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Review

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Epigenetics: a catalyst of plant immunity against pathogens

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Summary

The plant immune system protects against pests and diseases. The recognition of stress-related molecular patterns triggers localised immune responses, which are often followed by longer-lasting systemic priming and/or up-regulation of defences. In some cases, this induced resistance (IR) can be transmitted to following generations. Such transgenerational IR is gradually reversed in the absence of stress at a rate that is proportional to the severity of disease experienced in previous generations. This review outlines the mechanisms by which epigenetic responses to pathogen infection shape the plant immune system across expanding time scales. We review the *cis*- and *trans*-acting mechanisms by which stress-inducible epigenetic changes at transposable elements (TEs) regulate genome-wide defence gene expression and draw particular attention to one regulatory model that is supported by recent evidence about the function of AGO1 and H2A.Z in transcriptional control of defence genes. Additionally, we explore how stress-induced mobilisation of epigenetically controlled TEs acts as a catalyst of Darwinian evolution by generating (epi)genetic diversity at environmentally responsive genes. This raises questions about the long-term evolutionary consequences of stress-induced diversification of the plant immune system in relation to the long-held dichotomy between Darwinian and Lamarckian evolution.

I. Introduction

1. Plant immunity: the blurred lines between innate and adaptive

To survive in their natural environment, plants rely on their immune system for protection against pests and diseases. The plant immune system includes an innate component, which is genetically determined, and an adaptive component, which is shaped by environmental factors. Unlike animals, in which innate and adaptive immunity are controlled by different mechanisms and cells, innate and adaptive immunity in plants are more closely intertwined as they rely on similar pathways and mechanisms (Mauch-Mani *et al.*, 2017).

The main pillar of the plant's innate immune system controls the perception of danger signals and the subsequent activation of

chemical and mechanical defences. These immune-eliciting signals are typically molecules from the attacking organism itself (nonself recognition; Bigeard *et al.*, 2015; Boutrot & Zipfel, 2017), or molecules that are produced as a consequence of cellular damage (damaged-self recognition; Li *et al.*, 2020). The resulting pattern-triggered immunity (PTI; see Box 1 for a list of acronyms and their meanings) protects against the majority of potentially harmful organisms and involves a multitude of signalling mechanisms, including pattern recognition receptors (PRRs; Macho & Zipfel, 2014) and phytohormones, such as jasmonic acid (JA) and salicylic acid (SA; Pieterse *et al.*, 2012). Specialised attackers, however, have evolved means to suppress PTI through effector molecules that de-regulate immune signalling and expression. In some interactions, this effector-triggered susceptibility (ETS) has resulted in an evolutionary arms race, which has equipped plants with specific resistance (*R*) genes that enable detection of immune-suppressing effector activity, while the corresponding attackers co-evolved new effectors that evade or suppress *R*-gene recognition (Jones & Dangl, 2006; Keller *et al.*, 2016). Plant *R*-genes commonly encode for intracellular receptors with nucleotide-binding and leucine-rich repeat (NLR) domains, which signal for a hypersensitive immune response that is associated with localised cell death (Wersch *et al.*, 2020). The resulting effector-triggered immunity (ETI) offers high levels of protection against mostly biotrophic attackers (Cui *et al.*, 2015). However, due to the gene-for-gene nature of ETI, each *R*-gene offers protection against a relatively narrow taxonomic range of attackers with limited evolutionary durability. In compatible interactions, where the attacker successfully infects and colonises the host, residual levels of PTI and ETI are commonly referred to as basal or quantitative disease resistance. This form of innate immunity is typically too weak to prevent disease or infestation by the attacker but nevertheless contributes to slowing down its colonisation (Poland *et al.*, 2009; Corwin & Kliebenstein, 2017). Like PTI, basal resistance is effective against a broad spectrum of microbes.

Genetically susceptible plants have the ability to adapt to biotic stress by raising their pre-existing level of innate immunity. This induced resistance (IR) is a form of phenotypic plasticity as it allows the plant to change its defence phenotype in response to specific environmental signals. Accordingly, IR is often regarded as the adaptive component of the plant immune system (Mauch-Mani *et al.*, 2017; for a recent classification of IR phenomena, see De Kesel *et al.*, 2021). Induced resistance can be triggered by a variety of danger signals, including microbe-associated molecular patterns (MAMPs), herbivore-induced volatiles from neighbouring plants, and endogenous defence signals (Conrath *et al.*, 2006; Heil & Ton, 2008). Well-known examples of long-lasting systemic IR responses are systemic acquired resistance (SAR) after localized pathogen attack (Fu & Dong, 2013) and induced systemic resistance (ISR) after colonisation by plant-beneficial microbes (Pieterse *et al.*, 2014). In most cases, IR develops after an initial burst of immune activity and involves prolonged up-regulation and/or priming of PTI-related defences that enable a faster and/or stronger immune response upon future attack (Gowda *et al.*, 2007; Wilkinson *et al.*, 2019). While IR can reach full protection if the augmented defence response precedes active immune suppression by the attacker, in most cases it offers improved levels of partial protection, which further restricts colonisation (Ahmad *et al.*, 2010). Since IR is based on an augmentation of innate immune responses, the pathways and mechanisms controlling IR and innate immunity overlap. However, there are regulatory mechanisms that are specific to IR. For instance, signals controlling the onset of SAR in systemic tissues, such as the FMO1/N-hydroxypipecolic acid signalling module, do not play a major role in local innate immune responses, but specifically amplify the immune signal in systemic tissues (Bernsdorff *et al.*, 2016; Hartmann *et al.*, 2018). Furthermore, while epigenetic mechanisms contribute to different forms of plant immunity, an increasing body of evidence suggests that epigenetic mechanisms are particularly important for the long-term maintenance of IR (Luna *et al.*, 2012, 2014; Rasmann *et al.*, 2012; López Sánchez *et al.*, 2016; Wilkinson *et al.*, 2019). Changes in DNA methylation and chromatin density offer a plausible explanation for the long-term nature of IR as they can direct changes in basal expression and/or responsiveness of defence genes that remain stable across cell divisions and generations.

Box 1 Acronyms and their meanings

5-mC: 5-methylcytosine
CRC: Chromatin remodelling complex
epiQTL: Epigenetic quantitative trait loci
epiRIL: Epigenetic recombinant inbred line
ERG: Environmentally responsive gene
ETI: Effector-triggered immunity
H3Kme: Methylation of lysine residue in histone H3
IR: Induced resistance
JA: Jasmonic acid
lncRNA: Long noncoding RNA
MAMP: Microbe-associated molecular patterns
miRNA: MicroRNA
mRNA: Messenger RNA
NLR: Nucleotide-binding and leucine-rich repeat protein
PRR: Pattern recognition receptor
PTGS: Post-transcriptional gene silencing
PTI: Pattern-triggered immunity
PTM: Post-translational modification (of proteins)
RdDM: RNA-directed DNA methylation
SA: Salicylic acid
SAR: Systemic acquired resistance
siRNA: Short interfering RNA
sRNA: Small RNA
TE: Transposable element
TIR: Transgenerational induced resistance
TSS: transcriptional start site

2. Plant epigenetics: an overview of the main mechanisms

The meaning of the term 'epigenetics' has changed since it was first used by Waddington in 1942, who defined epigenetics as the mechanisms by which genes and their products determine phenotypes. Epigenetics is currently defined as the study of changes in gene function that are mitotically and/or meiotically heritable,

and that occur independently from changes in DNA sequence (Armstrong, 2014). Accordingly, the cellular activities responsible for these heritable changes are referred to as epigenetic mechanisms.

DNA methylation is arguably the most extensively studied epigenetic mechanism in plants, which occurs when a methyl group forms a covalent bond with the 5-carbon in the pyrimidine ring of cytosine (C) and serves to repress the activity of transposable elements (TEs), invading viral DNA, and other potentially harmful genetic elements (Erdmann & Picard, 2020). In plants, DNA methylation occurs in three different sequence contexts: CG, CHG, and CHH (H = bases A, T, or C). *De novo* DNA methylation is established at unmethylated sequences by an RNA-dependent DNA methylation (RdDM) pathway, which is mechanistically connected to post-transcriptional gene silencing (PTGS). This pathway involves small RNAs (sRNAs) whose production is dependent on RNA polymerase II (Pol II); hence, it is commonly referred to as Pol-II-dependent RdDM (Cuerda-Gil & Slotkin, 2016; Erdmann & Picard, 2020). During this process, Pol-II transcription of active (unmethylated) TEs or microRNA (miRNA) precursors generates primary 21/22-nucleotide (nt) sRNAs that cleave TE-derived messenger RNAs (mRNAs). The degraded mRNAs can be processed into double-stranded RNAs by RNA-DEPENDENT POLYMERASE 6 (RDR6) and further sliced into 21/22-nt secondary short interfering RNAs (siRNAs) by DICER-LIKE (DCL) 2 and 4 (Cuerda-Gil & Slotkin, 2016). While the majority of these siRNAs are loaded onto ARGONAUTE 1 (AGO1) to reinforce post-transcriptional silencing of active TEs, some associate with AGO6 and interact with Pol-V-derived transcripts in a sequence-specific manner to recruit the DNA methyltransferase DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2) for the initiation of DNA methylation. This transcriptional silencing leads to the recruitment of histone-modifying enzymes that create a heterochromatic environment. This in turn facilitates the establishment of DNA methylation through Pol-IV dependent RdDM, which also requires DRM2 (Erdmann & Picard, 2020) but is controlled by 24-nt siRNAs from the Pol-IV-, RDR2-, and DCL3-dependent pathway (Matzke & Mosher, 2014). DNA methylation in the CG and CHG contexts is maintained by the DNA methyltransferases METHYLTRANSFERASE 1 (MET1) and CHROMOMETHYLASE 3 (CMT3), respectively, whereas DNA methylation in the CHH context is maintained by Pol-IV dependent RdDM and CMT2, which requires the chromosome remodeler DEFICIENT IN DNA METHYLATION 1 (DDM1; Zhang *et al.*, 2018).

To prevent the spread of DNA methylation from target TEs to neighbouring gene sequences, bifunctional 5-methylcytosine (5-mC) DNA glycosylase/lyases catalyse the first steps in a base excision repair pathway which results in active demethylation of cytosines (Zhang *et al.*, 2018; Roldan-Arjona *et al.*, 2019). There are four 5-mC DNA glycosylase/lyases in *Arabidopsis thaliana* (Arabidopsis): REPRESSOR OF SILENCING 1 (ROS1), DEMETER (DME), DEMETER-LIKE 2 (DML2), and DML3. Of these, ROS1 is the most active in vegetative tissues (Liu & Lang, 2020) and antagonises RdDM at TE-rich regions (Tang *et al.*, 2016). The *ROS1* gene itself is under positive transcriptional control by RdDM (Lei *et al.*, 2015; Williams *et al.*, 2015), creating a negative feedback loop to ensure tight homeostasis of DNA methylation at TE-rich regions. Another example of DNA methylation homeostasis comes from the INCREASE IN BONSAI METHYLATION2/ASI1-IMMUNOPRECIPITATED PROTEIN1/ENHANCED DOWNY MILDEW2 (IBM2/AIPP1/EDM2) protein complex (To *et al.*, 2015; Duan *et al.*, 2017), which binds to CHG-methylated heterochromatic introns to ensure full-length transcription of these genes. IBM1, which removes methylation of lysine residue 9 in histone H3 (H3K9me), is positively controlled in this manner, thereby creating negative feedback by reducing H3K9me2 and CHG methylation by the H3K9me2-binding CMT3 enzyme.

Enzymatic activities altering chromatin density are also considered to be epigenetic mechanisms since the associated changes can influence gene expression and be transmitted through cell division. Chromatin density is key to transcriptional activity as it determines access of the transcriptional machinery to DNA. Heterochromatic regions are tightly packed and transcriptionally silent regions that are typically associated with repetitive sequences and TEs, whereas euchromatin is less dense and enriched with transcriptionally active genes (Bourguet *et al.*, 2020). Chromatin density is dependent on the distribution of nucleosomes, each of which consists of two copies of four histone proteins (H2A, H2B, H3, H4), wrapped by *c.* 147 bp of DNA (Luger *et al.*, 1997) and connected by variable stretches of internucleosomal DNA associated with linker H1 histones (Rutowicz *et al.*, 2019). Chromatin remodelling complexes (CRCs) can release the binding between DNA and histones and alter nucleosome distribution by using adenosine triphosphate (ATP) (Han *et al.*, 2015). Eukaryotic CRCs include four major families based on their catalytic ATPase subunit: SWItch/Sucrose Non-Fermentable (SWI/SNF), imitation SWI (ISWI), chromodomain and helicase-like domain (CHD), and Inositol Requiring 80 (INO80; Bhadouriya *et al.*, 2021). Chromatin remodelling complexes often include or interact with enzymes controlling the deposition of histone variants or post-translational modifications (PTMs) of histones, respectively (Clapier *et al.*, 2017). These PTMs include phosphorylation, ubiquitination, SUMOylation, acetylation and methylation, collectively known as the histone code (Banniseter & Kouzarides, 2011). Many histone PTMs have been linked to changes in chromatin density. Of these, lysine acetylation and methylation at histone H3 are most commonly used as markers for the chromatin state: H3K9me and H3K27me mark heterochromatin, whereas H3K9ac, H3K4me and H3K36me2/3 mark transcriptionally active chromatin (Xiao *et al.*, 2016). In some cases, histone PTMs are causally linked to DNA methylation in a self-perpetuating mechanism, enabling their stable inheritance through cell division (Du *et al.*, 2015; Li *et al.*, 2018). However, recent evidence indicates that maintenance of repressive H3K27me3 is controlled by H3.1 at the replication fork (Borg *et al.*, 2021), representing a self-perpetuating mechanism that acts independently of DNA methylation.

Finally, activities by noncoding RNA (ncRNA) are often regarded as epigenetic mechanisms, because they can direct changes in DNA methylation and/or chromatin density. The group of ncRNAs can be divided into two categories: sRNAs (21–30 nt), including miRNAs and siRNAs (Zhu *et al.*, 2019), and long ncRNAs (lncRNAs; > 200 nt; Kapranov *et al.*, 2007). MiRNAs are responsible for PTGS through association with AGO proteins,

resulting in mRNA cleavage or translational repression at the endoplasmic reticulum (Li *et al.*, 2013; Fang & Qi, 2016; Liu *et al.*, 2018), whereas both siRNAs and miRNAs can drive transcriptional silencing through RdDM (Cuerda-Gil & Slotkin, 2016). LncRNAs are transcribed from both genic and nongenic regions by Pol-II, resulting in polyadenylated lncRNAs, or from Pol-IV and Pol-V, as part of RdDM (Budak *et al.*, 2020). LncRNAs can silence protein-coding genes in *cis* by participating in RdDM or recruitment of CRCs that facilitate repressive H3K27me3 deposition (Fonouni-Farde *et al.*, 2021). However, lncRNAs can also act in *trans* as target mimics of miRNAs, which reduces the silencing of miRNA-targeted genes (Wu *et al.*, 2013).

3. Epigenetics and plant immunity: an emerging field with cross-disciplinary implications

Throughout the late 1990s and early 2000s, independent research groups reported that mutations in epigenetic regulatory machinery affect plant disease resistance, while others reported that biotic stress exposure alters DNA methylation and histone PTMs (reviewed by Bruce *et al.*, 2007; van den Burg & Takken, 2009; Alvarez *et al.*, 2010). In subsequent years, more evidence emerged about the causal factors linking epigenetic mechanisms to plant immunity. López *et al.* (2011) demonstrated that Arabidopsis RdDM mutants express increased basal resistance against the bacterial pathogen *Pseudomonas syringae* pv *tomato* DC3000 (*Pst*), which was associated with priming of SA-dependent defence genes. In support, Yu *et al.* (2013) reported that the *ros1-4* mutant exhibits enhanced susceptibility to *Pst* and that PTI expression is associated with transcriptional downregulation of genes enabling RdDM. The availability of next-generation DNA sequencing allowed Dowen *et al.* (2012) to perform genome-wide analyses of DNA methylation and gene transcription in SA- and *Pst*-treated Arabidopsis, which revealed that immune-related changes in DNA methylation mostly occur at TEs and are associated with the induction of 21-nt siRNAs. Together, these findings pointed to a model whereby the repression of DNA methylation at TEs during the expression of plant innate immunity leads to the priming of defence genes. This was consistent with results reported by Jaskiewicz *et al.* (2011), who found that SAR in Arabidopsis is associated with permissive histone PTMs and priming of SA-dependent WRKY genes. On the other hand, heterochromatization and CHG methylation at the first intron of the *R*-gene *RPP7* was found to enable full-length transcription and ETI against avirulent downy mildew (Tsuchiya & Eulgem, 2013; Lei *et al.*, 2014), illustrating that heterochromatin and DNA methylation can also act as positive regulators of plant immunity. Finally, four independent research groups between 2010 and 2012 reported that progeny from plants exposed to pathogens, herbivores, and/or IR-eliciting agents develop transgenerational induced resistance (TIR) that is associated with priming of defence-related genes (Kathiria *et al.*, 2010; Luna *et al.*, 2012; Rasmann *et al.*, 2012; Slaughter *et al.*, 2012). Together, these studies established biological context and pointed to an important ecological function of epigenetic mechanisms in stress adaptation. Furthermore, they generated a foundation for further research into the epigenetic basis of plant immunity and the evolutionary implications thereof.

In this review, we will discuss the latest evidence on the regulatory functions of epigenetic mechanisms across different stages of plant adaptation to biotic stress, with a predominant focus on plant–pathogen interactions. The multifaceted impacts of epigenetics can be presented as a circular process that shapes the plant immune system over expanding time-scales (Fig. 1), ranging from stress-induced epigenetic changes controlling IR (stage 1), to longer-lasting consequences for the genetic diversification of immune-regulatory genes (stage 2), and wider implications for the evolution of the plant immune system (stage 3).

II. Stage 1: the regulatory role of pathogen-induced epigenetic change

1. Role of DNA (de)methylation

The primary function of DNA methylation – to repress activity of TEs, invading viral DNA, and other potentially harmful genetic elements – has been adopted by the plant immune system. Consequently, immune activation by biotic stress is associated with widespread loss of DNA methylation (hypomethylation) at TE-rich regions, while mutations reducing global DNA methylation increase biotic stress resistance (Dowen *et al.*, 2012; Atighi *et al.*, 2020; Annacondia *et al.*, 2021). This link between plant immunity and TE hypomethylation can be explained by the discovery that immune activation leads to transcriptional repression of genes encoding RdDM components. For example, *AGO4* is repressed in Arabidopsis treated with the bacterial PAMP flagellin-22 (flg22), while *AGO4a* expression in the wheat diploid progenitor *Aegilops tauschii* is repressed in response to *Blumeria graminis f. sp. tritici* (*Bgt*) infection (Yu *et al.*, 2013; Geng *et al.*, 2019). But how does DNA hypomethylation at TEs stimulate defence gene expression? The most straightforward mechanism is *cis*-regulation, whereby TE hypomethylation causes regional euchromatisation, which increases the accessibility of transcriptional machinery to nearby defence genes (Wilkinson *et al.*, 2019). For example, DNA demethylation by ROS1 facilitates MAMP-induced expression of the disease resistance gene *RMG1* by limiting RdDM at the 3′ boundary of a TE-derived repeat sequence embedded in its promoter (Halter *et al.*, 2021). Similarly, expression of the NLR gene *PigmS* in rice, which controls resistance against the rice blast fungus *Magnaporthe oryzae*, is repressed by RdDM at miniature inverted-repeat TEs (MITEs) in its promoter region (Deng *et al.*, 2017). Another example of *cis*-regulation comes from the positive effect of intronic CHG methylation on EDM2-dependent expression of full-length *NLRs*, such as *RPP7* (Tsuchiya & Eulgem, 2013; Lei *et al.*, 2014; Lai *et al.*, 2020). However, this defence-stimulatory activity by EDM2 is limited to selected ETI interactions, whereas a much larger number of *NLRs* are repressed by EDM2 through a function in genome-wide TE silencing (Lai *et al.*, 2020).

Recent genome-wide DNA methylation and RNA profiling experiments suggest that the resistance-enhancing activity of hypomethylated TEs may not only be limited to *cis*-acting mechanisms (Wilkinson *et al.*, 2019). Global transcriptome

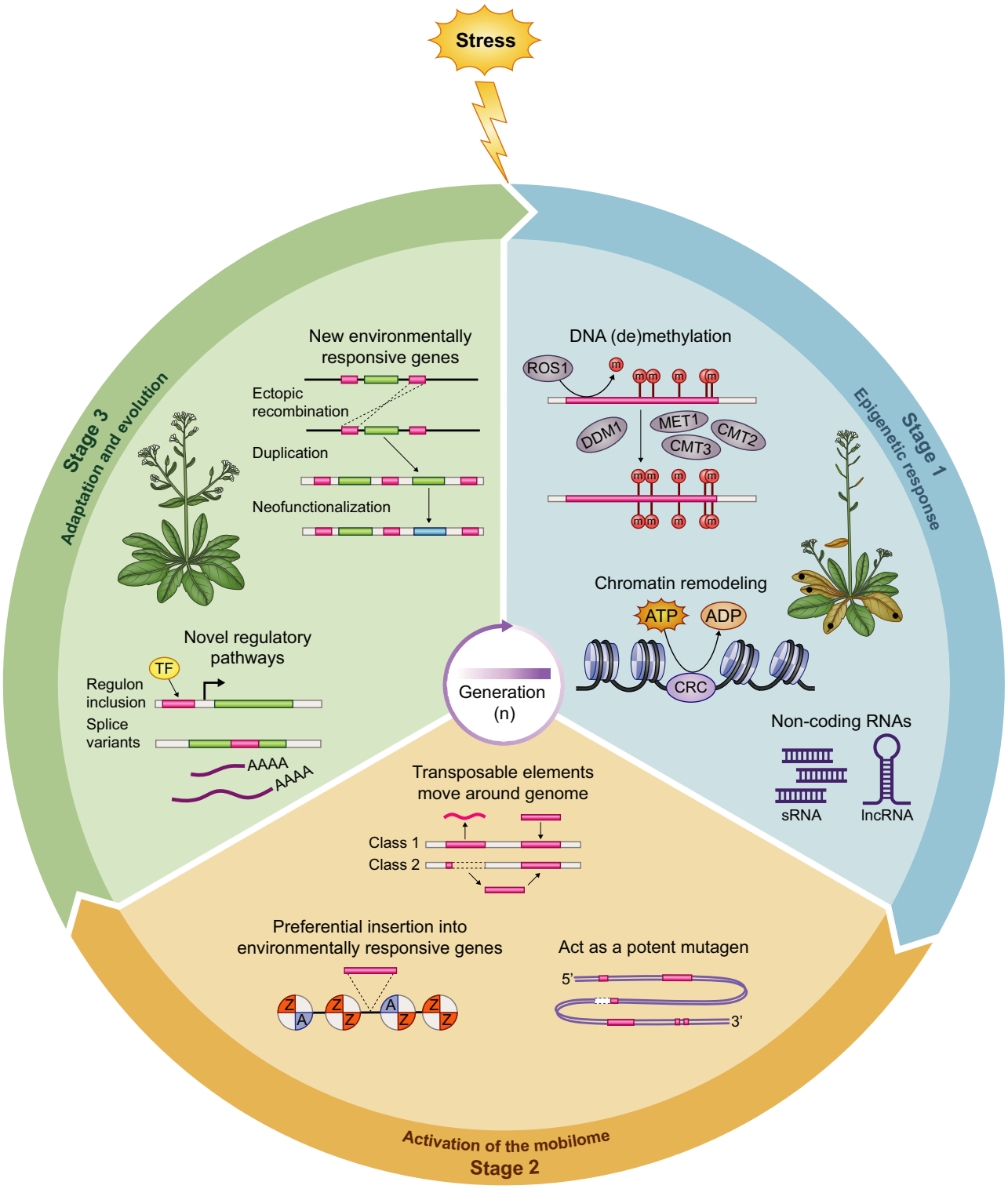

Fig. 1 The effects of stress-induced epigenetic changes on short- and long-term adaptation of the plant immune system. Stage 1: upon recognition of biotic stress, the plant epigenome undergoes changes that enable long-term up-regulation and/or priming of defence genes. This epigenetic stress memory can be transmitted to following generations and involves changes in the silencing of transposable elements (TEs) by DNA methylation, histone modifications, and noncoding RNAs. Stage 2: enduring stress increases the mutagenic activities of functional class I ('copy and paste') and class II ('cut and paste') TEs, collectively referred to as the mobilome. This process results in small and large mutations at the sites of excision (class 2) and insertion (class 1 and 2). Since TE integration is guided by the histone variant H2A.Z (Quadrana *et al*., 2019), the mobilome preferentially targets environmentally responsive genes (ERGs), which are enriched with H2A.Z (Coleman-Derr & Zilberman, 2012). Stage 3: mobilome-induced mutations increase the genetic diversity of ERGs, thereby accelerating the evolution of novel defence regulatory genes. Since TEs are tightly regulated by epigenetic mechanisms, the newly evolved defence genes and associated pathways remain under stress-dependent epigenetic control, thereby diversifying both the genetic and epigenetic regulatory potential to resist biotic stress.

analysis of the Arabidopsis mutants *ros1-4* and *nrpe1-1*, which are oppositely affected in TE methylation and basal resistance to virulent *Hyaloperonospora arabidopsidis* (*Hpa*), revealed that nearly half of the defence-related transcriptome during the early stages of *Hpa* colonisation was controlled by RdDM/ROS1-dependent TE (de)methylation. However, only 15% of these genes were associated with nearby TEs, indicating that the majority of RdDM/ROS1-dependent defence genes are regulated indirectly by hypomethylated TEs (López Sánchez *et al.*, 2016). Similarly, Halter *et al.* (2021) found that only 10% of all genes showing altered immune responsiveness in the *ros1* mutant were hypermethylated, demonstrating that most ROS1-repressed defence genes are controlled indirectly by DNA methylation. Furci *et al.* (2019) analysed a population of Arabidopsis epigenetic recombinant inbred lines (epiRILs) for basal resistance to virulent *Hpa*. These epiRILs are derived from a cross between wild-type Arabidopsis and the *ddm1-2* mutant and carry mosaic epigenomes due to stable inheritance of TE-rich hypomethylated DNA from the *ddm1-2* parent (Johannes *et al.*, 2009). In this population, four hypomethylated epigenetic quantitative trait loci (epiQTLs) were found to enhance resistance against virulent *Hpa* by priming SA-dependent and SA-independent defences. Surprisingly, however, whole-genome methylome and transcriptome analysis of *Hpa*-resistant epiRILs failed to identify hypomethylated TEs within the epiQTLs that were in close proximity to primed defence genes, suggesting that hypomethylated TEs in these regions prime defence genes through *trans*-acting mechanisms. In support, Cambiagno *et al.* (2018) reported that transient induction of TEs during infection by *Pst* leads to increased accumulation of RdDM-dependent siRNAs, which were complementary to both TEs and distal defence genes. Following the initial immune response, these siRNA-targeted TEs were re-silenced, but complementary defence genes remained active (Cambiagno *et al.*, 2018), indicating that siRNAs generated during the re-silencing of TEs *trans*-stimulate distal defence genes. Evidence supporting this model comes from Liu *et al.* (2018), who showed that 21/22-nt siRNAs *trans*-activate defence genes through interactions with AGO1 and SWI/SNF chromatin remodelling complexes (CRCs), as explained further in section II.4.

2. Role of chromatin remodelling proteins

CRCs play diverse roles in the regulation of plant immunity. For example, the SWI2/SNF2 class chromatin remodeler SPLAYED (SYD) in Arabidopsis shows transient induction by mechanical wounding and positively regulates genes controlling JA- and ethylene (ET)-dependent defence responses against the necrotrophic fungus *Botrytis cinerea* (Walley *et al.*, 2008). By contrast, the SWI/SNF2 ATPase BRHIS1 in rice suppresses defence gene promoters under normal growth conditions. Upon immune activation by *M. oryzae*, transcriptional down-regulation of *BRHIS1* and a concomitant increase in H2A.Xa and H2B.7 reduces BRHIS1 presence at defence promoters, leading to rapid induction of the associated defence genes (Li *et al.*, 2015). In Arabidopsis, various members of the SWI2/SNF2 subfamily have been implicated in the regulation of immune responses including BRAHMA (BRM) (Bezhani *et al.*, 2007), SWI2/SNF2-Related 1 CRC (SWR1-C) (March-Díaz *et al.*, 2008; Berriri *et al.*, 2016), and DDM1 (Li *et al.*, 2010). This regulation can be either positive or negative. For instance, the NLR gene *SNC1* is suppressed by DDM1 and SYD but is stimulated by CHROMATIN-REMODELING FACTOR 5 (Zou *et al.*, 2017; Ramirez-Prado *et al.*, 2018). Recently, the SWI/SNF protein SWP73A was implicated in the onset of ETI against avirulent *Pst* (Huang *et al.*, 2021). This protein suppresses multiple *NLRs*, either directly by binding to promoters, or indirectly via suppression of the RNA splicing regulator CDC5. Upon recognition of the *Pst* effector AvrRpt2, accumulation of miR3440 and siRNA-SWP73A silences *SWP73A*, resulting in the transcriptional induction and CDC5-dependent splicing of active *NLR* variants that stimulate ETI.

In addition to CRCs, microrchidia (MORC) proteins have emerged as conserved immune regulators (Koch *et al.*, 2017). Microrchidia proteins were first implicated in plant immunity by Kang *et al.* (2008) who identified *At*MORC1/CRT1 in a genetic screen for Arabidopsis mutants in ETI against Turnip Crinkle Virus (TCV). In subsequent years, it was found that *At*MORC1/CRT1 and *At*MORC2 act as positive regulators of early-acting PTI against nonhost pathogens (Kang *et al.*, 2012), while *At*MORC1, 2, 4, 6 and 7 contribute to ETI against avirulent *Hpa* (Harris *et al.*, 2016). Microrchidia proteins have also been implicated in immune regulation of barley (Langen *et al.*, 2014), potato, tomato, and *Nicotiana benthamiana* (Manosalva *et al.*, 2015), although their exact role differs between plant species. Mutations in *AtMORC1/CRT1* and *AtMORC6* lead to decondensation of pericentromeric heterochromatin, activation of TEs, and increased interactions between pericentromeric heterochromatin and euchromatic chromosome arms (Lorković, 2012; Moissiard *et al.*, 2012; Brabbs *et al.*, 2013; Feng *et al.*, 2014). In addition, plant MORCs have been reported to display ATP-dependent relaxation and catenation activity of DNA, the latter of which is suppressed upon their binding with SA (Manohar *et al.*, 2016). These biochemical activities support a function of MORCs in the control of higher-order heterochromatic interactions, which have been suggested to act as a *trans*-acting mechanism by which hypomethylated TEs prime distal defence genes (Furci *et al.*, 2019; Wilkinson *et al.*, 2019).

Like MORCs, the chromatin-remodelling ATPase-like protein MORPHEUS MOLECULE 1 (MOM1) silences TEs at pericentromeric heterochromatic regions independently of DNA methylation (Amedeo *et al.*, 2000; Vaillant *et al.*, 2006; Yokthongwattana *et al.*, 2010). The *mom1* mutant of Arabidopsis displays enhanced basal resistance to *Pst*, which is associated with elevated expression of *NLR/PRR* genes (Cambiagno *et al.*, 2018). Intriguingly, these defence genes are not in close proximity to MOM1-targeted pericentromeric TEs, but are homologous to RdDM-related siRNAs that accumulate in *mom1*. As noted under section II.1, these findings amount to evidence that hypomethylated TEs can *trans*-activate/prime distal defence genes through the production of siRNAs.

3. Role of post-translational modifications and histone variants

Post-translational modifications of histones have been implicated in priming and activation of plant immune responses

(Ramirez-Prado *et al*., 2018). For instance, treatment with the priming agent benzothiadiazole (BTH) induces deposition of euchromatic histone marks H3K4me3 H3K9ac and reduces heterochromatic marks H3K9me2 and H3K36me2 at primed SA-dependent defence genes (Jaskiewicz *et al*., 2011; López *et al*., 2011). H2 monoubiquitination is another histone PTM associated with plant immune regulation. Loss of H2 monoubiquitination ligases HISTONE MONOUBIQUITINATION1 (HUB1) and HUB2 is associated with increased susceptibility to necrotrophic fungi in Arabidopsis and tomato but causes increased resistance against hemibiotrophic *Pst* in tomato (Dhawan *et al*., 2009; Zhang *et al*., 2015). H2 monoubiquitination has also been linked to increased expression of three *NLRs* in the Arabidopsis *RPP4* cluster (Zou *et al*., 2014; Ramirez-Prado *et al*., 2018).

In addition to their role in PTMs of histones, CRCs can exchange histone variants in response to environmental stress. The highly conserved H2A variant H2A.Z is predominantly deposited by SWR1-C in environmentally responsive genes (ERGs), which are transcriptionally responsive to cell-external stimuli and play a role in environmental and developmental plant responses (Box 2; Coleman-Derr & Zilberman, 2012). Only a handful of studies have investigated the role of SWR1-C and H2A.Z in biotic stress responses. Mutations in the SWR1-C subunits PHOTOPERIOD-INDEPENDENT EARLY FLOWERING1 (PIE1), SWR1-C SUBUNIT 6/SERRATED LEAVES AND EARLY FLOWERING (SWC6/SEF), and ACTIN-RELATED PROTEIN 6 (ARP6) reduce H2A.Z accumulation (Box 2) and alter resistance to biotrophic and necrotrophic pathogens, albeit with partially contrasting results (March-Díaz *et al*., 2007; Berriri *et al*., 2016). Transcriptome analysis suggested complex specialised functions of these SWR1-C subunits in defence gene regulation (Berriri *et al*., 2016). More recently, Cai *et al*. (2021) confirmed that components of SWR1-C have different effects on plant immunity: while the *pie1* mutation caused enhanced susceptibility to the necrotrophic fungus *Slerotinia sclerotiorum*, the *arp6* and *sef* mutations did not affect resistance in the background of wild-type accession Col-0. By contrast, *arp6* and *sef* affected *S. sclerotiorum* resistance in genetic backgrounds impaired in ERECTA kinase signalling. It was concluded that the ERECTA pathway enhances binding of WRKY33 to promoters of resistance-enhancing YODA DOWNSTREAM genes during *S. sclerotiorum* infection, which requires deposition of H3K4me3, and H2A.Z at ± 1 nucleosomes. Together, these studies highlight how H2A.Z incorporation can have both stimulating and repressive effects on defence-related gene expression, which depend not only on the plant–pathogen interaction but also SWR1-C composition, histone PTMs and genetic background.

Despite the complex regulation of defence genes by SWR1-C, H2A.Z eviction is thought to be a key step in the transcriptional activation of ERGs (Box 2). Wang *et al*., (2020) recently provided evidence that the histone chaperones NAP1-RELATED PROTEIN1 and 2 (NRP1 and NRP2) counteract SWR1-C activity by removing H2A.Z from nucleosomes in Arabidopsis. Notably, the *nrp1 nrp2* double mutant has been reported to be more susceptible to *S. sclerotiorum* and *Pst*, while overexpression of *NRP1* increased basal resistance against these pathogens, which was associated with transcriptomic enrichment of defence-related genes (Barna *et al*., 2018). Together, these findings suggest that NRP1/2 evicts H2A.Z from nucleosomes of defence-related genes to enable full transcriptional induction. To confirm this role of NRP1/2, future experiments need to establish that the reduced responsiveness of defence genes in the *nrp1 nrp2* mutant during pathogen infection is associated with a lack of H2A.Z eviction, using RNA-seq in combination with Chip-seq of H2A.Z- and NRP1/2-associated DNA.

Box 2 Transcriptional regulation by H2A.Z

H2A.Z is a highly conserved histone variant that diverged from other H2As before the diversification of eukaryotes. Its abundance in the genome is enriched at nucleosomes flanking the transcriptional start sites (TSSs) of genes (± 1 nucleosomes) (Talbert & Henikoff, 2010). In Arabidopsis, H2A.Z is encoded by three genes (*HTA8*, *HTA9*, *HTA11*; Yi *et al*., 2006) and is deposited by the SWR1 complex (SWR1-C). The catalytic subunit of SWR1-C is PIE1 but other noncatalytic subunits, such as ARP6 and SWC6/SEF, are also crucial for the nucleosomal incorporation of H2A.Z (Aslam *et al*., 2019). Recent studies have provided mechanistic evidence for targeted H2A.Z deposition in Arabidopsis: SWC4 and MBD9 guide H2A.Z deposition near TSSs by recognising DNA sequences and chromatin features associated with these regions, respectively (Gómez-Zambrano *et al*., 2019; Potok *et al*., 2019; Sijacic *et al*., 2019; Luo *et al*., 2020). Despite this, the role of H2A.Z on gene expression remains puzzling. In Arabidopsis, H2A.Z occupancy at the +1 nucleosome has both repressive and stimulating effects on gene expression (Lei & Berger, 2020), which may depend on other PTM histone marks, such as ubiquitination and acetylation (Crevillén *et al*., 2019; Gómez-Zambrano *et al*., 2019). By contrast, H2A.Z incorporation into gene-body nucleosomes generally has a repressive effect on transcription (Coleman-Derr & Zilberman, 2012; Lei & Berger, 2020); these genes tend to be environmentally responsive, and their activation is associated with H2A.Z eviction (Cortijo *et al*., 2017; Dai *et al*., 2017; Sura *et al*., 2017). Hence, H2A.Z controls both abiotic stress responses (Hu & Lai, 2015; Jarillo & Piñeiro, 2015; Sura *et al*., 2017; Kumar, 2018) and plant immune responses to biotic stress (March-Díaz *et al*., 2008; Berriri *et al*., 2016; Cai *et al*., 2021) through transcriptional regulation of environmentally responsive genes (ERGs).

4. Role of noncoding RNAs and nuclear AGO1

Hundreds of long noncoding RNAs (lncRNAs) are differentially expressed in response to fungal pathogens in several plant species, including maize, wheat, barley, and tomato (Zhang *et al*., 2020). However, a functional link between these pathogen-inducible lncRNAs and plant immunity has currently only been characterised in Arabidopsis. Liu *et al*., (2012) performed a screen for lncRNAs that are induced by the PTI-eliciting MAMP elf18, resulting in the identification of ELF18-INDUCED LONG-NONCODING RNA1 (ELENA1). Subsequent research revealed that overexpression of ELENA1 augments defence gene expression against *Pst* by evicting the repressor FIBRILLARIN 2 from the activating Mediator subunit 19a of the Pol-II transcription mediator complex

(Seo *et al.*, 2019). It is plausible that other PTI-related lncRNAs stimulate defence genes in *trans* through target-mimicry of corresponding miRNAs (Wu *et al.*, 2013; Canto-Pastor *et al.*, 2019).

The wide-ranging regulatory activities of small RNAs are commonly assumed to have evolved from their function in combating viruses. Plants can process viral RNA/DNA into viral sRNAs via DCL and RDR proteins, which are loaded onto AGO proteins to target viral RNA for degradation and achieve antiviral immunity (Zhu *et al.*, 2019). Endogenous miRNAs have been shown to regulate ETI by suppressing *NLR* expression via PTGS in the absence of an ETI-eliciting pathogen. The degraded *NLR* mRNAs can be processed into phased secondary siRNAs (phasiRNAs) that can silence other homologous *NLRs* in *trans* (Halter & Navarro, 2015). Recent evidence revealed that some miRNAs can also stimulate ETI by repressing the SWP73A SWI/SNF protein, which suppresses *NLR* expression via direct and indirect mechanisms (Huang *et al.*, 2021). MiRNAs also play a role in PTI. For instance, *miR160a* positively regulates MAMP-induced callose deposition, whereas *miR398b* and *miR773* suppress MAMP-induced callose and basal resistance to *Pst* (Li *et al.*, 2010).

As detailed in section I.2, 24-nt siRNAs predominantly suppress plant immunity through RdDM. By contrast, 21/22-nt siRNAs can have opposite activities by stimulating defence gene expression through a novel nuclear function of AGO1. Liu *et al.* (2018) demonstrated that siRNA-loaded AGO1 associates with the SWI3 and BSI subunits of SWI/SNF CRCs at ERGs, where it recruits Pol-II. Moreover, priming plants with JA, flg22, or BTH increased nuclear AGO1 occupancy at ERGs with associated immune-regulatory functions (Liu *et al.*, 2018). Given the emerging evidence that hypomethylated TEs can *trans*-regulate defence gene expression (Cambiagno *et al.*, 2018; Furci *et al.*, 2019; Wilkinson *et al.*, 2019), we propose a model in which the re-silencing of hypomethylated and transcriptionally active TEs contributes to long-term priming and/or up-regulation of distal defence genes. The initiation of TE re-methylation by Pol-II dependent RdDM generates primary and secondary 21/22-nt sRNAs that associate with nuclear AGO1 and then interact with the SWR1-C in defence gene promoters to recruit Pol-II (Fig. 2). Based on the regulatory function of SWR1-C and H2A.Z in the expression of defence-related ERGs (Box 2), we propose that Pol-II is kept in a paused state by H2A.Z, which primes defence genes for augmented induction. Additional transcriptional signals upon secondary pathogen infection, including NRP1/2-dependent eviction of H2A.Z, induce Pol-II elongation resulting in the augmented expression of the defence genes (Fig. 2). To confirm the nuclear role of AGO1 in the priming of defence genes, future studies should test *ago1* mutants for their ability to maintain IR, and determine whether AGO1-bound sRNAs share sequence homology with pathogen-inducible TEs and/or defence genes. Additionally, future studies should determine whether AGO1 orthologs in maize (Xu *et al.*, 2016) and rice (Wu *et al.*, 2009) localise to the nucleus after pathogen attack to determine whether our model of AGO1-dependent defence gene priming translates to other plant species.

III. Stage 2: genetic consequences of the stress-induced mobilome

1. The stress-induced mobilome

Transposable elements that are capable of transposing within the genome are collectively referred to as the mobilome (Quadrana *et al.*, 2016). The mobilome encompasses two major TE classes: class I retrotransposons that 'copy-and-paste' themselves via an RNA intermediate, and class II DNA transposons that 'cut-and-paste' themselves as a DNA molecule. Class I includes TEs with and without long terminal repeat (LTR) sequences. In plants, the order of LTR retrotransposons includes the *Ty1/copia* and *Ty3/gypsy* superfamilies, while non-LTR retrotransposons are made up of short- and long-interspersed nuclear element (SINE and LINE) TEs. The majority of class II TEs contain terminal inverted repeats, some of which encode transposases to facilitate excision and reintegration. In the absence of functional transposases, class II TEs can be activated in *trans* by other TEs (Quesneville, 2020). Other class II TEs include Helitrons, which transpose by a rolling-circle mechanism.

In the absence of epigenetic silencing mechanisms, the mobilome is a potent mutagen that threatens the structural integrity of genomes (Tsukahara *et al.*, 2009; Quadrana *et al.*, 2019); TEs are associated with the majority of intraspecific structural variations in Arabidopsis (Kawakatsu *et al.*, 2016), maize (Sun *et al.*, 2018), and rice (Hurwitz *et al.*, 2010). Thus, under stress-free growth conditions, TEs are predominantly silenced to maintain genome stability. However, reduced epigenetic silencing of TEs under biotic stress (stage 1) increases the chance of TE mobilisation, which in turn facilitates (epi)genetic diversification. In the following section, we review the emerging link between the stress-induced mobilome and *NLR* diversification, and discuss recent evidence that the mobilome specifically targets ERGs, including defence genes (Negi *et al.*, 2016; Quadrana *et al.*, 2019).

2. The epigenetic catalyst of resistance gene diversification

Resistance genes encoding NLR immune receptors often co-localise with TEs in dense clusters and show high levels of intraspecific diversity (Zhang *et al.*, 2014; Kawakatsu *et al.*, 2016; Lai *et al.*, 2020). Nonallelic homologous recombination (NAHR) between TE sequences and gene paralogues has been implicated in the evolution of *NLR* clusters (Michelmore & Meyers, 1998; McDowell & Simon, 2006). Using a GUS reporter construct to quantify NAHR, Lucht *et al.* (2002) were the first to report that somatic NAHR in Arabidopsis increases upon *Hpa* infection or SA treatment. Kovalchuk *et al.* (2003) used a similar luciferase-based reporter construct to show that local inoculation of tobacco with virulent tobacco mosaic virus (TMV) increases NAHR in systemic leaves, which occurred several hours before the virus reached these distal plant parts. Two subsequent studies reported that increased NAHR upon exposure to biotic stress signals can be transmitted to a subsequent stress-free generation in Arabidopsis and tobacco (Molinier *et al.*, 2006; Boyko *et al.*, 2007). Moreover, progeny from TMV-infected tobacco displayed DNA hypomethylation at NAHR-targeted *NLR* clusters, suggesting that DNA

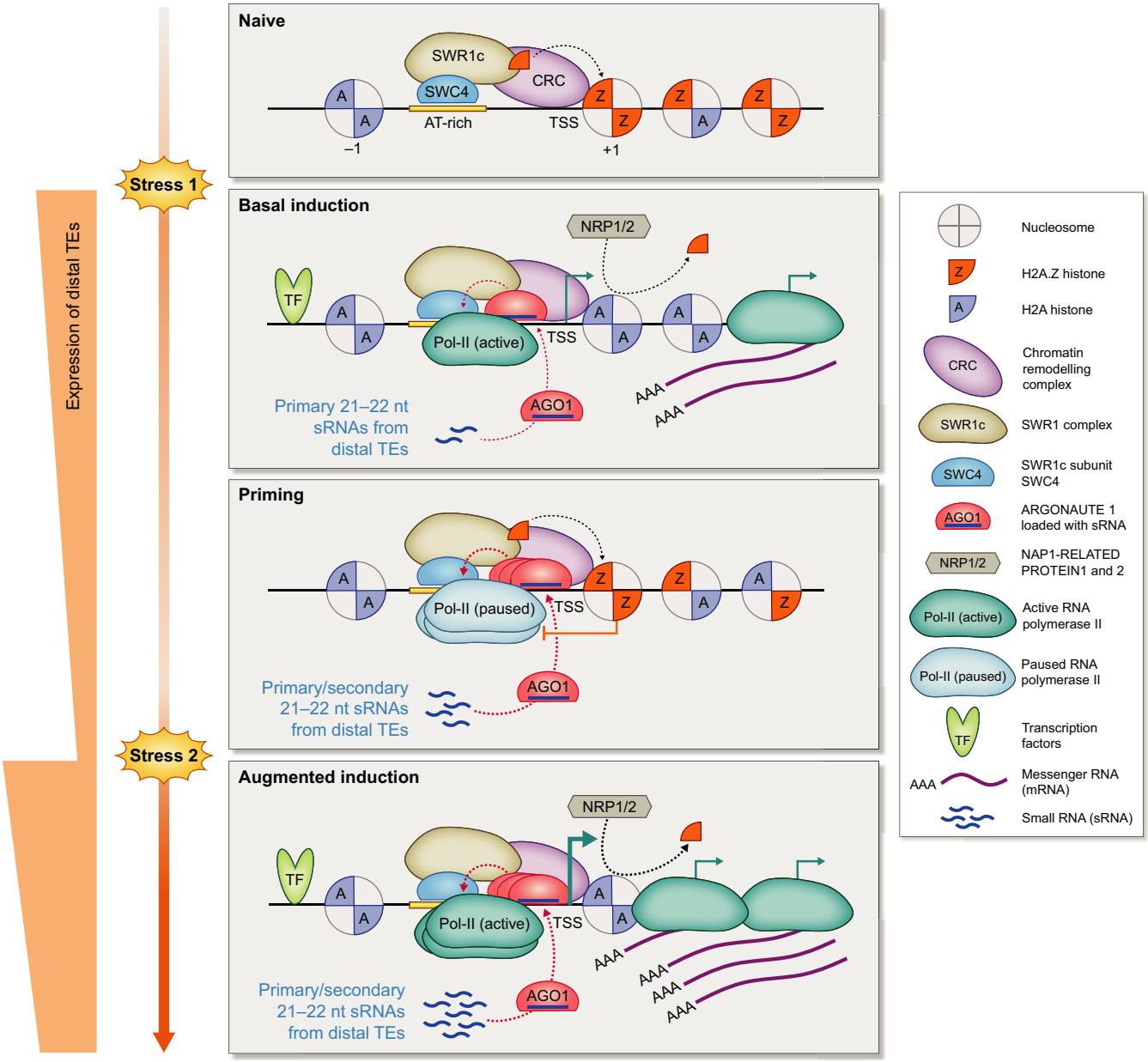

Fig. 2 Model for the role of AGO1 and H2A.Z in *trans*-priming of defence genes by TE-derived sRNAs. *Naive:* pathogen-responsive defence genes in naive plants without prior disease exposure are transcriptionally repressed by H2A.Z at the +1 nucleosome and across the gene body (Coleman-Derr & Zilberman, 2012; Box 2). H2A.Z deposition is catalysed by the chromatin remodelling complex SWR1 (SWR1-C), which recognises AT-rich sequences upstream of the transcription start site (TSS) via subunit SWC4 (Gómez-Zambrano *et al*., 2019). Other chromatin remodelling complexes (CRC) at the promoter regions interact with SWR1-C and the extended acidic patch of H2A.Z to keep the gene silenced (Goldman *et al*., 2010; Torres & Deal, 2019; Luo *et al*., 2020). *Basal induction*: primary pathogen attack stimulates eviction of H2A.Z from the nucleosomes downstream of the TSS to allow for transcriptional induction, which depends on activity by the histone chaperones NRP1/2 (Wang *et al*., 2020). In parallel, stress-induced DNA hypomethylation and transcription of distal transposable elements (TEs) generates primary 21/22-nucleotide (nt) sRNAs (miRNAs and/or *cis*-natural antisense transcript siRNAs), which are loaded onto AGO1. Sequence-specific binding of the sRNA-loaded AGO1 to the CRCs in defence gene promoters recruits Pol-II (Liu *et al*., 2018). This, in combination with the binding and activity of other stress-inducible transcription factors (TFs), lifts the transcriptional silencing resulting in basal defence gene induction. *Priming*: as the primary stress signal diminishes, NRP1/2 activity dwindles, resulting in re-incorporation of H2A.Z downstream of the TSS and reversion to a transcriptionally silenced state. However, the transcriptional memory of the initial stress is maintained by primary AGO1-sRNA complexes, facilitating cleavage of distal TE transcripts to produce secondary 21/22-nt sRNAs. Some primary and/or secondary sRNAs initiate TE silencing through Pol-II dependent RdDM, while others are loaded onto AGO1 to generate even more 21/22-nt secondary sRNAs (Cuerda-Gil & Slotkin, 2016). As TEs become progressively silenced and TE transcripts diminish, complementary AGO1-sRNA complexes accumulate at the defence gene promoter and recruit Pol-II to the TSS, which are kept in a paused state by H2A.Z (Kumar & Wigge, 2010; Dai *et al*., 2017). *Augmented induction*: upon secondary stress exposure, H2A.Z is again evicted by NRP1/2, which induces elongation of the augmented pool of Pol-II for rapid transcriptional induction. As distal TEs have not been fully silenced yet, there is greater stress-induced expression of TEs and production of primary 21/22-nt sRNAs. These, in combination with the secondary sRNAs from the first exposure, continue to recruit AGO1 and Pol-II to the promoter, mediating augmented expression of the defence gene.

hypomethylation catalyses NAHR-induced diversification of these gene clusters (Boyko *et al.*, 2007).

Wilkinson *et al.* (2019) proposed a model that links *NLR* diversification to biotic stress, changes in DNA methylation, TE mobilisation, and NAHR. In this model, exposure to biotic stress activates and mobilises class I TEs, which generate duplication sites within the *NLR* cluster that subsequently promote tandem duplication through NAHR. As stress signals diminish, TEs gradually become re-silenced by RdDM, which then spreads to neighbouring *NLRs* (Ahmed *et al.*, 2011; Kawakatsu *et al.*, 2016; Quadrana *et al.*, 2016). The increased G:C → A:T mutation rate of methylated cytosines (Ossowski *et al.*, 2010) accelerates the occurrence of nonsynonymous mutations in functionally redundant genes, allowing for rapid evolution of new recognition specificities (Zhang, 2003; Wilkinson *et al.*, 2019). Experimental support for this model comes from prior characterisation of the Arabidopsis *bal* mutant, which was generated from a backcross of the extensively hypomethylated *ddm1-2* mutant. The genomic instability of *ddm1-2* is believed to have generated a duplication of *SNC1*, which has staggering numbers of nonsynonymous mutations in *bal* plants (Yi & Richards, 2009). Thus, (epi)genetic diversity that TEs introduce into *NLR* clusters may carry a selective advantage as they accelerate neofunctionalisation in stressful environments.

3. Lessons from the adaptive immune system in animals?

The process of *NLR* diversification and neofunctionalisation in plants bears similarity to B-cell diversification in mammals, whereby exposure to antigens initiates a proliferative burst of class-switch recombination (CSR) and somatic hypermutation (SHM) in immunoglobulin genes (Di Noia & Neuberger, 2007). These changes are dependent on the enzyme activation-induced cytidine deaminase (AID) which converts deoxycytosines into deoxyuracils (Dominguez *et al.*, 2015). AID-dependent DNA

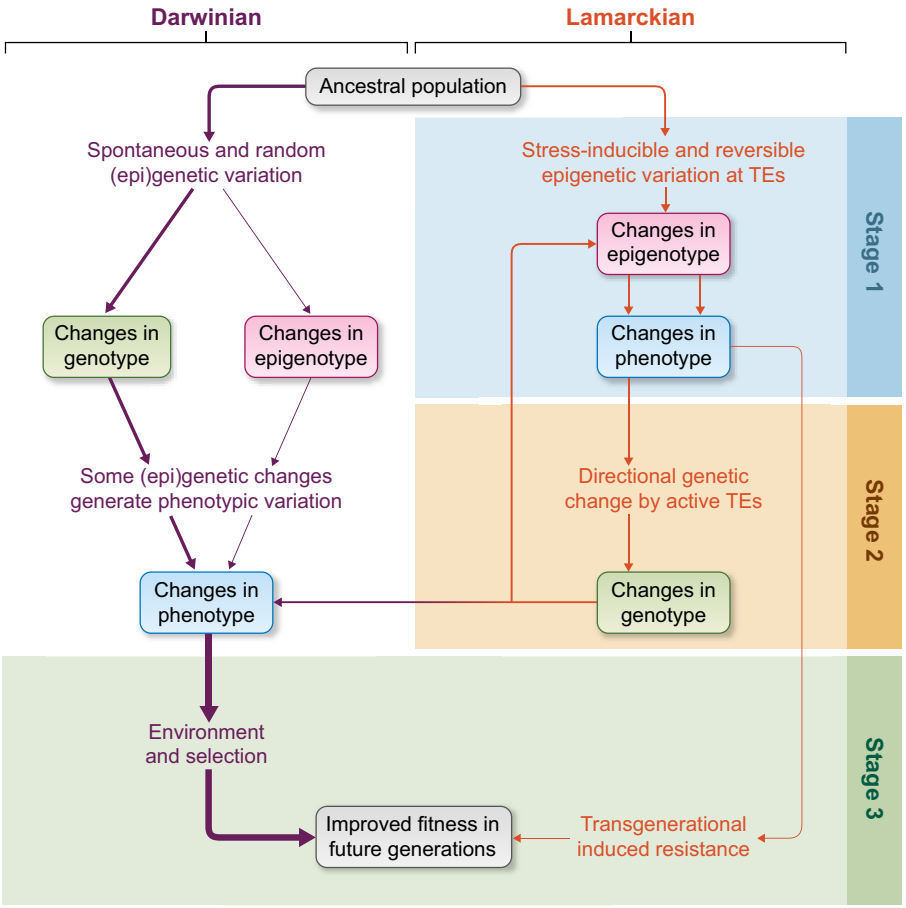

Fig. 3 Schematic model of Darwinian and Lamarckian elements in the evolution of plant immune traits. Darwinian evolution (left; purple) indicates the differential survival of individuals as a result of (epi)genetic variation, whereas Lamarckian evolution (right; orange) indicates the inheritance of acquired adaptive traits. While the dominant evolutionary principle shaping plant immunity remains Darwinian, stress-inducible and often reversible epigenetic changes at transposable elements (TEs) prime the expression of environmentally responsive genes (ERGs) with functions related to plant defence, which can provide individuals with adaptive resistance traits that enhance survival in populations of subsequent generations (thin orange arrow). The reduced epigenetic silencing of TEs facilitates their mobilisation and directional insertion in/near ERGs, which increases the rate of genetic and phenotypic diversification among individuals (orange-to-purple arrow). Through subsequent natural selection, this process acts as a catalyst on Darwinian evolution of plant immunity. Since TEs are under epigenetic control, the rapid diversification of TEs and ERGs also boosts epigenetic regulatory potential in response to stress (orange feedback arrow). The thickness of arrows indicates estimated evolutionary importance. Shown on the right are stages 1 (blue), 2 (orange), and 3 (green) of the plant immune adaptation as explained in the main text and depicted in Fig. 1.

hypomethylation is an important step in the maturation of germinal centre B-cells, and many AID-dependent hypomethylated regions overlap with SHM hotspots (Dominguez *et al.*, 2015). Interestingly, genes encoding for cytidine and adenine deaminases have been shown to be induced in rice upon infection by *Magnaporthe grisea* (Gowda *et al.*, 2007). Furthermore, Arabidopsis cytidine deaminase 1 (CDA1) mutates the Cauliflower Mosaic Virus genome and has also been linked to SA-dependent resistance against *Pst* and *Hpa* (Carviel *et al.*, 2009; Martín *et al.*, 2017). It is therefore tempting to speculate that cytidine deaminases (CDAs) play a role in plant *NLR* diversification, whereby stress-induced CDA activity boosts TE-hypomethylation within *NLR* clusters, followed by CDA-dependent G:C → A:T mutations that accelerate *NLR* diversification in a stress-dependent manner.

4. Catching transposable elements in the act and the directing role of H2A.Z

Quadrana *et al.* (2019) used an Arabidopsis population of epiRILs, the creation of which is described in section II.1, to investigate the dynamics of TE mobilisation and reintegration in Arabidopsis. The exaggerated level of DNA hypomethylation in epiRILs, in combination with the short generation time of Arabidopsis and lack of selection pressure, has enabled this experimental approach to confirm evolutionary processes that normally unfold over longer time scales and/or are masked by changes in environmental selection pressures. In the F8 generation, 95% of epiRILs were found to contain at least one *de novo* TE insertion, of which the majority were caused by the LTR-retrotransposon family *ATCOPIA93* (64.4%) and the DNA transposon families *ATENSPM3* (22.5%) and *VANDAL21* (11.2%). Once initiated, TE transposition rates in the population increased exponentially, generating (epi)genetic diversity at substantially faster rates than spontaneous mutations. For *ATCOPIA93*, however, this increased transposition seemingly halted at a threshold of *c.* 50 copies by F16, which correlated with TEs becoming silenced by DNA methylation (Quadrana *et al.*, 2019). A natural endogenous copy of *ATCOPIA93*, *Évadé* (*EVD*), is also known to be transiently activated in Arabidopsis upon elicitation of PTI (Zervudacki *et al.*, 2018), raising the possibility that *EVD* hypomethylation by biotic stress triggers a controlled burst of *ATCOPIA93* mobilisation.

Quadrana *et al.* (2019) also reported that *ATCOPIA93* preferentially targets defence genes enriched with H2A.Z. Crossing an epiRIL with an H2A.Z-deficient mutant abolished the integration preference of *ATCOPIA93* that was observed in the wild-type background, and increased the proportion of insertions at housekeeping genes by almost 3-fold. This supports previous evidence that constitutively transcribed genes are depleted in H2A.Z, whereas ERGs are enriched with H2A.Z (Box 2; Coleman-Derr & Zilberman, 2012). Thus, H2A.Z diverts the stress-induced mobilome towards ERGs, and protects essential house-keeping genes from potentially harmful insertions. In tomato, intraspecific *COPIA* TE insertion polymorphisms have been reported to occur predominantly within or nearby ERGs (Domínguez *et al.*, 2020), suggesting that the directed diversification of ERGs by H2A.Z is conserved between plant species. Indeed, insertions of *Ty1/copia* TEs into H2A.Z-enriched regions were found across the distantly related species Arabidopsis and rice, as well as yeast (*Saccharomyces cerevisiae*) (Quadrana *et al.*, 2019). Combined, these results suggest that plants direct the stress-induced mobilome towards ERGs, which increases (epi)genetic diversity of the immune system for natural selection to act on (stage 3).

IV. Stage 3: evolutionary consequences of stress-induced (epi)genetic change

1. Domestication of epigenetically controlled transposable elements renders genes environmentally responsive

As a consequence of purifying selection against deleterious TEs, the Arabidopsis genome contains relatively few TEs and repeat sequences compared to other plant species (Quesneville, 2020; Baduel *et al.*, 2021). Of all annotated TEs in Arabidopsis, only 3% are intragenic, of which 85% are intronic (Le *et al.*, 2015). This indicates that intronic TEs are less likely to face purifying selection than exonic insertions and/or have genomic features that favour insertions. Plants have evolved mechanisms to recognise and tolerate intronic heterochromatic blocks arising from intragenic TE insertions (Sigman & Slotkin, 2016). For instance, the IBM2/AIPP1/EDM2 protein complex binds to CHG/H3K9me2-enriched intronic TEs to ensure full-length transcription (Duan *et al.*, 2017; Lai *et al.*, 2019). For some *NLR* genes, IBM2/AIPP1/EDM2 is necessary for the expression of functional full-length transcripts during pathogen attack. Subsequent IBM1-dependent loss of H3K9me2 at these loci causes proximal polyadenylation, reducing the proportion of full-length transcripts and functional activity (Tsuchiya & Eulgem, 2013; Lai *et al.*, 2020). Thus, epigenetic homeostasis of intronic TEs by IBM2/AIPP1/EDM2 and IBM1 enables tightly regulated expression of TE-containing *NLRs* during pathogen attack. Since deregulated expression of *NLRs* can cause autoimmunity and associated reductions in growth and reproductive fitness (Richard *et al.*, 2018a,b), this epigenetic control of *NLR* expression offers a selective advantage. Indeed, only 6 out of 80 Arabidopsis accessions investigated lack the intronic *COPIA-R7* TE insertion in *RPP7*, indicating that this intronic TE has been conserved across a number of populations (Tsuchiya & Eulgem, 2013). Similarly, 67% of insertions by the non-LTR retrotransposon *Au* SINE in wheat are associated with genes, including defence-related genes, with the majority of insertions within introns (Keidar *et al.*, 2018). In pine, TE insertions have been shown to be enriched within defence genes, including *NONEXPRESSOR OF PATHOGENESIS-RELATED PROTEINS-1*, which controls SA signalling and SAR (Voronova *et al.*, 2020). In rice, CHG/H3K9me2-enriched introns are present in 11% of all genes (Espinas *et al.*, 2020). These genes tend to be plant-hormone and environmentally responsive and have expression patterns that are tissue-specific. Genomic sequence comparison with a wild rice relative revealed that these heterochromatic introns have higher base substitution rates than nonheterochromatic introns (Espinas *et al.*, 2020), supporting the notion that DNA methylation acts as a catalyst of genetic mutation (Wilkinson *et al.*, 2019).

Transposable elements inserted in gene promoters can adopt a *cis*-regulatory function in the transcriptional control of the corresponding gene. This TE domestication can tie genes into novel environmentally responsive pathways. A striking example comes from the conserved biosynthetic gene *CYP82C4*, which is required for the production of sideretin under conditions of iron limitation (Rajniak *et al.*, 2018). Within the *Arabidopsis* genus, the *CYP82C2* gene has been duplicated from *CYP82C4*, after which, in *Arabidopsis thaliana*, it was recruited into the WRKY33 regulon through the insertion of the LINE retrotransposon *EPCOT3* into its promoter (Barco *et al.*, 2019). The presence of a chromatin-accessible WRKY33-binding site within *EPCOT3* has equipped *CYP82C2* with a new expression pattern, which allows it to function in stress-responsive production of the defence metabolite 4-hydroxyindole-3-carbonylnitrile (4-OH-ICN; Raijniak *et al.*, 2015; Barco *et al.*, 2019). Interestingly, the plausible ancestor of *EPCOT3* is enriched with heterochromatic H3K27me3 and is weakly bound by WRKY33 (Barco *et al.*, 2019). Therefore, loss of H3K27me3 at *ETCOP3* appears to have been an essential epigenetic modification to render *CYP82C2* immune-responsive, illustrating how selection can shape the epigenetic state of a domesticated TE. Other domesticated TEs in defence gene promoters, such as *RMG1* and *RLP43*, are targeted by ROS1 to selectively antagonise RdDM at WRKY-binding sequences in the promoter regions near TEs (Halter *et al.*, 2021), keeping these motifs free from DNA methylation within mostly heterochromatic promoters. This epigenetic homeostasis by ROS1 and RdDM allows plants to launch efficient immune responses during pathogen attack while keeping *NLRs* transcriptionally silent under stress-free conditions. Again, these examples illustrate how epigenetic control of domesticated TEs offers a selective advantage, whereby unnecessary defence expression is prevented while maintaining full immune responsiveness to biotic stress.

2. Harmony of evolutionary theory through epigenetics

The fusion of Darwinian evolution and Mendelian genetics in the early to mid-20th century formed the modern synthesis (MS) of evolutionary theory. Core to MS theory is the mantra that randomly occurring genetic variation generates phenotypic diversity among individuals. Those that are then better suited to the environment are more likely to survive and reproduce, resulting in an increased occurrence of advantageous traits within the population. Thus, spontaneously occurring genetic variation precedes the occurrence of genetic and phenotypic change in a population (Fig. 3). While spontaneously occurring epigenetic variation can have a contribution to heritable phenotypic change (Fig. 3), this mostly occurs at gene bodies in unstressed plants (Becker *et al.*, 2011). Accordingly, the contribution of this variation to phenotypic change remains a minor factor, since gene body methylation, unlike TE methylation, does not influence gene expression (Bewick & Schmitz, 2017), nor does it facilitate structural genetic variation (Kawakatsu *et al.*, 2016). Alternative evolutionary theory proposes a phenotype-first form of evolution, as championed by Jean-Baptiste Lamarck in the 1800s. Under Lamarckian evolution, environmental cues drive individual phenotypic change, after which these acquired traits are passed to populations of future generations. This has been rejected by orthodox MS theory, which has dominated evolutionary thinking since the 1930s. However, since Waddington introduced epigenetics in 1942, theorists have debated whether epigenetic inheritance contradicts MS, and thus, whether evolutionary theory needs revision (for contrasting arguments see Dickins & Rahman, 2012 and Jablonka, 2017). This debate has been intensified after the discovery of CRISPR-cas immunity in prokaryotes against bacteriophages (Kooning & Wolf, 2016). CRISPR-cas immunity is based on the insertion of a piece of phage DNA into the genomic CRISPR array, resulting in the acquisition of heritable immunity against the attacking phage. Thus, CRISPR-cas immunity represents an adaptive and heritable trait that is acquired in response to environmental stress, hence following the Lamarckian principle of evolution. Despite overwhelming evidence for Darwinian evolution for adaptive plant phenotypes, arising from random changes in DNA sequence (Mitchell-Olds & Schmitt, 2006; Anderson *et al.*, 2011), directional and adaptive impacts of stress-inducible epigenetic changes on plant resistance challenge orthodox MS theory and support calls for an extended evolutionary synthesis (Danchin *et al.*, 2011; Laland *et al.*, 2015). Accordingly, we propose an alternative model for the evolution of the plant immune system, which remains largely Darwinian but includes Lamarckian elements arising from stress-inducible epigenetic mechanisms, which can mediate adaptive parental effects and accelerate genetic variation of immune-regulatory genes under conditions of prolonged stress (Fig. 3).

Within a generation, plants exposed to biotic stress undergo a range of epigenetic changes that facilitate a tightly regulated innate immune response and mediate an adaptive IR response (Mauch-Mani *et al.*, 2017; De Kesel *et al.*, 2021). Beyond a generation, stressed plants can epigenetically transmit IR to their progeny (Kathiria *et al.*, 2010; Luna *et al.*, 2012; Rasmann *et al.*, 2012; Slaughter *et al.*, 2012). This TIR departs from MS theory because phenotypic change precedes genetic change and gives rise to a directional and heritable trait that is adaptive (Fig. 3). The evolutionary and ecological significance of TIR was recently highlighted in a study by López Sánchez *et al.* (2021), who used a full factorial design to examine the specificity, costs and transgenerational stability of TIR after exposure of Arabidopsis to increasing intensities of (a)biotic stresses. Transgenerational induced resistance by biotrophic and necrotrophic pathogens was found to provide progeny with specific protection against pathogens with similar lifestyles (matched environments), while it incurred costs from increased susceptibility to other types of (a)biotic stress (mismatched environments). Moreover, the intensity, costs and transgenerational stability of TIR were proportional to the disease severity experienced by parents, indicating that biotic stress intensity serves as an environmental proxy for TIR investment (López Sánchez *et al.*, 2021). The potential strength and stability of epigenetically controlled disease resistance are illustrated by studies of Arabidopsis epiRILs, which carry artificially induced epialleles from the *ddm1-2* mutant that remain stable over at least eight generations (Johannes *et al.*, 2009). In addition to Furci *et al.* (2019), who identified four hypomethylated epiQTLs controlling quantitative resistance against *Hpa*, Liégard *et al.* (2019) reported

multiple epiQTLs controlling quantitative resistance against the clubroot-causing protist *Plasmodiophora brassicae*. In both studies, the epigenetic resistance reached near-complete levels of protection in selected epiRILs. Although it remains unclear whether these epiQTLs can occur in nature in response to biotic stress, the strength and stability of these resistance epiQTLs illustrate the potential evolutionary impact of epigenetic variation on plant immunity.

Like genetic mutations, epialleles arise spontaneously in natural populations (Becker *et al.*, 2011), where they can generate phenotypes that follow Mendelian inheritance (He *et al.*, 2018; Bondada *et al.*, 2020). Hence, epigenetic variation provides an alternative transmissible component driving evolutionary change (Hirsch *et al.*, 2012), which challenges the MS tenet that genetic change solely determines phenotypic variation on which natural selection acts. The dichotomy between Darwinism and Lamarckism breaks down further when one considers that stress-induced epigenetic change could facilitate genetic change via preferential insertions of TEs into ERGs (Quadrana *et al.*, 2019; Domínguez *et al.*, 2020). However, occurrence of genetic changes in this process remain largely random and thus create phenotypic diversity on which Darwinian evolution can act (Fig. 3). Moreover, epigenomes that facilitate this diversification can be selected through a genetic proxy, which is subject to Darwinian evolution. For example, several natural Arabidopsis accessions carry partially compromised *NRPE1* alleles that stimulate genome-wide CHH hypomethylation and transposition events. These alleles occur mostly in geographical locations with relatively high heat exposure and are thus implicated to be adaptive under heat stress (Baduel *et al.*, 2021). While the epigenetic state is likely driving the presumed benefits of enhanced TE-transposition, natural selection for a genetic *NRPE1* variant has given rise to epigenomic variation. Finally, earlier mentioned examples of stress-inducible diversification of *NLRs* are driven by epigenetic mechanisms but are still shaped by natural selection and Darwinian evolution.

There is no doubt that Darwinian evolution is the dominant principle driving adaptive changes in plant immunity. However, stress-induced epigenetic change can act as a catalyst to Darwinian evolution of the plant immune system (Fig. 3). Apart from mediating TIR, which can offer relatively short-term benefits to progeny in parent-matched environments (López Sánchez *et al.*, 2021), stress-induced epigenetic change can accelerate genetic change in immune-regulatory genes through mobilome-induced structural variants and 5-mC-induced point mutations, which are selected for by Darwinian evolution (Ossowski *et al.*, 2010; Kawakatsu *et al.*, 2016; Wilkinson *et al.*, 2019; Espinas *et al.*, 2020).

V. Conclusions and translation to crop protection

In this review, we have described how biotic stress-induced epigenetic change facilitates short- and long-term adaptation of the plant immune system, which can be summarised by a three-stage circular model (Fig. 1). The first stage describes how biotic stress triggers epigenetic changes, and how these changes induce and/or prime genome-wide expression of defence genes, which prepares individuals and their progeny for future attacks by pathogens. Based on emerging evidence that hypomethylated TEs induce/prime ERGs via *cis*- and *trans*-acting mechanisms, we highlight one *trans*-acting mechanism involving 21/22-nt sRNAs, which are generated during the initial stages of TE re-silencing (Fig. 2). We propose that these sRNAs bind to AGO1 and stimulate its nuclear activity by associating with the chromatin of defence genes and recruiting Pol-II, resulting in transcriptional induction/priming. Since ERGs are enriched with the histone variant H2A.Z (Box 2), we furthermore propose that the induction of these defence genes is tightly regulated by H2A.Z. This enrichment of H2A.Z also plays a role in stage 2 of our model, which describes the genetic consequences of the stress-induced TE mobilome. Recent evidence suggests that H2A.Z guides TE insertion towards ERGs, which can facilitate a cascade of (epi)genetic diversification through homologous recombination, DNA methylation and point mutations. Finally, stage 3 of our model addresses the evolutionary implications of biotic stress-induced (epi)genetic change. We conclude that these changes act as a catalyst for Darwinian evolution of the plant's innate immune system.

Epigenetic regulatory mechanisms and variation controlling disease resistance can be targeted by crop breeding programs and lead to new varieties expressing durable multigenic resistance. For example, TEgenesis (https://epibreed.com/) is a method by which Pol-II is chemically inhibited *in vivo*, after which plants are exposed to stress to promote TE transposition. This innovative technology takes advantage of the accelerated rates of stress-induced epigenetic-dependent adaptation and has been confirmed to work in Arabidopsis and rice (Thieme *et al.*, 2017). Other future crop protection technologies may involve the transgenic expression of ncRNAs that 'mop-up' immune-suppressive miRNAs (Canto-Pastor *et al.*, 2019) and/or use epiRIL lines that express high levels of stable quantitative disease resistance (Agarwal *et al.*, 2020). However, the epigenetic regulatory potential of plant immunity and IR is a relatively new field, and much remains to be explored. Many ideas presented in this review draw evidence from the model system Arabidopsis, which reflects a bias in the literature. To translate this knowledge into epigenetic crop protection technology, more studies of crop species are needed, since there are major differences in epigenetic regulation and epigenomes between plant species. For example, gene bodies of *NLRs* in common bean (*Phaseolus vulgaris*) are targeted by RdDM, of which approximately half are methylated in all three contexts (CG, CHH, CHG) (Richard *et al.*, 2018b), while other plant species lack gene body methylation altogether (Bewick *et al.*, 2016). Furthermore, conifers differ from flowering plants in that 21-nt sRNAs, rather than 24-nt sRNAs, make up the majority of the sRNA population in vegetative tissues, despite their huge TE-rich genomes (Nakamura *et al.*, 2019; Wilkinson *et al.*, 2021). Perhaps most importantly, TEs make up only *c.* 20% of the genome in Arabidopsis, compared to > 80% in maize and wheat (Quesneville, 2020), which makes these crops more sensitive to the introduction of epigenetic variation (Li *et al.*, 2014). Accordingly, there is a need to develop adjustable and more precise methods of introducing epigenetic variation in crops. Apart from sequence-targeted CRISPR-dCas9-based methods (Nuñez *et al.*, 2021), chemical epi-mutagenesis and transgenic tools will allow for adjustable DNA

demethylase activity. A continuation of the fundamental research highlighted in this review, in combination with a stronger translational focus on epigenetic immune regulation in crop and tree species, will enable a deeper understanding of the versatile nature of plant immunity and drive ground-breaking innovations in epigenetic plant protection technologies.

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