CURRENT REVIEW

Epigenetic Mechanisms: An Emerging Player in Plant-Microbe Interactions

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Plants have developed diverse molecular and cellular mechanisms to cope with a lifetime of exposure to a variety of pathogens. Host transcriptional reprogramming is a central part of plant defense upon pathogen recognition. Recent studies link DNA methylation and demethylation as well as chromatin remodeling by posttranslational histone modifications, including acetylation, methylation, and ubiquitination, to changes in the expression levels of defense genes upon pathogen challenge. Remarkably these inducible defense mechanisms can be primed prior to pathogen attack by epigenetic modifications and this heightened resistance state can be transmitted to subsequent generations by inheritance of these modification patterns. Beside the plant host, epigenetic mechanisms have also been implicated in virulence development of pathogens. This review highlights recent findings and insights into epigenetic mechanisms associated with interactions between plants and pathogens, in particular bacterial and fungal pathogens, and demonstrates the positive role they can have in promoting plant defense.

Apart from structural barriers and constitutive secondary metabolites (Bednarek et al. 2009; Clay et al. 2009), plants have evolved inducible defense mechanisms to counteract microbial infections, including pathogen-associated molecular pattern-triggered immunity (PTI) and pathogen-derived effector-triggered immunity (ETI) (Jones and Dangl 2006). The activation and effectiveness of PTI and ETI rely on the plant's capacity to extensively reprogram its gene expression upon recognition of pathogen infection. Among mechanisms involved in this vital transcriptional reprogramming, the importance of epigenetic modifications, such as DNA methylation, chromatin modifications and remodeling, in the transcriptional regulation of defense-related genes is rapidly emerging (Alvarez et al. 2010). Here, we summarize the most recent progress on studies of epigenetic regulation of plant-microbe (bacteria and fungi) interactions with a focus on the role of host genome DNA methylation and histone modifications in disease resistance and defense priming. Epigenetic regulation involved in plant-virus interaction, including virus-induced transgenerationally inherited epigenetic modifications, will not be discussed in this review. We refer readers to recent reviews on these topics by Baulcombe and Dean (2014) and Sharma et al. (2013).

DNA methylation in plant-microbe interaction.

Methylation of cytosine nucleotides in nuclear DNA is an epigenetic modification found in diverse eukaryotic organisms and, in plants, cytosine methylation can occur in all sequence contexts, i.e., CG, CHG, and CHH (H represents A, C, or T). Plant de novo methylation is catalyzed by DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2) through a plant-specific pathway known as RNA-directed DNA methylation (RdDM) (Matzke and Mosher 2014). Methylation at the symmetric CG and CHG contexts can be maintained during DNA replication by DNA METHYLTRANSFERASE 1 (MET1) (for CG methylation) and CHROMOMETHYLASE 3 (CMT3) (for CHG methylation). However, the maintenance of methylation at the asymmetric CHH context requires persistent de novo methylation by DRM2 during every cell cycle (Law and Jacobsen 2010; Matzke and Mosher 2014), except for long transposable element (TE) sequences in highly repetitive regions of the genome in which CHH methylation can be maintained by CMT2 (Zemach et al. 2013).

Pathogen recognition induces dynamic changes in plant DNA methylation. An early study by Guseinov and Vanyushin (1975) reported alterations in host plant cytosine methylation at the biochemical level in response to pathogen infection. At the molecular level, the impact of pathogen infection on plant DNA methylation patterns has been recently investigated in several studies that mainly focused on a few selected genes and genomic regions (Agorio and Vera 2007; Luna et al. 2012; Pavet et al. 2006; Wang et al. 2013). In *Arabidopsis*, infection with the virulent bacterial pathogen *Pseudomonas syringae* pv. *tomato* DC3000 resulted in DNA hypomethylation in various genomic sequences including peri/centromeric repeats and *Athila* retrotransposon. Hypomethylation was found to occur at both symmetric and asymmetric cytosines and takes place in the absence of DNA replication, suggesting that it occurred as a result of an active demethylation process (Pavet et al. 2006).

The plant genome hypomethylation associated with a defense response can influence the expression of defense genes. In *Arabidopsis*, ELONGATOR COMPLEX SUBUNIT2 (ELP2) is an epigenetic regulator required for rapid defense transcriptome reprogramming and genetically interacts with NONEXPRESSOR OF PATHOGENESIS-RELATED GENES1 (NPR1), a key transcription coactivator of plant defense (Cao et al. 1997; DeFraia et al. 2010; Wang et al. 2013). In the promoter region of *NPR1*, methylation occurs at all three sequence contexts (CG, CHG, and CHH). Generally, the DNA methylation levels of *NPR1* were higher in the *elp2* mutant than in the wild-type plants, suggesting that *ELP2* modulates basal DNA methylation levels of *NPR1*. Following infection with avirulent *P. syringae* pv. *tomato*

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DC3000/*avrRpt2* the DNA methylation levels at CG and CHG sites of *NPR1* were significantly reduced in wild-type plants but remained relatively high and stable in the *elp2* mutant. The *elp2* mutation, therefore, blocks pathogen-responsive DNA methylation changes in *NPR1* and delays the induction of defense genes, suggesting that *ELP2* is required for pathogen-induced DNA methylation changes in *NPR1* and plays an important role in regulating defense gene transcription (Wang et al. 2013).

A recent study investigated genome-wide changes of DNA methylation in *Arabidopsis* mutants defective in maintenance of CG methylation (*met1-3*) or non-CG methylation (*ddc*, or *drm1-2 drm2-2 cmt3-11*) before and after infection with virulent *P. syringae* pv. *tomato* DC3000 (Downen et al. 2012). Compared with wild-type plants, both mutant types were more resistant to bacterial colonization and failed to develop the characteristic chlorotic phenotype associated with compatible pathogen infection. Bacterial growth of avirulent *P. syringae* pv. *tomato* D3000/*avrPphB* strains was also more restricted in the *met1-3* and the *ddc* triple mutants, indicating that genome-wide loss of DNA methylation enhanced plant bacterial resistance. Upon infection with virulent *P. syringae* pv. *tomato*, both mutants showed differential regulation of numerous pathogen-responsive genes compared with wild-type plants, indicating that recognition of *P. syringae* pv. *tomato* infection induces transcriptional networks that interface with DNA methylation to activate a defense response. Overall, genome-wide DNA methylation levels of CG, CHG, and CHH sites were similar in infected (5 days postinfection [dpi]) and uninfected *met1-3* or *ddc* plants, but localized differential methylation occurred particularly in gene-rich regions of the genome, suggesting an involvement of pathogen-responsive methylation patterns in the regulation of defense genes (Downen et al. 2012). In addition, it was found that methylation levels at *P. syringae* pv. *tomato*-induced differentially methylated CG and CHG sites were also similar in plants exposed to salicylic acid (SA), whereas CHH methylation was unique to *P. syringae* pv. *tomato* infection, suggesting a differential role for this latter methylation pattern in plant stress responses (Downen et al. 2012).

Cytosine methylation in promoter-regions generally plays a repressive role in modulating gene expression; however, reduced DNA methylation at promoters does not necessarily lead to increased gene expression. *Pib* is a well-characterized rice blast disease-resistance gene of the nucleotide binding site leucine-rich repeat (NBS-LRR) superfamily. The expression level of *Pib* is usually low in uninfected rice plants, due to heavy CG-methylation at two critical regions of the *Pib* promoter, but strongly induced by the blast disease-causing fungal pathogen *Magnaporthe grisea*, which presumably helps promote resistance to this pathogen. Surprisingly, the methylation level at the two critical promoter regions of *Pib* was unaffected by *M. grisea* infection. In fact, partial demethylation by 5-azacytidine treatment actually reduced *Pib* expression and compromised blast disease resistance (Li et al. 2011). This result suggests that DNA methylation at the promoter of *Pib* has a positive role in the *M. grisea*-induced expression of *Pib*. Thus, DNA methylation may play both a positive and negative role in regulating plant defense gene expression.

RdDM pathway and plant-microbe interactions. As mentioned earlier, RdDM is a plant-specific de novo DNA methylation pathway that can induce cytosine methylation at all sequence contexts (Matzke and Moshier 2014). In this pathway, RNA polymerase IV (Pol IV), a plant-specific DNA-dependent RNA polymerase, produces transcripts that are copied by RNA-dependent RNA polymerase 2 into double-stranded RNA, which are then processed by DICER-LIKE 3 into 24-nt small interfering RNAs (siRNAs). One strand of these siRNAs is

loaded onto ARGONAUTE 4 (AGO4) to form an RNA-induced silencing complex, which binds, through sequence complementarity, to nascent long noncoding transcripts generated by another plant-specific RNA polymerase, Pol V. This Pol V complex subsequently recruits other downstream components of RdDM, such as DRM2, DRM1, and DEFECTIVE IN RNA-DIRECTED DNA METHYLATION 1 to the corresponding nuclear target locus, resulting in de novo DNA methylation and transcriptional silencing of the target locus (Matzke and Moshier 2014; Wang and Dennis 2009). RdDM targets primarily TEs and repetitive DNA regions in the genome but can also target protein-coding genes.

Components of the RdDM pathway appear to play an important role in regulating the plant's response to pathogen attack. AGO4 is one of the key components of the RdDM pathway and *Arabidopsis ago4* mutants have decreased levels of DNA methylation at different genomic locations, including TEs and repetitive DNA regions. This mutant shows increased susceptibility to virulent *P. syringae* pv. *tomato* DC3000 (Agorio and Vera 2007). Conversely, single mutants of NRPE1 (the largest subunit of Pol V) and NRPD2 (the second largest subunit for both Pol IV and Pol V) and double mutants of NRPD1 (the largest subunit of Pol IV) and NRPE1, all of which have lost the Pol V function, show enhanced disease resistance toward virulent *P. syringae* pv. *tomato* DC3000 when compared with wild-type plants, whereas the *nrpd1* single mutant plants showed no altered response (López et al. 2011). When mutants defective in different steps of the RdDM pathway, such as *nrpd1*, *nrpd2*, *nrpe1*, *ago4*, *drd1*, *rdr2*, and *drm1drm2*, were exposed to the necrotrophic fungal pathogens *Botrytis cinerea* and *Plectosphaerella cucumerina*, all except *nrpd1* showed increased disease susceptibility (López et al. 2011). Increased susceptibility to the fungal pathogen *Fusarium oxysporum* was also observed in *nrpe1* and *ago4* but not *nrpd1* mutants (Le et al. 2014).

The general lack of an effect of Pol IV mutations on plant responses to bacterial and fungal pathogens is interesting, as it suggests that, while the downstream RdDM complex involving Pol V, AGO4, and other factors is required for plant immunity, the upstream Pol IV component can be dispensable. Potentially, this could be due to some RdDM-inducing siRNAs being derived from Pol IV-independent transcripts, such as those generated by Pol V (López et al. 2011). The contrasting phenotypes observed in the *ago4* mutant and plants defective in Pol V in response to *P. syringae* pv. *tomato* DC3000 may be an indication that AGO4 has targets outside of the canonical RdDM pathway (Agorio and Vera 2007; López et al. 2011). Furthermore, the generally increased resistance of Pol V-defective mutants and other DNA methylation-deficient mutants to the biotroph *P. syringae* pv. *tomato*, in contrast to the enhanced susceptibility of Pol V-defective mutants to necrotrophic fungi, raises the possibility that RdDM has inverse effects on biotrophic and necrotrophic pathogen growth.

Recent evidence suggests that Pol IV is involved in plant resistance against *Agrobacterium tumefaciens*, resulting in reduced plant transformation efficiencies. *A. tumefaciens* is a soil borne bacterium that is widely used in plant genetic transformation due to its ability to insert its transfer DNA (T-DNA) into the host plant genome. The efficiency of *A. tumefaciens*-mediated stable transformation increased by 3.5-fold in *nrpd1*, a Pol IV-defective *Arabidopsis* mutant, when compared with wild-type plants. Furthermore, NRPD1 was shown to directly interact with *Agrobacterium* T-DNA in planta (Bilichak et al. 2014). These results suggest that Pol IV is directly involved in protecting the plant genome against *Agrobacterium* T-DNA insertion. However, it is also possible that a potentially reduced frequency of selectable marker gene silencing in the

NRPD1-defective mutant also contributes to the increased plant transformation efficiency.

DNA demethylation in transposon-containing promoters enhances plant disease resistance. Plants possess an active DNA demethylation process catalyzed by the DNA glycosylase family of DNA demethylases (Gong et al. 2002; Penterman et al. 2007; Zhu 2009). Four DNA demethylases, namely, DME (DEMETER), ROS1 (REPRESSOR OF SILENCING 1), which is also known as DML1 (DME-like 1), DML2, and DML3, have been identified in *Arabidopsis*. These DNA glycosylases remove 5-methylcytosine and replace it with an unmethylated cytosine through a base excision–repair mechanism (Zhu 2009). DME is thought to be expressed primarily in the central cell of the female gametophyte and required for maternal allele-specific expression of imprinted genes in the central cell and endosperm (Bauer and Fischer 2011). The other three *Arabidopsis* demethylases are believed to account for all demethylase activity in somatic tissues, but their biological functions are poorly understood. Of these three, ROS1 is the most highly expressed and has been shown to repress transcriptional silencing of transgenes and endogenous genes (Gong et al. 2002). No obvious developmental defects were observed in the *Arabidopsis ros1* mutant or *ros1 dml2 dml3* (*rdd*) triple mutant under normal growth conditions (Penterman et al. 2007), and only a small number of genomic loci in the *rdd* mutant showed changes in DNA methylation or gene expression (Lister et al. 2008; Penterman et al. 2007). As described below, *ros1* shows increased susceptibility to *P. syringae* pv. *tomato*.

The methylation-deficient mutants *met1* and *ddc* show enhanced resistance to *P. syringae* pv. *tomato* DC3000 (Downen et al. 2012), and mutants such as *ddc* and *met1 nrpd2*, which are impaired in both the RdDM pathway and maintenance of CG or CHG methylation, show greater resistance to *P. syringae* pv. *tomato* DC3000 (Yu et al. 2013), suggesting that DNA demethylation plays a positive role in plant disease resistance. Although widespread pericentromeric hypomethylation was not observed in these mutants in response to *P. syringae* pv. *tomato* DC3000 infection, numerous plant defense genes were located in those regions that did show differential methylation upon *P. syringae* pv. *tomato* DC3000 infection (Downen et al. 2012). Early studies have shown that DNA methylation contributes to transcriptional silencing of TEs and proximal genes within heterochromatin as well as dynamic regulation of some imprinted euchromatic genes (Lippman et al. 2004). In SA-treated *Arabidopsis* plants, transcriptional upregulation and demethylation of TEs was observed, with some of these TEs located in potential regulatory regions of stress responsive genes (Downen et al. 2012). The *ros1* mutant shows increased susceptibility to *P. syringae* pv. *tomato* DC3000, which coincides with substantial increased cytosine methylation in a TE (*AtREP11*) present in the promoter of a disease resistance gene (*RMG1* or *At4g11170*) and concomitant reduced expression of this gene (Yu et al. 2013).

We recently found that the triple DNA demethylase mutant (*rdd*) is more susceptible to the fungal pathogen *F. oxysporum* compared with wild-type Col-0 plants. A total of 348 genes were differentially expressed in *rdd* relative to the wild-type, of which the majority were downregulated, and a significant proportion of these downregulated genes have known functions in stress responses, including response to *F. oxysporum* infection. These results suggest that DNA demethylases are required for stress-responsive gene regulation and maintenance of expression or positive regulation of these genes by DNA demethylases is necessary for *F. oxysporum* resistance (Le et al. 2014). Forty-two of the 348 differentially expressed genes identified in the *rdd* mutant were TEs. In addition, *rdd*-downregulated stress response genes were enriched for short TE sequences in their

promoters. For example, the eight most downregulated genes in *rdd* plants all contained one or multiple TE sequences in their promoter regions, many of which had reduced CHH methylation in *rdd*. These promoter TEs appear specifically targeted by DNA demethylases, and RdDM-mediated CHH methylation seems to participate in DNA demethylase-mediated regulation of these stress response genes. Consistent with this hypothesis, many of the *rdd*-downregulated stress response genes are also suppressed in the RdDM mutants *nrpe1* and *nrpd1*. Overall, these results suggest that a primary function of DNA demethylases in plants is to regulate the expression of stress response genes by targeting promoter TE sequences.

Posttranslational histone modifications in plant-microbe interactions.

In eukaryotic cells, genomic DNA is packaged into a highly organized nucleoprotein complex known as chromatin. Nucleosomes, the basic building block of chromatin, contain two subunits of each histone H2A, H2B, H3, and H4. Histones are characterized by a large number of posttranslational modifications that regulate chromatin architecture and, consequently, the accessibility of the transcriptional complex to DNA. Generally, open chromatin increases the accessibility of the genome to the transcriptional apparatus, thereby enabling gene transcription to occur (Probst and Mittelsten Scheid 2015). Many different types of posttranslational histone modifications have been described, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, carbonylation, and glycosylation. The best understood modifications are lysine acetylation, lysine and arginine methylation, serine, threonine, and tyrosine phosphorylation, and serine and threonine ubiquitylation (Kouzarides 2007). Typically, histone acetylation by histone acetyltransferases (HATs) is associated with transcriptional activation, while histone deacetylation by histone deacetylases (HDAs) results in transcriptional repression. Depending on their targets, histone methylation or ubiquitination, or both, can either activate or repress transcription (Berger 2007). For instance, trimethylation of lysine 4 at histone 3 (H3K4me3) is associated with active gene transcription, whereas histone 3 lysine 27 trimethylation (H3K27me3) corresponds to transcriptional repression. Although the involvement of histone modification in plant development has been well established (Liu et al. 2010), their role in plant immunity is just emerging.

Histone methylation and demethylation. Histone methylation patterns are established by evolutionally conserved SET-domain proteins, also called histone methyltransferases (HMTs). The first example implicating HMTs in the plant immune response comes from work on ARABIDOPSIS TRITHORAX 1 (ATX1, also called SDG27) (Alvarez-Venegas et al. 2007). ATX1 is a Trithorax family, SET-domain protein with histone methyltransferase activity and it regulates expression of a large number of genes. In the *atx1* mutant, a high proportion of defense-related genes exhibit reduced expression, including a number of the *NBS-LRR* disease resistance genes and *WRKY* transcription factor genes, such as *WRKY70*, which is a key regulator of the antagonistic SA and jasmonic acid (JA) pathways required for plant defense (Alvarez-Venegas et al. 2006). Expression of *WRKY70* depends on ATX1-mediated H3K4me3 of the *WRKY70* promoter (Alvarez-Venegas et al. 2007).

In contrast, the SA-responsive gene *PATHOGENESIS-RELATED 1* (*PR1*) and JA-responsive gene *THI2.1* have H3K4me3 patterns different from those of *WRKY70* and these histone modification patterns appear unrelated to the gene transcription states (Alvarez-Venegas et al. 2007). H3K4me3 is present at *PR1* and *THI2.1* promoter chromatin before stress stimulation (Mosher et al. 2006), suggesting that these histone modifications keep the nucleosome in an

'actively' modified, permissive state in preparation for efficient expression when needed. These observations also suggest that other histone methyltransferases could be involved in regulating the chromatin configuration of *PR1* and *THI2.1*.

Similar to *WRKY70*, H3K4me3 modifications seem to be essential for the correct expression of two toll interleukin 1 receptor-nucleotide binding-LRR-encoding genes, *SUPPRESSOR OF NPR1*, *CONSTITUTIVE 1 (SNC1)* and *RECOGNITION OF PERONOSPORA PARASITICA 4 (RPP4)*, and for resistance against the oomycete pathogen *Hyaloperonospora arabidopsidis* (Xia et al. 2013). In *Arabidopsis* plants lacking functional MODIFIER OF SNC1,9 (MOS9), which functions together with histone lysine methyltransferase ARABIDOPSIS TRITHORAX-RELATED 7 (ATXR7), H3K4me3 levels are reduced at the promoters of *SNC1* and *RPP4*. Mutant *atxr7* plants have reduced expression levels of both *SNC1* and *RPP4* and are more susceptible to *H. arabidopsidis*, suggesting that ATXR7 plays a role in plant pathogen defense by regulating *SNC1* and *RPP4* expression levels via H3K4 methylation (Xia et al. 2013).

The major H3K36 di- and trimethyltransferase in *Arabidopsis*, SET DOMAIN GROUP 8 (SDG8), has been recently reported to be required for *P. syringae* pv. *tomato* DC3000-triggered plant defense (Palma et al. 2010). Gene expression and chromatin immunoprecipitation (ChIP) analyses showed that SDG8 is required for the expression of resistance (*R*) gene *LAZARUS 5 (LAZ5)*, which is achieved through H3K36me3 of *LAZ5* chromatin to maintain a transcriptionally active state. A significant decrease in H3K36me3 of *LAZ5* chromatin was observed in an *sdg8* mutant, which was associated with an absence of *LAZ5* expression. *LAZ5* is induced by *P. syringae* pv. *tomato* DC3000 inoculation in wild-type plants but not in *sdg8* plants and these mutants are more susceptible to virulent and avirulent *P. syringae* pv. *tomato* DC3000 (De-La-Peña et al. 2012; Palma et al. 2010). SDG8 may, therefore, function by H3K36 chromatin methylation of particular *R* genes, such as *LAZ5*, to establish a permissive chromatin structure for basal expression of *R* genes.

SDG8 has also been shown to play a role in plant defense against fungal pathogens by H3K36me3-mediated activation of a subset of genes within one or both the JA or ethylene (ET) signaling pathways (Berr et al. 2010). The expression level of *SDG8* was significantly induced by infection with the necrotrophic fungal pathogens *Alternaria brassicicola* and *B. cinerea*, while the loss-of-function *sdg8-1* mutant had reduced resistance to these same pathogens. Although the level of JA remained unchanged in *sdg8-1*, induction of several defense genes within the JA/ET signaling pathway (*PDF2.1*, *VSP2*, *ERF1*, and *MYC2*) was severely compromised in response to fungal infection or JA treatment. While whole-genome levels of H3K36me1, a modification associated with transcriptional repression, and H3K36me3 in Col-0 were not affected by *Alternaria brassicicola* infection, H3K36me1 levels increased at *PDF2.1* and *VSP2* and H3K36me3 levels decreased at the same genes. No change in histone modification was observed for these genes in *sdg8-1* upon *Alternaria brassicicola* infection (Berr et al. 2010). SDG8-mediated H3K36me3, therefore, appears directly associated with transcriptional induction of these pathogen defense genes. In addition, the levels of H3K27me3, a histone modification usually associated with transcriptional repression, were low at *PDF2.1* and *VSP2* for both Col-0 and *sdg8-1* and were unchanged following fungal infection. This could be beneficial for the plant, by enabling rapid transcriptional induction of these pathogen defense genes (Berr et al. 2010). The role of SDG8 in H3K36me3 regulation was further confirmed by genome-wide histone modification analysis, using ChIP sequencing (Li et al. 2015). The H3K36me3 levels of thousands of *Arabidopsis* genes were maintained by SDG8.

Approximately 700 genes were direct targets and were bound by this protein, while these same genes were hypomethylated at H3K36 in the *sdg8-5* mutant. The genes targeted by SDG8 were enriched for specific biological processes, including plant defense (Li et al. 2015).

The transcriptional repressive histone mark H3K27me3 is removed from several cold-inducible genes upon gene activation (Kwon et al. 2009). Two protein groups, the lysine-specific demethylase 1 group and the Jumonji C (JmjC) group have been reported to be involved in the demethylation of the histone lysine 27 residue. *JMJ705* is a rice JmjC gene that encodes a histone lysine demethylase that specifically reverses H3K27me2/3 and targets biotic stress-responsive genes (Li et al. 2013). *JMJ705* expression is induced by infection with the rice bacterial blight disease pathogen *Xanthomonas oryzae* pv. *oryzae*. Transgenic rice plants overexpressing *JMJ705* had reduced H3K27me3 levels in a number of genes associated with oxidative stress, JA biosynthesis and signaling as well as pathogenesis-related genes, such as *PR5* and *PR10*, and these plants showed enhanced *X. oryzae* pv. *oryzae* disease resistance. Conversely *jmj705* mutant rice plants showed increased susceptibility to this pathogen (Li et al. 2013). These results suggest that *JMJ705* contributes to plant defense by activation of defense-related genes via reduction of H3K27me3 levels at these genes.

Histone acetylation and deacetylation. The antagonistic activities of HATs and HDAs determine the acetylation level of lysine residues on histone tails. Acetylation was recognized as an indicator of actively transcribed genes, although HDAs can also be associated with transcriptional activation. Plant HDAs can be grouped into four families, RPD3, HDA1, SIR2, and HD2. Among them, HD2 is unique to plants (Pandey et al. 2002). Several lines of evidence suggest that HDAs may promote defense responses against plant pathogens. In *Arabidopsis*, two highly similar RPD3 and HDA1-type deacetylase genes, *HDA6* and *HDA19*, were induced by either JA or the ET precursor 1-aminocyclopropane-1-carboxylic acid, whereas this was not the case for other RPD3-like HDA genes, such as *HDA5*, *HDA8*, *HDA9*, and *HDA14* (Zhou et al. 2005). Overexpression of *HDA19* leads to increased expression of *ETHYLENE RESPONSE FACTOR 1 (ERF1)*, a gene that integrates JA/ET signaling pathways, and increased plant resistance to *Alternaria brassicicola*. In addition, several JA/ET-induced *PR* genes were also upregulated in the *HDA19*-overexpressing transgenic lines and were downregulated in the *HDA19*-silenced lines (Zhou et al. 2005). Similarly, *HDA6*-deficient lines had downregulated expression of JA-responsive genes (i.e., *PDF1.2a*, *VSP2*, *JIN1*, and *ERF1*), although no data were available on histone acetylation states of the differentially expressed genes investigated (Wu et al. 2008).

SA plays an important signaling role in establishing plant resistance against biotrophic pathogens such as *P. syringae* pv. *tomato* DC3000 as well as in systemic acquired resistance (SAR) activation (Jones and Dangl 2006). The SA pathway is also controlled by histone modifications. HDA19 is involved in the repression of SA-mediated defense responses in *Arabidopsis* and loss of HDA19 activity enhanced expression of many downstream SA-responsive genes, such as *PR1*, *PR4*, and *PR5* (Tian et al. 2005). Loss of HDA19 activity also increased SA content and the expression of genes required for accumulation of SA, resulting in enhanced resistance to *P. syringae* pv. *tomato* DC3000 (Choi et al. 2012). An earlier study proposed a role for HDA19 in positively regulating the expression of *PR1* and SA-mediated basal defense by suppressing the activity of transcriptional activator *WRKY38* and *WRKY62* through physical interactions with them (Kim et al. 2008); however, recent ChIP assays and quantitative polymerase chain reaction revealed that the promoters of *PR1* and *PR2* are direct targets of HDA19

and this protein is involved in histone deacetylation at these promoters (Choi et al. 2012). Expression analyses of *PR1* and *PR2* in *hda19*, wild type, and *Arabidopsis* mutants defective in SA biosynthesis indicate that HDA19, under unchallenged conditions, functions to maintain a low basal level of defense gene expression by modifying chromatin to a repressive state but also to ensure defense gene induction, without overstimulation, during pathogen attack. HDA19 is, therefore, a key regulatory component of plant defense and helps prevent unnecessary activation or self-destructive overstimulation of the defense response (Choi et al. 2012). Following pathogen attack, probably within different multiprotein complexes, HDA19 may participate through its histone deacetylase activity in the repression of several negative defense regulators, leading to the activation of plant immune responses. Further evidence for the involvement of histone modification control in the SA pathway and, consequently, disease resistance was shown in *F₁* hybrids of *Arabidopsis*, in which levels of histone H3 acetylation at the promoters of key SA biosynthesis genes (*PAD4*, *EDS1*) increased in *F₁* hybrids along with resistance to *P. syringae* pv. *tomato* DC3000 in these plants. A concomitant upregulation of *PAD4* and *EDS1* expression and increased SA accumulation in *F₁* hybrids infected with *P. syringae* pv. *tomato* DC3000 was observed compared with parental lines (Yang et al. 2015).

ELP3 is the catalytic subunit of the elongator complex and has a C-terminal HAT domain and an N-terminal cysteine-rich motif that resembles an iron-sulfur radical *S*-adenosylmethionine domain. Both domains are essential for ELP3 function in plant immunity (DeFraia et al. 2013) and ELP3 has intrinsic HAT activity and is capable of acetylating all four histone types (Winkler et al. 2002). *ELP3* loss-of-function mutant showed a delay in induction of all nine defense genes tested, including *PR1*, *PR5*, and *WRKY18*, following SA treatment or *P. syringae* pv. *tomato* D3000 infection (DeFraia et al. 2013). It is unclear, however, whether this delayed gene induction is linked with the HAT activity of ELP3. Similar to ELP3, ELP2 has a role in plant defense by interacting with *NPR1*, a key transcription coactivator of plant immunity (Wang et al. 2013). ELP2 also has a demonstrated regulatory role in both DNA methylation and histone modification. In *elp2* mutants, the levels of histone H3K9/14ac in *NPR1*, *PR2*, *PR5*, *EDS1*, and *PAD4* were lower compared with wild-type plants, although a similar phenomenon was not observed in *PR1* (Wang et al. 2013). This reduced histone acetylation may partially explain the delayed or decreased induction of defense genes in *elp2*. Compared with other epigenetic regulators, ELP2 is unique in that it regulates both global histone acetylation levels and genome-wide DNA methylation profiles. The delayed transcriptional response of *elp2* to pathogen infection likely results from altered chromatin structure caused by both reduced histone acetylation levels and altered DNA methylation profiles throughout the genome (Wang et al. 2013). Although the exact relationship between histone acetylation and the DNA methylation status in *elp2* is unknown, it would be of interest to determine whether histone acetylation is epistatic to DNA methylation during plant defense responses. Recent studies have also shown that HDA6 and MET1 interact directly and function together in locus-directed heterochromatin silencing (Liu et al. 2012; To et al. 2011). Whether elongator counteracts HDA/DNA methyltransferase complexes in epigenetic regulation of plant immunity is unknown (Wang et al. 2013). Both ELP2 and ELP3 are required for basal immunity but not for SAR (DeFraia et al. 2013; Wang et al. 2013).

HDT701, a plant-specific HD2 family histone H4 deacetylase, has been shown to negatively regulate rice innate immunity by modulating H4ac of defense-related genes (B. Ding et al. 2012). Overexpression of *HDT701* in transgenic rice leads

to decreased levels of H4ac and enhanced susceptibility to the rice pathogens *Magnaporthe oryzae* and *X. oryzae* pv. *oryzae*, the causal agents of blast and bacterial blight diseases, respectively. By contrast, silencing of *HDT701* causes elevated levels of H4ac and enhanced resistance to both pathogens, probably due to elevated transcription levels of defense-related genes (B. Ding et al. 2012). The H3ac level was not changed in transgenic rice plants overexpressing or silencing *HDT701*, suggesting that HDT701 is a histone H4-specific deacetylase. Compared with wild-type plants, the susceptible phenotype observed in the *HDT701* transgenic plants was obvious, while the resistant phenotype observed in the *HDT701*-silenced plants was relatively mild. In addition, no disease symptoms were observed in an incompatible reaction in transgenic plants overexpressing or silencing *HDT701*. These results suggest that HDT701 may modulate PTI rather than ETI. This hypothesis is supported by the expression profiles and H4ac levels of several pattern recognition receptors and PTI-related genes and by the generation of reactive oxygen species after flg22 and chitin treatment in *HDT701*-silenced transgenic plants (B. Ding et al. 2012). ChIP and transcriptional analyses showed that transcription and histone acetylation (H4K5 and H4K16) levels of *MAPK6* and *WRKY53* were increased in *HDT701*-silenced plants but decreased in overexpressing lines. Furthermore, HDT701 was found to directly bind the promoter regions of *MAPK6* and *WRKY53* but not *WRKY71*, suggesting that HDT701 may regulate basal resistance by controlling a specific group of defense-related genes (B. Ding et al. 2012).

Fungal pathogens are known to produce HDA inhibitors such as HC toxin and depudecin. Depudecin produced by *Alternaria brassicicola* inhibits HDA activity in vitro and in vivo (Kwon et al. 1998; Privalsky 1998), although depudecin-defective *Alternaria brassicicola* strains do still maintain virulence on *Arabidopsis* (Wight et al. 2009). In contrast, HC toxin produced by *Cochliobolus carbonum* is required for the pathogen to infect maize and probably acts by interfering with the expression of genes necessary for maize to mount an effective defense against *C. carbonum* through inhibiting HDA activity (Brosch et al. 1995; Ransom and Walton 1997). However, the extent to which different pathogens directly manipulate host cell transcription through modification of histone acetylation levels needs further investigation.

Histone ubiquitination. Protein ubiquitination is a common regulatory mechanism that controls a range of cellular processes in plants. Two types of protein ubiquitination, i.e., monoubiquitination and polyubiquitination, have been described. Histone H2B monoubiquitination (H2Bub) is mainly linked to transcriptional activation (Weake and Workman 2008), and in *Arabidopsis*, H2Bub is carried out by two E3 ubiquitin ligases, HISTONE MONOUBIQUITINATION (HUB1) and HUB2 (Cao et al. 2008). Loss-of-function mutants of *HUB1* show increased susceptibility to the necrotrophic fungal pathogens *B. cinerea* and *Alternaria brassicicola*, whereas overexpression of *HUB1* confers resistance to *B. cinerea* (Dhawan et al. 2009). Despite the obvious altered response to *B. cinerea* of these mutant plants, the expression of the JA defense marker *PDF1.2a* was not altered in either background, suggesting that HUB1 acts independently of the JA pathway (Dhawan et al. 2009).

Recent studies have shown that HUB1 and HUB2 regulate the expression of *R* genes *SNC1* and *RPP4*. HUB1 directly regulates chromatin configuration at the *SNC1/RPP4* locus and, consequently, the expression of both genes and other members at this *R* gene cluster. Loss of HUB1 or HUB2 function reduces *SNC1* upregulation following infection with *P. syringae* pv. *tomato* DC3000. *SNC1* is moderately up-regulated in wild-type plants following infection with this pathogen, which coincides with increased H2B monoubiquitination levels at the *SNC1*

locus, suggesting that induced expression of *SNC1* after pathogen infection is HUB1- and HUB2-dependent (Zou et al. 2014). However, responses to *P. syringae* pv. *tomato* DC3000 are unaltered in *hub1* and *hub1 hub2* plants compared with wild-type plants (Dhawan et al. 2009; Zou et al. 2014), although it is possible that *HUB1* plays a role in resistance to *H. arabidopsidis*, because *RPP4* confers resistance to isolates of this oomycete pathogen (Xia et al. 2013). *SNC1* expression can be regulated by both H3K4me3 and H2B monoubiquitination and the two modifications may interact (Xia et al. 2013; Zou et al. 2014). It will be of interest to determine whether one modification is dependent on the other at the *SNC1* locus, although it has been shown that HUB1-mediated histone H2B modification is independent of H3K4me2, H3K4me3, and DNA methylation (Dhawan et al. 2009).

In response to *Verticillium dahliae* (Vd) toxin *hub1* and *hub2* mutants showed a reduction in *V. dahliae* toxin-induced H₂O₂ production, cell death, and defense gene induction compared with wild-type *Arabidopsis* plants (Hu et al. 2014). Further studies found that HUB2 is a positive regulator of genes encoding protein tyrosine phosphatases, such as *AtPTP1* (PROTEIN TYROSINE PHOSPHATASE 1) and *AtPFA-DSP5* (PLANT AND FUNGI ATYPICAL DUAL-SPECIFICITY PHOSPHATASE 5). HUB2-mediated protein tyrosine phosphorylation appears to play a critical role in the regulation of cortical microtubules (MT), as *hub2* mutant plants have a weaker depolymerization of MT (Hu et al. 2014).

Epigenetic control of defense priming and transgenerational inheritance.

Defense priming. Priming refers to an induced physiological state that enables a plant to react more rapidly and efficiently to biotic or abiotic stress (Conrath 2011). Primed plants show faster and stronger activation of defense responses against pathogens. Plants pretreated with JA, SA, the SA analog acibenzolar *S*-methyl (BTH), proteins involved in plant hormone synthesis, signaling metabolites, or pre-exposure to pathogens, display enhanced transcription of defense-related genes and increased SAR upon subsequent attack, leading to increased resistance (Ameye et al. 2015; Conrath 2011; Jaskiewicz et al. 2011; Jung et al. 2009; Návárová et al. 2012; Noutoshi et al. 2012; Singh et al. 2012; V. Singh et al. 2014; Slaughter et al. 2012). In most studies, defense priming was observed after a single treatment of priming activator, although multiple short-time treatments were more efficient for priming (P. Singh et al. 2014). In contrast to the large body of information describing the phenomenon of defense priming, little is known about the underlying molecular basis. Accumulation of dormant mitogen-activated protein kinases, molecular modifications of primary metabolism pathways, and chromatin modifications have all been implicated in defense priming (Conrath 2011). P. Singh et al. (2014) showed that abiotic stresses such as heat, cold, or salt were equally efficient in promoting *Arabidopsis* resistance to *P. syringae* pv. *tomato* DC3000, suggesting that primed resistance against one type of stress can be induced by pre-exposure to other stresses and that different environmental stresses may induce defense priming by a common molecular mechanism.

Early studies suggested that the H3K4me3 histone configurations seen in *PR1* and *THI1.2* promoters may keep the nucleosomes in an 'actively' modified state in preparation for rapid changes in transcription during times of stress (Alvarez-Venegas et al. 2007). This model is supported by H3K4me3 modifications also being required for gene priming in several *WRKY* transcription coactivators (Jaskiewicz et al. 2011). *WRKY6*, *WRKY29*, and *WRKY53* show priming responses following application of the SA analog BTH as a priming agent

followed by water infiltration. Either BTH or water infiltration alone was not as effective in gene priming (Jaskiewicz et al. 2011). This study suggests that prestress application of BTH induced H3K4me3 chromatin modification of *WRKY* promoters, which facilitated the activation of gene expression upon a subsequent stress, such as water infiltration. Further studies using mutants defective in gene priming (*npr1*) or showing permanent priming (*cpr1* and *edr1*) and constitutive pathogen resistance (*sn1l*) showed a clear correlation between H3K4me3 and gene priming (Jaskiewicz et al. 2011).

The exact molecular mechanism that results in H3K4me3 accumulation at primed genes without active transcription is unknown but the 'open chromatin' characterized by H3K4me3 may provide access sites for transcription apparatus to facilitate the rapid, enhanced expression of primed defense related genes upon pathogen infection (Jaskiewicz et al. 2011). This hypothesis is supported by the enrichment of RNA polymerase II at the promoters of PTI marker genes *FRK1*, *WRKY53*, and *NHL10* in heat, cold, or salt stress-treated plants following, but not prior to, *P. syringae* pv. *tomato* DC3000 infection (P. Singh et al. 2014). Exposure to recurrent heat, cold, or salt stress was associated with increased H3K9ac, H3K14ac, H3K4me2, and H3K4me3 in the promoters of PTI-responsive genes *FRK1*, *WRKY53*, and *NHL10* and of SA marker genes *PR1* and *WRKY70*. At the *FPK1* promoter, increased H3K9ac and H3K14ac was present up to 2 kb upstream of the ATG translation initiation site. No increase in these histone modifications were observed at the promoters of the JA- and ET-responsive genes *PDF2.1*, *PR3*, and *PR4* (P. Singh et al. 2014). Chromatin modifications after exposure to abiotic stress were found in SA pathway genes like *PR1*; however, these changes were transient and regulated by HISTONE ACETYLTRANSFERASE 1. Increased H3K9ac, H3K14ac, H3K4me2, and H3K4me3 were observed in wild-type Col-0 plants but not in *hac1* mutant plants treated by repetitive heat, cold, or salt stress. Mutant *hac1* plants also did not show priming of PTI-responsive genes and increased bacterial resistance after repetitive stress (P. Singh et al. 2014).

SBT3.3, which encodes an extracellular subtilase, activates a SA-dependent enhanced activation of defense genes following the perception of pathogen signals, suggesting that this protein may be an integral component in inducing primed immunity in *Arabidopsis*. ChIP assays revealed that the enhanced gene expression triggered by *SBT3.3* was mediated by increased levels of H3K4me3 and H3K9ac at promoter regions of *PR1*, *WRKY6*, and *WRKY53* (Ramírez et al. 2013). This observation, together with the findings of Jaskiewicz et al. (2011), support the idea that *SBT3.3* acts as a positive regulator of chromatin remodeling at SA-responsive genes for primed immunity. The Jaskiewicz et al. (2011) study also revealed that localized foliar infection by *P. syringae* pv. *maculicola* can also prime *WRKY* genes in unchallenged leaves to augment increased responses to secondary stress. This priming activation is not only linked to increased methylation of H3K4 but also acetylation of several lysines of histone H4, suggesting that pathogen exposure induces one or more systemic signals that are also stored on gene promoters in uninfected leaves in the form of histone modifications (Jaskiewicz et al. 2011). Therefore, chromatin modifications seem to serve as a memory for priming systemic plant immunity as well as transgenerational SAR (discussed further below).

Two histone lysine methyltransferases, SDG8 and ATX1, have also been implicated in memory responses to repetitive mechanical stress for both the touch-inducible *TCH3* gene and dehydration stress-response genes in *Arabidopsis* (Cazzonelli et al. 2014; Y. Ding et al. 2012). It is of interest to know whether these proteins have a similar role in regulating memory response

to pathogens. Histone acetylation and methylation therefore appear to be important in establishing a 'permissive' chromatin context rendering defense genes transcriptionally inducible. More studies are necessary to firmly establish histone modification dynamics during pathogenic infection and to identify enzymes involved in the process.

Epigenetic regulation of transgenerational defense priming. The majority of studies on defense priming have been carried out by using the same plants to compare the levels of disease resistance before and after priming treatment. In fact, it was found decades ago that progeny from parental tobacco (*Nicotiana tabacum*) plants infected with *Tobacco mosaic virus* show increased resistance compared with the progeny of uninfected plants (Roberts 1983). This phenomenon, known as transgenerational induced resistance or transgenerational defense priming, has recently also been demonstrated by increased resistance in the progeny of plants attacked by nonviral pathogens or herbivores (Balmer et al. 2015; Holeski et al. 2012; Luna et al. 2012; Rasmann et al. 2012; Slaughter et al. 2012). Priming effects are not limited to plant defense and Molinier et al. (2006) found that increased levels of homologous recombination of genomic DNA persist for at least four generations in descendants from plants that were exposed to either ultraviolet radiation or flagellin, a bacterial protein containing the biologically recognized flg22 elicitor domain.

When challenged with virulent *P. syringae* pv. *tomato* DC3000 or virulent isolates of the oomycete *H. arabidopsidis*, the progeny of previously challenged *Arabidopsis* plants show enhanced disease resistance and strongly enhanced expression of defense-related genes involved in the SA signaling pathway, compared with progeny from uninoculated parents (Luna et al. 2012; Slaughter et al. 2012). When transgenerationally primed *Arabidopsis* plants were subjected to an additional priming treatment, their descendants displayed an even stronger primed phenotype, suggesting that plants can inherit increased sensitization for the priming phenomenon (Slaughter et al. 2012). These results demonstrate that the primed state of plants can be transferred to their progeny and confer improved protection from pathogen attack. The involvement of epigenetic mechanisms in transgenerational defense priming is further suggested by studies showing that DNA methylation-deficient *Arabidopsis* mutants mimic the primed plants in defense gene expression and disease resistance phenotype (López et al. 2011; Luna et al. 2012). Mutant *ddc* plants as well as the progeny of the *P. syringae* pv. *tomato*-infected *ddc* plants displayed increased resistance against the bacterial pathogen *P. syringae* pv. *tomato* DC3000 and enhanced susceptibility to the necrotrophic pathogen *Alternaria brassicicola* when compared with wild-type plants. These observations suggest that transgenerational resistance against *P. syringae* pv. *tomato* DC3000 involves DNA hypomethylation at non-CG sites (Luna et al. 2012). In further support, repeated inoculation of several RdDM pathways mutants (*ago4-3*, *clsyl-1*, *nrpd2a-1*, *drd1-6*, and *dcl3-1*) with *P. syringae* pv. *tomato* DC3000 did not result in their progeny being more resistant to the downy mildew pathogen *H. arabidopsidis* (Luna and Ton 2012). Furthermore, while the progeny of herbivore-exposed and JA-treated wild-type *Arabidopsis* showed increased resistance to the herbivore *Pieris rapae*, those of similarly treated *nrpd2a nrpd2b* double mutant and *dcl2 dcl3 dcl4* triple mutant plants failed to show an increase in resistance compared with untreated mutants (Rasmann et al. 2012). Together, these results suggest RdDM and non-CG methylation play a critical role in transgenerational priming of both JA and SA dependent defenses.

While these studies suggested the involvement of RdDM factors in transgenerational inheritance of defense priming, the

primed state of a gene is often associated with a change in histone modification rather than DNA methylation. Promoters of the SA-inducible *PRI*, *WRKY6*, and *WRKY53* genes in progeny of primed plants have increased H3K9ac, a chromatin modification associated with a permissive state of transcription. Conversely, the promoter of the JA-inducible *PDF1.2* gene has unaltered H3K9ac levels but increased H3K27me3, a modification associated with repressed gene transcription (Luna et al. 2012). Consistently, progeny of primed plants displayed enhanced induction of SA-inducible genes *PRI*, *WRKY6*, *WRKY53*, and *WRKY70* and reduced induction of JA-inducible genes *PDF1.2* and *VSP2*. These plants also showed enhanced susceptibility to the necrotrophic pathogen *Alternaria brassicicola* (Luna et al. 2012). Interestingly, the Pol V-defective mutants *nrpd2* and *nrpe1*, which mimic primed wild-type *Arabidopsis* plants with increased resistance to *P. syringae* pv. *tomato* DC3000 and enhanced induction of *PRI*, also showed an enrichment of active chromatin H3K9ac and H3K4me3 modifications in the promoter of *PRI* and no DNA methylation footprint (López et al. 2011). Together, these results suggest a direct link between RdDM and histone modification in the control of transgenerational inheritance of defense priming.

Epigenetic regulation in plant pathogens and its effect on pathogenesis.

Like plants, DNA methylation and histone modifications are important epigenetic mechanisms regulating development of plant pathogens (Jeon et al. 2015). A growing body of evidence suggests that epigenetic mechanisms are also used by pathogens to promote virulence during infection (Gómez-Díaz et al. 2012; Jeon et al. 2014). Epigenetic modifications of avirulence effector genes in plant pathogens have been proposed to serve as switches to escape from host recognition (Gijzen et al. 2014). Despite the emerging importance of epigenetic components in host-pathogen interactions, the role of such mechanisms regarding plant pathogens has received comparatively little attention.

In the phytopathogenic fungus *Fusarium fujikuroi*, the causal agent of the bakanae disease in rice, histone deacetylation appears to play a role in regulating the biosynthesis of secondary metabolites, including phytohormones, pigments, and mycotoxins, which are important for the virulence of the fungus (Studt et al. 2013). Deletion of two genes encoding HDA (*FfHDA1* and *FfHDA2*) resulted in changes in metabolite biosynthesis and disabled the capacity of the fungus to cause gibberellin-induced bakanae disease in rice. Furthermore, the *ffhda1* mutant showed differential expression of several secondary metabolite gene clusters and these gene clusters displayed significant alterations in their acetylation state compared with the wild-type *F. fujikuroi* (Studt et al. 2013). These observations suggest that HDA genes regulate secondary metabolism by controlling the level of acetylation and, hence, transcriptional activity of secondary metabolite biosynthesis genes. Strains of *C. carbonum*, a fungal pathogen of maize, with a mutated histone deacetylase-encoding gene, *HDC1*, showed a significant reduction in virulence that could be caused by decreased efficiency in fungal penetration of the maize leaf epidermis due to downregulated extracellular depolymerase activity (Baidyaroy et al. 2001). Similarly, it was found that FTL1, a component of the SET3 complex that functions as a histone deacetylase in *Fusarium graminearum*, is required for conidiation and pathogenesis of this pathogen on wheat and barley (Ding et al. 2009) and that *Tig1*, an *FTL1* ortholog of the rice blast fungus *Magnaporthe oryzae*, is important for conidiogenesis and growth of *M. oryzae* inside host cells (Ding et al. 2010). For the fungal pathogen *Rhynchosporium commune*, which causes barley leaf scald disease, histone acetylation is also important for its pathogenicity. When the *R. commune*

PP1 gene, which encodes a subunit of the HAT complex, is mutated, this fungus becomes nonpathogenic (Siersleben et al. 2014).

The oomycete pathogen *Phytophthora ramorum* has more than 100 known host species. The genetic diversity of *Phytophthora ramorum* is extremely low in Californian forests, but isolates of this pathogen show diverse phenotypic variation in colony morphology, colony senescence, and virulence. The phenotypic variation observed among different *Phytophthora ramorum* isolates was correlated with the host species from which the microbe was originally cultured. The majority of isolates from California coastal oak (*Quercus agrifolia*) showed de-repression of TEs and downregulation of crinkler effector homologs (CRN), a group of genes known to be involved in pathogenicity, which led to reduced isolate viability. By contrast, expression of CRN was significantly up-regulated in *Phytophthora ramorum* isolates from California bay laurel (*Umbellularia californica*). Because oak is a nontransmissible, dead-end host for *Phytophthora ramorum*, these results suggest that interactions between the oak host and *Phytophthora ramorum* triggers a physiological stress on *Phytophthora ramorum* that results in disruption of TE silencing and, hence, activation of TEs (Kasuga et al. 2012). TEs are usually a major target of epigenetic gene-silencing mechanisms and, therefore, it is reasonable to speculate that epigenetic mechanisms also may control some of the phenotypic differences existing between *Phytophthora ramorum* isolates from different host plants.

Concluding remarks.

Studies in the past decade have clearly established a role for epigenetic mechanisms in plant-pathogen interactions. DNA methylation and demethylation and various types of histone modifications have all been implicated in control of plant defense responses. These mechanisms can act independently or be coupled to regulate transcriptional activity of defense genes, although very little is known about the dynamics of interactions between different epigenetic mechanisms during plant disease responses. Our knowledge of the role of epigenetic mechanisms during plant-microbe interactions is currently fragmented and largely based on only a few epigenetic gene targets. Genome-wide analysis of changes in host plant DNA methylation and histone modification coupled with changes in gene expression during various plant-microbe interactions is likely to provide a better understanding of epigenetic regulation in plant defense. Similar analyses of pathogen genomes and transcriptomes will help elucidate epigenetic modifications that assist pathogen virulence and environmental adaptation. Recent advances in high-throughput sequencing technologies make such analyses now possible.

Epigenetic inheritance provides plants with both long- and short-term means to adapt to specific environmental conditions. Studies using *Arabidopsis* have provided compelling evidence for the involvement of epigenetic mechanisms in transgenerational defense priming. This phenomenon has gained much attention because defense priming is believed to confer a fitness advantage when compared with SAR responses that usually incur a high cost in the absence of pathogens. However, transgenerational defense priming has only been demonstrated in a few cases using model plants. Comprehensive studies on the long-term, multigenerational stability of defense priming are required and the general applicability of this defense mechanism to other pathosystems is yet to be determined. Nonetheless, a greater understanding of how epigenetic mechanisms contribute to plant defense and how pathogens may counteract this response for their own benefit could open new possibilities for novel crop protection strategies.

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