Arabidopsis, that reveal how covalent modifications of histones and DNA or ATP-dependent chromatin remodelling events regulate the defence cascades. In addition, we discuss how pathogen-induced epigenetic modifications may contribute to the transgeneration memory of stress. The effects of smRNAs on chromatin structure and plant disease resistance have been summarized recently in excellent reviews and will not be covered here (Chan, 2008; Jin, 2008; Ruiz-Ferrer and Voinnet, 2009).

POST-TRANSLATIONAL MODIFICATIONS (PTMs) OF HISTONE PROTEINS

Modifications that occur on all core histones have been characterized recently by mass spectrometric studies in Arabidopsis (Zhang *et al*., 2007b). Most, but not all, are present in the animal kingdom where they display similar functions as in plants (Fuchs *et al*., 2006; Kouzarides, 2007; Pfluger and Wagner, 2007). Nearly 60 residues on histones are modified by enzymes that add or remove chemical groups. Residues from the N- or C-terminal histone tails that protrude from the core (30% of the protein mass) are the most frequently altered. However, residues from the central domain of histones that maintain the structural organization of nucleosomes also undergo modification (Luger *et al*., 1997). Histone-modifying enzymes seem to be recruited to specific genomic regions by transcription factors. The major PTMs include methylation, acetylation, phosphorylation, ubiquitylation, sumoylation and ADP-ribosylation, with the first three being the best characterized (Berger, 2007; Fuchs *et al*., 2006; Kouzarides, 2007; Pfluger and Wagner, 2007). Most histone PTMs are removable and the heritability of these marks through cell division is still controversial (Berger, 2007; Kouzarides, 2007). However, in plants, methylation and acetylation of histone proteins are required for the maintenance of imprinting mechanisms (Haun and Springer, 2008).

Histone PTMs are thought to change chromatin structure through at least two different mechanisms. The first includes local alterations of electrostatic charges that modify contacts between nucleosomes. The second involves the recruitment of nonhistone proteins to open or close chromatin. Although several histone PTMs affect transcriptional competence, a modification by itself does not define active or silenced chromatin (Fuchs *et al*., 2006; Vaillant and Paszkowski, 2007). Rather, its effect may depend on the extent of the modification (i.e. mono- to trimethylation), the gene region involved, the combination of other chromatin modifications and the nature of the genome (Fuchs *et al*., 2006; Kouzarides, 2007; Pfluger and Wagner, 2007). In plants, transcriptionally silent chromatin contains hypoacetylated H3 and H4, methylated lysine 27 (H3K27) and lysine 9 of histone H3 (H3K9), and hypermethylated DNA. Conversely, active chromatin in plants exhibits enhancement of H3 and H4 acetylation, trimethylation of lysine 4 from histone H3 (H3K4me3) and DNA hypomethylation (Bernatavichute *et al*., 2008; Cokus *et al*., 2008; Lister *et al*., 2008; Pfluger and Wagner, 2007; Tian *et al*., 2005; Vaillant and Paszkowski, 2007; Zhang *et al*., 2006, 2007c, 2009; Zilberman *et al*., 2007).

Histone acetylation

Histone acetyltransferases (HATs) and histone deacetylases (HDACs)

The combined antagonistic activities of HATs and HDACs determine the acetylation level of lysine residues on histone tails. Acetylation was recognized early on as an indicator of actively transcribed genes, and several HATs have been identified as transcriptional co-activators (Berger, 2007; Kouzarides, 2007; Pfluger and Wagner, 2007; Yang and Seto, 2008). In addition, HDACs have been found to mediate gene repression (Tanaka *et al*., 2008; Tian *et al*., 2005; Wu *et al*., 2000). However, in some cases, HDACs have been associated with transcriptional activation (Wang *et al*., 2002, 2009; Zupkovitz *et al*., 2006). For instance, the distribution analysis of five HATs and four HDACs in human T cells showed that, in addition to HATs, HDACs are enriched in active genes and correlate with transcription. These HDACs are thought to avoid cryptic transcriptional initiation and chromatin instability through the removal of acetyl groups introduced by HATs (Wang *et al*., 2009).

In plants, HATs and HDACs modulate the expression of developmental and stress-sensitive genes (Bharti *et al*., 2004; Chen and Tian, 2007; Kim *et al*., 2004; Sridha and Wu, 2006; Zhu *et al*., 2008). In addition, HDACs have been implicated in defences against pathogens.

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HDACs and JA-dependent defences

A fungal product called HC-toxin was identified by looking for primary determinants of the corn leaf disease caused by *Cochiobolus* (*Helminthosporium*) *carbonum*. Resistance to this pathogen was found to be conferred by maize alleles that encode a carbonyl reductase which inactivates the HC-toxin (*Hm1/2* alleles; Johal and Briggs, 1992). This toxin is a cyclic tetrapeptide that acts as a potent inhibitor of HDACs from yeast, insects, mammals and plants. Among the plant HDACs, proteins from the Reduced Potassium Dependency protein 3/Histone Deacetylase 1 (RPD3/HDA1) and HD2 classes are the only members that become inhibited by the toxin. Silent Information Regulator 2 (SIR2)-like HDACs and HATs are not affected by this toxin (Brosch *et al*., 1995; Chen and Tian, 2007; Walton, 2006; Yang and Seto, 2008). Treatments with the HC-toxin or virulent fungal strains cause histone hyperacetylation in susceptible, but not resistant, maize plants. Therefore, HDACs seem to act as primary targets of the HC-toxin, with histones being the major substrates of HDACs during infection (Brosch *et al*., 1995; Ransom and Walton, 1997). However, transcription factors, cytoskeletal proteins, proteins involved in DNA repair and others are also substrates of HDACs (Cohen *et al*., 2004; Glozak *et al*., 2005; Hubbert *et al*., 2002; Juan *et al*., 2000). This fact, together with the abundant list of maize genes encoding HDACs that are sensitive to the HC-toxin, prevented the elucidation of the role of these enzymes in resistance to *C. carbonum* (Walton, 2006). Unfortunately, in the genetically tractable *Arabidopsis thaliana*–*Alternaria brassicicola* pathosystem, in which plant HDACs are inhibited by the fungal derivative depudecin, depudecin was shown not to be an important virulence factor (Wight *et al*., 2009). Therefore, novel or improved models will be required to elucidate the contribution of HDACs in fungal resistance.

Additional evidence that HDACs are involved in defence responses against pathogens implicates the activation of the JA pathway in Arabidopsis. HDAC19 is a nuclear RPD3/HDA1 family protein that has HDAC activity *in vitro*. Loss of this protein increases acetylation on histones by 10-fold and mainly affects gene promoters (Fong *et al*., 2006; Zhou *et al*., 2005). The *AtHDAC19* gene is induced by *Alternaria brassicicola* and exogenous JA. Overexpression of the gene enhances fungal resistance through the apparent activation of the Ethylene Responsive Factor 1 (ERF1), whereas silencing of the gene increases fungal susceptibility (Zhou *et al*., 2005). However, because HDAC19 deficiency affects multiple developmental traits, the direct effect of this enzyme on pathogen-induced defence pathways is questionable (Tian and Chen, 2001; Tian *et al*., 2005; Zhou *et al*., 2005). This type of effect may involve the recruitment of HDAC19 to the promoters of JA-sensitive genes by ERF factors, as similar hormone-sensitive complexes regulate stress-sensitive genes in Arabidopsis (Song and Galbraith, 2006). In addition, HDAC19 influences defences against *Pseudomonas syringae* through interaction with WRKY38 and WRKY62, two transcription factors that repress the SA pathway (Kim *et al*., 2008).

HDAC6 is another RPD3/HDA1-type HDAC from Arabidopsis that is involved in the activation of JA-dependent defences. This enzyme affects transgene silencing, DNA methylation and the activity of rRNA genes (Aufsatz *et al*., 2007). Similar to *AtHDAC19*, the expression of *AtHDAC6* is induced by exogenous JA (Zhou *et al*., 2005). Interestingly, HDAC6 interacts with Coronatine Insensitive 1 (COI1), an F-box protein that mediates JA signalling (Devoto *et al*., 2002). This interaction seems to have functional significance, as HDAC6 is required for JA-dependent responses, including *PDF1.2*, *VSP2* and *ERF1* expression (Wu *et al*., 2008). As HDAC6 would have less impact on development than HDAC19 (Aufsatz *et al*., 2007; Probst *et al*., 2004; Tian and Chen, 2001), the study of HDAC6 in disease resistance is encouraging.

In summary, compelling evidence suggests that HDACs promote defence responses against pathogens, with those dependent on the JA pathway being the best characterized (Table 1). The distribution profiles of HDACs in whole-plant genomes and the identification of their critical substrates in infection still remain to be elucidated. The precise mechanisms by which these enzymes modulate gene expression are also presently unknown.

Histone methylation

Methylation of H3 lysine residues

In plants, mono-, di- and trimethylation (me1,2,3) of lysine residues (K) at positions 4, 9, 27 and 36 of H3 histone are well-characterized modifications (Pfluger and Wagner, 2007; Vaillant and Paszkowski, 2007). High-resolution distribution maps of H3K27me3 (Turck *et al*., 2007; Zhang *et al*., 2007c), H3K9me2 (Bernatavichute *et al*., 2008) and H3K4me1,2,3 (Zhang *et al*., 2009) have been described for Arabidopsis. In this genome, H3K27me3 is a major euchromatic repressive modification associated with more than 4000 genes in their repressed state, which is abundant at the 5′ end of transcribed regions and is maintained by mechanisms that are independent of DNA methylation and smRNAs (Zhang *et al*., 2007c). H3K9me3 is another repressive euchromatic modification from gene-encoding regions that does not overlap with H3K27me3 (Turck *et al*., 2007). H3K9me2, in turn, associates with heterochromatic TEs, pseudogenes and repeat elements (Bernatavichute *et al*., 2008; Fuchs *et al*., 2006; Gendrel *et al*., 2002; Mathieu *et al*., 2005; Turck *et al*., 2007). In contrast, all three H3K4 methylation marks are associated with active chromatin, occur almost exclusively on genes and at least one is present on two-thirds of all genes (Zhang *et al*., 2009). H3K4me3 and H3K4me2 are enriched at the promoter and 5′ gene regions, with H3K4me2 located further downstream, whereas H3K4me1 is enhanced at the transcribed and 3′ end

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Table 1 Effects of plant chromatin components on immune responses.

Protein/gene and function	Role on immunity	References
Maize HDACs targeted by the HC-toxin from *Cochiobolus carbonum*	na	Brosch *et al*. (1995); Johal and Briggs (1992); Ransom and Walton (1997); Walton (2006)
HDAC19 (*At4g38130*)	Activation of resistance against *Alternaria brassicicola*	Zhou *et al*. (2005)
HDA6 (*At5g63110*)	Activation of JA-sensitive genes	Wu *et al*. (2008)
ATX1(*At2g31650*), putative H3K4 methyltransferase	Activation of *WRKY70* and SA-sensitive genes and basal resistance to *Pseudomonas syringae*	Álvarez-Venegas *et al*. (2006, 2007)
PIE1 (*At3g12810*), SEF (*At5g37055*), and H2A.Z (*At1g52740* and *At3g54560*), members of the Swr1-like complex	Constitutive repression of the SA pathway	March-Diaz *et al*. (2008); March-Diaz and Reyes (2009)
BRM (*At2g46020*), Snf2-like protein	Constitutive repression of the SA pathway	Bezhani *et al*. (2007)
SNI1 (*At4g18470*), putative chromatin remodeller exclusive from plants	Constitutive repression of the SA pathway	Durrant *et al*. (2007); Mosher *et al*. (2006)
SYD (*At2g28290*), Snf2-like protein	Activation of JA/ET-sensitive genes and resistance against *Botrytis cinerea*	Walley *et al*. (2008)
DDM1 (*At5g66750*), Snf2-like protein affecting DNA methylation	Maintenance of NBS-LRR gene stability?	Stokes *et al*. (2002); Yi and Richards (2007, 2009)

ATX1, Arabidopsis Trithorax 1; BRM, Brahma; DDM1, Decrease in DNA Methylation 1; ET, ethylene; HDAC, histone deacetylase; JA, jasmonic acid; na, not available; NBS-LRR, nucleotide binding site-leucine-rich repeat; PIE1, Photoperiod-Independent Early flowering 1; SA, salicylic acid; SNI1, Suppressor of NPR1, Inducible 1; SYD, Splayed.

regions. Among these modifications, H3K4me3 is the only one that is associated with active transcription. Interestingly, H3K4me2 and H3K4me3 are mutually exclusive with all three types of DNA methylation (Zhang *et al*., 2009).

Similarly, high-resolution maps of H3K4me2 and H3K4me3, and DNA methylation from two complete rice chromosomes, indicate that H3K4 methylation is enriched at the 5′ end of genes, displays a direct correlation with transcript abundance and shows an inverse relationship with DNA methylation (Li *et al*., 2008).

H3K4 methylation and SA-dependent defences

Interestingly, methylation of H3K4 at the nucleosomes of *WRKY70* stimulates SA-dependent defence responses (Álvarez-Venegas *et al*., 2007) (Table 1). In Arabidopsis, WRKY70 regulates the cross-talk between the SA- and JA-sensitive responses by stimulating the first pathway to repress the second. In wild-type plants, *P. syringae* induces the expression of WRKY70 as well as the reduction of H3K27me2 and the accumulation of H3K4me2 and H3K4me3 at *WRKY70* nucleosomes. Importantly, the modifications found at WRKY70 nucleosomes in infected plants are associated with the activity of Arabidopsis Trithorax 1 (ATX1), a SET-domain protein that acts as an H3K4 methylase (Alvarez-Venegas *et al*., 2003). Infected *atx1* mutant plants show weak activation of *WRKY70* and, in these plants, *WRKY70* nucleosomes lack H3K4me3 but contain H3K27me2 and H3K4me2 levels comparable with those of infected wild-type plants. Thus, transcriptional activation of *WRKY70* is induced by ATX1 through apparent trimethylation of H3K4 (Álvarez-Venegas *et al*., 2007) (Fig. 1). As ATX1 influences the expression of *TIR-NBS-LRR* genes and several transcription factors involved in defence, such as *WRKY*s, *TGA-bZIP* and *ERF*s (Álvarez-Venegas *et al*., 2006), H3K4 methylation may also modulate responses against other pathogens. The effect of H3K4me3 on transcription is currently being investigated. Its enhancement in active genes is observed in plants and other organisms, where it may recruit factors that stimulate gene activity (Li *et al*., 2008; Sims and Reinberg, 2006; Zhang *et al*., 2009). However, H3K4me3 is also associated with inactive genes that initiate, but do not complete, transcription (Guenther *et al*., 2007). The latter observation is consistent with the detection of H3K4me3 in inactive *PR1* and *THI2.1* genes (Álvarez-Venegas *et al*., 2007).

CHROMATIN REMODELLERS

Chromatin remodellers are multiprotein complexes that alter histone–DNA interactions to move, disrupt or form nucleosomes through the use of energy derived from ATP hydrolysis. These complexes include catalytic subunits from the Sucrose nonfermenting 2 (Snf2) family of DNA helicases/ATPases and are recruited to specific promoters through the interaction with accessory proteins or transcription factors (Mohrmann and Verrijzer, 2005; de la Serna *et al*., 2006). Snf2 proteins are evolutionarily conserved and are classified into groups of subfamilies, as well as subfamilies based on archetypal members (Flaus *et al*., 2006; Knizewski *et al*., 2008). Although no Snf2 complex has been isolated in plants as yet, our knowledge of these proteins has markedly increased in recent years (Jerzmanowski, 2007). Arabidopsis contains 41 Snf2-like genes belonging to six

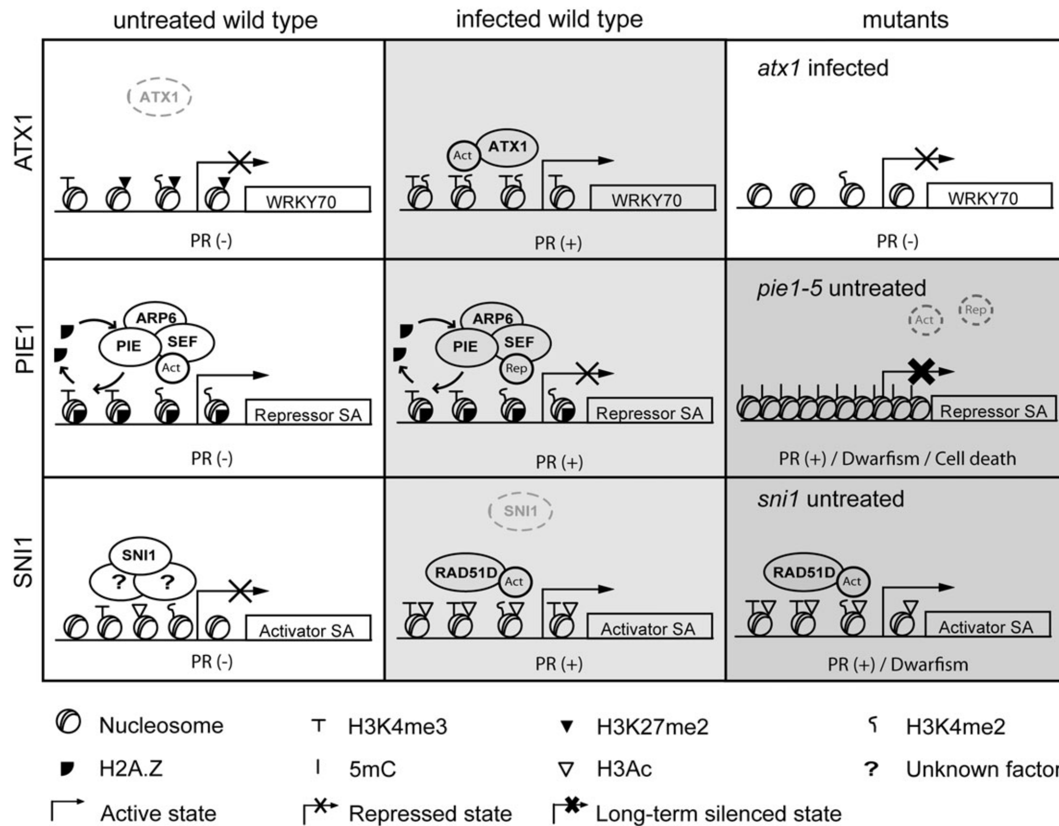

Fig. 1 Model for Arabidopsis Trithorax 1 (ATX1)-, Photoperiod-Independent Early flowering 1 (PIE1)- and Suppressor of NPR1, Inducible 1 (SNI1)-mediated epigenetic control of the salicylic acid (SA) pathway. Top: After infection, ATX1 binds the *WRKY70* nucleosomes and mediates the trimethylation of H3K4. This modification recruits transcriptional activators and leads to *WRKY70* expression and subsequent pathogenesis-related (*PR*) gene induction. The absence of H3K4-me3 on the *WRKY70* nucleosomes in the *atx1* mutant impairs the activation of *WRKY70* after infection. Middle: The Swr1 complex (PIE/SEF/ARP6) introduces H2A.Z at the promoter of a gene encoding a repressor of the SA pathway (Repressor SA). H2A.Z and methylated H3K4 maintain the accessibility of this promoter to transcriptional regulators. Activators (Act) or repressors (Rep) bind this region under basal or infection conditions, respectively. Although the removal of H2A.Z may take place during transcription (curved arrows), this modification protects the promoter from cytosine methylation (5mC). The absence of H2A.Z in *pie1-5* plants leads to chromatin compaction, DNA methylation and gene silencing, and the subsequent activation of defence mechanisms in noninfected tissues that causes growth retardation. Bottom: In basal conditions, SNI1 prevents the expression of positive regulators of the SA pathway (Activator SA) by maintaining local histone modifications that reduce chromatin accessibility. After infection, SNI1 is released from the promoter and chromatin is relaxed by RAD51D activity. SNI1 may affect chromatin structure through interactions with other proteins of unknown nature. The grey scale illustrates the degrees in SA pathway activation (white, no activation). Dwarfism and cell death phenotypes most probably result from constitutive activation of the pathway.

subfamily groups (http://www.chromdb.org), with four of these genes being functionally related to disease resistance (Table 2).

Photoperiod-Independent Early flowering 1 (PIE1)

PIE1 belongs to the Swr1-like group and Swr1 subfamily of Snf2 proteins (Table 2). The best characterized members of this group are Swr1 from yeast and SRCAP from humans, which are two conserved complexes formed by more than 10 subunits. These complexes regulate transcription by replacing the canonical H2A histone with the H2A.Z variant in a replication-independent process (Krogan *et al*., 2003; Mizuguchi *et al*., 2004). PIE1 is the catalytic component of the Arabidopsis Swr1-like complex, which includes other proteins, such as Serrated leaves and Early Flowering (SEF), Actin-Related Protein 6 (ARP6) and H2A.Z (Choi *et al*., 2007; Deal *et al*., 2007; March-Diaz *et al*., 2007; Noh and Amasino, 2003). PIE interacts with the H2A.Z histone protein encoded by the *HTA8* (*At2g38810*), *HTA9* (*At1g52740*) and *HTA11* (*At3g54560*) genes. The *pie1-5* null mutation disrupts the normal deposition of H2A.Z at multiple loci. Remarkably, 65% of the changes in gene expression that are detected in double homozygous *hta9-1/hta11-2* mutants are also found in *pie1-5* plants, suggesting that PIE1 and H2A.Z mediate common regulatory effects (Deal *et al*., 2007; March-Diaz *et al*., 2007).

Interestingly, the Arabidopsis Swr1-like complex regulates SA-dependent defence mechanisms. Nearly 40% of all genes

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Table 2 Classes of Arabidopsis Snf2 encoding genes involved in disease resistance.

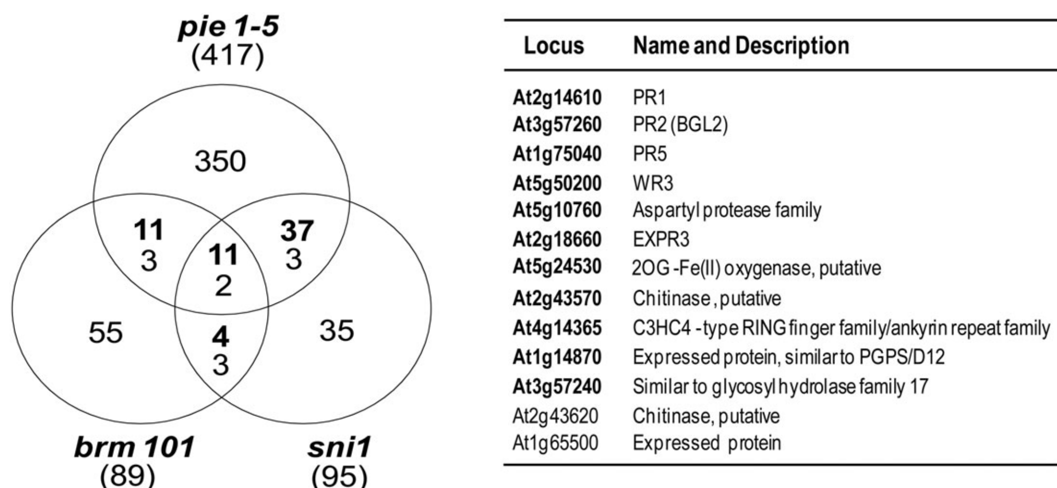
Groups of subfamilies*	Subfamilies	Genes involved in defence
Swr1-like	Swr1 (Swi2/Snf2-related 1)	*PIE1 (At3g12810)*
	Etl1 (Enhancer trap locus 1)	
	Ino80 (Inositol requiring protein 80)	
Snf2-like	Snf2 (Sucrose nonfermenting 2)	*SYD (At2g28290), BRM (At2g46020)*
	Iswi (Imitation switch)	
	Chd1 (Chromodomain and helicase-like domain 1)	
	Lsh (Lymphoid-specific helicase)	*DDM1 (At5g66750)*
	Mi-2 (Mitosis-2)	
	ALC1 (Amplified in Liver Cancer 1)	

*The groups are defined according to Knizewski *et al*. (2008) and Flaus *et al*. (2006). Only two groups of subfamilies contain members associated with disease resistance; the remaining groups include RAD54-like, RAD5/16-like, SSO1653-like and SMARCA1-like proteins.
BRM, Brahma; *DDM1*, Decrease in DNA Methylation 1; *PIE1*, Photoperiod-Independent Early flowering 1; *SYD*, Splayed.

with altered expression in *pie1-5* are sensitive to the SA analogue benzothiadiazole (BTH). In addition, *pie1-5* plants display enhanced resistance to virulent *P. syringae* and spontaneous cell death. Similar phenotypes, although weaker, are observed in untreated *sef* and *hta9/hta11* mutants (March-Diaz *et al*., 2008). Considering these features and the recessive nature of the *pie1-5* null mutation (Noh and Amasino, 2003), it is likely that PIE1 maintains negative control of the SA pathway in noninfected wild-type plants involving the action of SEF and/or H2A.Z (March-Diaz *et al*., 2008) (Table 1). The mechanisms underlying this control are unknown. It is well established that H2A.Z marks the 5′ end of genes in several eukaryotic genomes, including plants (Draker and Cheung, 2009; Guillemette and Gaudreau, 2006), although H2A.Z may be removed from nucleosomes during transcription (Deal *et al*., 2007; Zhang *et al*., 2005; Zlatanova and Thakar, 2008). H2A.Z is associated with acetylated (Auger *et al*., 2008; Durant and Pugh, 2007; Zhang *et al*., 2005) and methylated (Barski *et al*., 2007; Venkatasubrahmanyam *et al*., 2007) histone isoforms, but is mutually exclusive with DNA methylation (Henikoff, 2008; Zilberman *et al*., 2008). The mechanisms by which these chromatin marks are deposited at promoters and the effects of these marks on gene expression remain unresolved (Draker and Cheung, 2009; Guillemette and Gaudreau, 2006; Zlatanova and Thakar, 2008). In yeast, the Swr1 complex may be targeted to gene promoters by the recognition of DNA motifs and histone acetylation patterns. This recognition may involve the action of DNA binding factors, such as Reb1, as well as the Swr1 subunit Bdf1, whose bromodomains specifically bind acetylated tails of H3 and H4 (Raisner *et al*., 2005; Zhang *et al*., 2005). H2A.Z preferentially associates with methylated H3K4 and both marks may maintain the accessibility of regulatory proteins to chromatin (Draker and Cheung, 2009; Guillemette and Gaudreau, 2006; Venkatasubrahmanyam *et al*., 2007). Interestingly, Arabidopsis plants lacking Swr1 components have a reduction in H2A.Z as well as a reduction in histone acetylation and H3K4 trimethylation at the *FLC* locus (Deal *et al*., 2007; Lázaro *et al*., 2008). Therefore, the deposition of H2A.Z, methylated H3K4 and acetylated histones in plants may result from interconnected mechanisms. On the other hand, insertion of H2A.Z at the 5′ end of genes is inversely correlated with DNA methylation (Henikoff, 2008; Zilberman *et al*., 2008; Zlatanova and Thakar, 2008). Moreover, the incorporation of H2A.Z at these sites has been hypothesized to prevent gene silencing mediated by DNA methylation in Arabidopsis (Zilberman *et al*., 2008). On the basis of these data, we propose a model for Swr1-mediated negative control of SA-sensitive genes (Fig. 1). PIE and SEF may direct the incorporation of H2A.Z at promoters of genes encoding major repressors of the SA pathway. H2A.Z may maintain the competence of these genes for activation or repression and protect them from DNA methylation. As H2A.Z remains associated with chromosomes during mitosis (Deal *et al*., 2007), the effects of this mark can be eventually propagated to the daughter cells. The direct targets of Swr1 in infection are currently unknown. The identification and characterization of their DNA methylation status in *pie1-5*, *sef* and *hta9/hta11* mutants would be useful to assess the validity of the proposed model.

Splayed (SYD) and Brahma (BRM)

SYD and BRM belong to an Snf2 subfamily of essential proteins that are, as yet, poorly characterized at the functional level (Knizewski *et al*., 2008; Kwon and Wagner, 2007). The isolation of viable Arabidopsis null *syd* and *brm* mutant plants has allowed for the evaluation of their role *in vivo* (Flaus *et al*., 2006; Hurtado *et al*., 2006; Wagner and Meyerowitz, 2002). Similar to their homologues in vertebrates, SYD and BRM control vegetative and reproductive processes (Kwon and Wagner, 2007). Thus, several developmental genes are misregulated in *syd* and *brm* null mutants (Bezhani *et al*., 2007; Kwon and Wagner, 2007). In addition, *VSP2*, a gene sensitive to stress and JA, is stimulated by



Locus	Name and Description
At2g14610	PR1
At3g57260	PR2 (BGL2)
At1g75040	PR5
At5g50200	WR3
At5g10760	Aspartyl protease family
At2g18660	EXPR3
At5g24530	2OG -Fe(II) oxygenase, putative
At2g43570	Chitinase , putative
At4g14365	C3HC4 -type RING finger family/ankyrin repeat family
At1g14870	Expressed protein, similar to PGPS/D12
At3g57240	Similar to glycosyl hydrolase family 17
At2g43620	Chitinase, putative
At1g65500	Expressed protein

Fig. 2 Arabidopsis genes that are regulated by Suppressor of NPR1, Inducible 1 (SNI1), Photoperiod-Independent Early flowering 1 (PIE1) and Brahma (BRM). Left: Venn diagram including common genes that are upregulated in basal conditions in the *sni1* (Mosher *et al*., 2006), *brm101* (Bezhani *et al*., 2007) and *pie1-5* (March-Diaz *et al.,* 2008) mutants. The numbers in parentheses indicate the total number of genes upregulated in each mutant. Numbers in bold indicate genes that are sensitive to BTH. Right: Identity of the 13 genes which are common to all three mutants. The 11 genes that are sensitive to BTH are shown in bold.

SYD through the recruitment of SYD to the *VSP2* promoter, suggesting that this remodeller has a direct effect on transcription (Walley *et al*., 2008). SYD also regulates the JA-sensitive gene *PDF1.2a* and is required for the activation of JA-mediated defence responses against the necrotrophic pathogen *Botrytis cinerea* (Walley *et al*., 2008). Only a small fraction of Arabidopsis genes are affected by SYD or BRM, with some being sensitive to both co-regulators (Bezhani *et al*., 2007). Interestingly, a recent study has shown that noninfected *brm101* mutant plants display basal activation of pathogenesis-related (*PR*) genes (Bezhani *et al*., 2007) (Table 1). The *brm101* null mutation is recessive (Hurtado *et al*., 2006), suggesting that BRM, similar to PIE, maintains basal repression of the SA pathway. Interestingly, *brm101* plants display repression of auxin-related genes, such as *SAUR66* (*At1g29500*) and endo-xyloglucan transferase *EXGT-A1* (*At2g06850*) (Bezhani *et al*., 2007). This effect could be related to the overexpression of SA-dependent responses, as SA inhibits auxin signalling during plant defence (Wang *et al*., 2007).

PIE and BRM modulate defences that are sensitive to Suppressor of NPR1, Inducible 1 (SNI1)

SNI1 is a nuclear protein exclusively found in plants that lacks homology with chromatin-modifying enzymes and DNA-binding domains. This protein represses transcription, even in heterologous systems, most probably through a conserved mechanism, such as chromatin remodelling (Mosher *et al*., 2006). In addition, SNI1 inhibits somatic homologous recombination (Durrant *et al*., 2007), and both of these genomic responses seem to involve its interaction with other proteins, such as histone-modifying enzymes (Mosher *et al*., 2006). SNI1 was originally identified from a genetic screen for *npr1-1* suppressors, where the recessive *sni1* mutation rescued *PR* gene activation and resistance on the *npr1-1* background (Li *et al*., 1999). Similar to the *pie1-5* and *brm101* mutants, the untreated *sni1* plants overexpress BTH-sensitive genes and contain elevated levels of H3Ac and H3K4me2 at the *PR1* gene promoter. Therefore, it was suggested that SNI1 may inhibit basal *PR1* expression by reducing euchromatic marks at its promoter (Mosher *et al*., 2006). Interestingly, the defence phenotypes of *sni1* plants are suppressed by the mutation of RAD51D, a protein that promotes DNA homologous recombination during double-strand break repair events (Durrant *et al*., 2007). This finding is consistent with the hypothesis that SNI1 modulates plant immunity through chromatin remodelling (Table 1).

We compared the genes constitutively upregulated in *sni1* (Mosher *et al*., 2006), *brm101* (Bezhani *et al*., 2007) and *pie1-5* (March-Diaz *et al*., 2008) mutants. We found 13 genes that were common to all three mutants, including 11 genes inducible by BTH, such as *PR1*, *PR2*, *PR5* and others (Fig. 2). This observation reinforces the finding that the SA pathway is subject to epigenetic control, and reveals common effects of SNI1, PIE and BRM on this pathway. However, the promoters that are targeted by these remodellers remain to be identified. As mentioned previously, half of the genes that are overexpressed in untreated *sni1* plants are sensitive to BTH (Mosher *et al*., 2006), suggesting that SNI1 may control this pathway with a low energy cost by repressing the basal activity of positive regulators of the SA pathway (Fig. 1).

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Decrease in DNA Methylation 1 (DDM1)

DDM1 is a helicase from the Lsh subfamily (Table 2) that strongly affects genomic DNA methylation. In Arabidopsis, *ddm1* mutants display reduced cytosine methylation, TE activation and modification of histone marks in heterochromatic repeats (Jeddeloh *et al*., 1999; Miura *et al*., 2001; Tsukahara *et al*., 2009; Vongs *et al*., 1993). Deficiency in the mouse homologue *Lsh* produces similar alterations in heterochromatin (Dennis *et al*., 2001). Neither DDM1 nor Lsh encodes DNA methyltransferases (DNMTs) and this type of enzymatic activity is not significantly altered in *ddm1* or *Lsh* –/– tissues (Dennis *et al*., 2001; Kakutani *et al*., 1995). Therefore, DDM1/Lsh may regulate DNA methylation indirectly by modulating the access of DNMTs and/or DNA demethylases to the genome (Dennis *et al*., 2001; Gendrel *et al*., 2002; Zemach *et al*., 2005). In support of this idea, DDM1 has been shown to remodel nucleosomes *in vitro* independent of DNA methylation (Brzeski and Jerzmanowski, 2003).

Stable alleles that were not linked to the *ddm1* mutation were identified in the progeny of *ddm1* hypomethylated plants (Kakutani *et al*., 1996; Vongs *et al*., 1993). Among them, the *bal* defect causes dwarfism, curled leaves and enhanced pathogen resistance. These *bal* phenotypes depend on EDS1 and result from the overexpression of *R* genes from the Recognition of *Peronospora parasitica* 5 (*RPP5*) locus (Stokes *et al*., 2002; Yi and Richards, 2007). The *RPP5* locus includes the Suppressor of *npr1-1*, Constitutive 1 (*SNC1*), RPP4 and *RPP5*-like genes, whose expression is potentiated by an SNC1-dependent amplification loop and downregulated by smRNAs generated at the locus (Yi and Richards, 2007). The *bal* allele has been proposed to have an epigenetic nature, because it arose from a *ddm1* hypomethylation background and displayed high-frequency phenotypic suppression in ethyl-methanesulfonate-treated lines, apparently by reversion of the *bal* defect (Stokes *et al*., 2002). Surprisingly, it has been found recently that *bal* carries a tandem duplication of a 55-kb fragment from the *RPP5* locus, which probably originated from homologous recombination between two *R* genes from this locus. Several *R* genes are duplicated in *bal* plants; however, over-expression of *SNC1* sufficiently generates the *bal* phenotypes. Interestingly, the instability of these phenotypes seems to be caused by hypermutation of the duplicated copies of *SNC1* (Yi and Richards, 2009).

One question that arises is whether the generation of *RPP5* fragment duplication occurring in the *bal* background is mechanistically associated with DDM1 deficiency. In mammals, Lsh interacts with *de novo* DNMTs and HDACs, and this recruitment has been proposed to generate deacetylated, inactive chromatin that can be stabilized by DNA methylation at a later time (Myant and Stancheva, 2008; Zhu *et al*., 2006). Therefore, it is plausible that DDM1 has similar effects that reinforce chromatin compaction and prevent recombination between repeats from the *RPP5* cluster (Table 1).

DNA METHYLATION

Enzymes and patterns of plant DNA methylation

In several eukaryotes, methylation of the fifth carbon of cytosine (5mC) modulates chromatin structure and thus affects DNA recombination, genomic imprinting, gene expression and other genomic processes (Bender, 2004; Gehring and Henikoff, 2007; Henderson and Jacobsen, 2007; Zhang, 2008; Zilberman, 2008). In plants, DNMTs target cytosines located at both symmetric (CG and CHG; H corresponds to A, C and T) and asymmetric (CHH) sites. Methyltransferase 1 (MET1) maintains CG methylation (Finnegan *et al*., 1996), Chromomethylase 3 (CMT3) is primarily responsible for CHG methylation (Lindroth *et al*., 2001) and Domains Rearranged Methyltransferase1/2 (DRM1/2) mediates RNA-directed *de novo* methylation that affects cytosines in all contexts (Cao and Jacobsen, 2002; Chan *et al*., 2004).

High-resolution DNA methylation maps of the Arabidopsis genome have confirmed that all methylation types are concentrated in pericentromeric transposons and repetitive sequences. In addition, they revealed that one-third of all genes contain CG methylation in transcribed regions, whereas only a small fraction of these genes have methylation at their promoters (Cokus *et al*., 2008; Lister *et al*., 2008; Zhang *et al*., 2006; Zilberman *et al*., 2007). Similar but slightly distinct DNA methlyation traits were revealed by high-resolution profiling of DNA and H3K4 methylation in two complete rice chromosomes (Li *et al*., 2008).

The plant DNA methylation patterns are determined by DNMTs, proteins such as DDM1 (Jeddeloh *et al*., 1999; Vongs *et al*., 1993) and enzymes involved in histone PTMs. RNA-directed DNA methylation requires HDA6 (Aufsatz *et al*., 2007). CHG methylation correlates with H3K9me2 at TEs, pseudogenes and repeat elements, where gene silencing is reinforced by the combined actions of CHG and H3K9me2 methyltransferases (Bernatavichute *et al*., 2008; Fuchs *et al*., 2006; Gendrel *et al*., 2002; Jackson *et al*., 2002; Malagnac *et al*., 2002; Mathieu *et al*., 2005).

Remarkably, plant methylation patterns can be propagated to progeny and, conversely, can also be removed by the activity of 5mC glycosylases (Gehring *et al*., 2009; Kakutani *et al*., 1996; Zilberman, 2008). Therefore, the epigenetic marks that are generated by DNA methylation can permanently affect genomic activities, but can also facilitate a dynamic control of processes such as gene expression and DNA recombination.

Pathogen-induced plant DNA methylation changes

Interestingly, plant DNA methylation patterns become altered by pathogen infection. Work from our laboratory has described the

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occurrence of massive hypomethylation and net chromocentre decondensation in Arabidopsis tissues infected with *P. syringae*. This hypomethylation targets peri/centromeric 180-bp units, retrotransposons, mtDNA and other loci. In addition, it involves symmetric and asymmetric cytosines and takes place in the absence of DNA replication, suggesting that it occurs as a result of an active demethylation process (Pavet *et al*., 2006). Alterations in cytosine methylation in response to pathogens have been reported in previous studies (Guseinov and Vanyushin, 1975; Wada *et al*., 2004), but the effects of these alterations on disease resistance remain unknown.

Pathogen-induced host genome hypomethylation can influence the expression of defence genes. Chemically induced demethylation of the rice *R* gene *Xa21G* abolishes silencing of this gene and provides heritable resistance to *Xanthomonas oryzae* pv. *oryzae* (Akimoto *et al*., 2007). The biogenesis of smRNAs, which are strongly implicated in the post-transcriptional regulation of defences to pathogens (Jin, 2008; Ruiz-Ferrer and Voinnet, 2009), can also be modified by hypomethylation (Chan, 2008; Lister *et al*., 2008; Zhang, 2008).

At the structural level, hypomethylation may affect the stability of *NBS-LRR* genes. These genes are usually clustered in regions rich in TEs and repetitive sequences that concentrate repressive chromatin modifications, such as DNA and H3K9 methylation (Bernatavichute *et al*., 2008; Cokus *et al*., 2008; Lister *et al*., 2008; Zilberman *et al*., 2007). These modifications, together with smRNAs, prevent TE expression (Bernatavichute *et al*., 2008; Kato *et al*., 2003; Lister *et al*., 2008; Miura *et al*., 2001; Singer *et al*., 2001; Weil and Martienssen, 2008). Therefore, the release of DNA methylation from these regions may promote TE activation with a consequent impact on *NBS-LRR* gene integrity. The induction of TEs by biotic and abiotic stresses has been reported in many studies, and some of these stresses were later associated with genomic DNA methylation changes (Grandbastien *et al*., 2005; Hashida *et al*., 2003, 2006; Steward *et al*., 2002; Takeda *et al*., 1999). Remarkably, endogenous long-terminal repeat (LTR)-type retrotransposons, which are the major family of TEs in plants, have been found to be reactivated by DNA hypomethylation in Arabidopsis (Tsukahara *et al*., 2009). In addition, disruption (Luck *et al*., 1998), remodelling (Wang *et al*., 1998) and refunctionalization (Hayashi and Yoshida, 2009) of *NBS-LRR* genes by the insertion of TEs have been demonstrated in several plant genomes.

The reduction of 5mC residues from *NBS-LRR* gene clusters may also increase mispairing between repeats (Bender, 2004; Maloisel and Rossignol, 1998; Peng and Karpen, 2008; Weber and Schubeler, 2007). Recombination events involving repetitive sequences from *R* gene clusters contribute to the evolution of *R* genes (Baumgarten *et al*., 2003; McHale *et al*., 2006; Meyers *et al*., 2003). In support of this, a homologous recombination event that involved a 186-bp region common to *At4g16960* and *RPP4 R* genes from the *RPP5* locus has been shown to create a novel *NBS-LRR* gene in hypomethylated *bal* plants (Yi and Richards, 2009). In addition, DNA hypomethylation at *N*-like loci has been detected in the progeny of tobacco plants exposed to the tobacco mosaic virus, and the changes in methylation correspond to enhanced genomic rearrangements at these loci (Boyko *et al*., 2007). Similarly, somatic recombination increases in plants treated with DNA demethylation agents, elicitors, pathogens or abiotic stresses (Kovalchuk *et al*., 2003; Lucht *et al*., 2002; Molinier *et al*., 2006; Pecinka *et al*., 2009). Stress-induced, enhanced homologous recombination has been proposed to occur in the absence of pathogens (Kovalchuk *et al*., 2003) and may even be transmitted as a dominant trait to successive generations (Molinier *et al*., 2006). However, transgeneration memory of increased homologous recombination in response to stress does not seem to be a general response in plants (Pecinka *et al*., 2009). Therefore, it is possible that DNA hypomethylation promotes an increase in somatic recombination in tissues that are exposed to pathogens, and the resultant effect is transmitted to offspring as a stochastic process.

On the basis of these data, it is conceivable that DNA hypomethylation changes contribute to the generation of chromatin modifications that affect the activity or integrity of *NBS-LRR* genes, resulting in either an expansion or reduction in the subset of functional *R* genes in the plant. The genomic marks generated by DNA methylation can either be stably preserved through generations or erased under particular conditions.

CHROMATIN REMODELLERS AS PUTATIVE TARGETS OF MICROBIAL EFFECTORS

If the plant inducible defences that counteract pathogen attack are under epigenetic control, host components that are involved in these functions may constitute attractive targets for microbial effectors or toxins. Although this has not yet been demonstrated in plants, studies from the animal kingdom suggest that this may be true (Arbibe *et al*., 2007; Hamon *et al*., 2007). Resistance to the intestinal pathogen *Shigella flexneri* involves the activation of nuclear factor-κB-dependent proinflammatory genes by the phosphorylation of histone H3 at Ser10 (H3S10ph) at promoters. This modification has relevant effects on defence mechanisms, as the *S. flexneri* effector OspF inhibits mitogen-activated protein kinase (MAPK)-mediated H3S10ph at these sites and causes the reprogramming of host gene expression for its own benefit (Arbibe *et al*., 2007). OspF is a homologue of HopAI1 from plant pathogenic bacteria (Shan *et al*., 2007) and both effectors dephosphorylate MAPKs (Li *et al*., 2007). Moreover, HopAI1-mediated MAPK3/6 dephosphorylation inhibits basal defence in Arabidopsis (Zhang *et al*., 2007a). One question is whether HopAI1 inhibits disease resistance at the epigenetic level by affecting nuclear MAPKs. Although these enzymes have been

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found in plants (Ahlfors *et al*., 2004; Miao *et al*., 2007; Prestamo *et al*., 1999; Qiu *et al*., 2008), and proteins that mediate epigenetic modifications (core histones, Snf2 and other nuclear proteins) have been described as substrates of MAPK3/6 *in vitro* (Feilner *et al*., 2005), the phosphorylation of chromatin remodelling proteins by plant nuclear MAPKs has not been demonstrated.

CONCLUSIONS

Plant immune responses are subject to strict regulatory mechanisms that ensure prompt defence stimulation and robust basal defence repression without a fitness cost. Recent evidence has revealed that both kinds of mechanism involve epigenetic control. Proteins that affect histone PTMs, deposition of histone variants, ATP-dependent chromatin remodelling and DNA methylation modulate the expression of SA- or JA-dependent defence genes. Presumably, these chromatin remodellers bind gene promoters to alter their accessibility to transcriptional regulators. However, only a few promoters that are targeted by these components have been described thus far. Genomic binding studies will be required to identify gene promoters that are targeted by chromatin remodellers during infection in order to elucidate their impact on defence programmes. Further understanding of the signals and networks that trigger chromatin remodelling after the recognition of PAMPs or effectors is of equal importance. In addition, the extent and nature of epigenomic changes induced by different pathogens remain to be elucidated. Future research will be required to determine the specific epigenetic modifications affecting plant immunity that are transmitted to offspring and how the stability of these modifications is affected by the selective pressure of coexisting pathogens.

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