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Surviving in a Hostile World: Plant Strategies to Resist Pests and Diseases

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Keywords

inducible defenses, acquired resistance, priming, epigenetics, genetic assimilation, plant-associated microbiomes, soil feedback responses

Abstract

As primary producers, plants are under constant pressure to defend themselves against potentially deadly pathogens and herbivores. In this review, we describe short- and long-term strategies that enable plants to cope with these stresses. Apart from internal immunological strategies that involve physiological and (epi)genetic modifications at the cellular level, plants also employ external strategies that rely on recruitment of beneficial organisms. We discuss these strategies along a gradient of increasing timescales, ranging from rapid immune responses that are initiated within seconds to (epi)genetic adaptations that occur over multiple plant generations. We cover the latest insights into the mechanistic and evolutionary underpinnings of these strategies and present explanatory models. Finally, we discuss how knowledge from short-lived model species can be translated to economically and ecologically important perennials to exploit adaptive plant strategies and mitigate future impacts of pests and diseases in an increasingly interconnected and changing world.

INTRODUCTION

Our planet is inhabited by a wide range of different plant species, from short-lived desert angiosperms to long-lived coniferous species that dominate boreal forests. Although variable in phenotype, generation time, and geographical range, all plants are primary producers. Consequently, they face constant pressure from opportunistic attackers, such as viruses, bacteria, fungi, nematodes, arthropods, and large herbivores. Despite this pressure, land plants have continued to thrive for 500 million years (95), which would not have been possible without sophisticated defense strategies.

All plants have an innate immune system, which provides instant protection against most attackers (33, 62). Plants can also acquire resistance after the perception of specific environmental stimuli (110). This acquired resistance (AR) is typically long-lasting and can even be transmitted to following generations through changes in DNA methylation and associated chromatin density (81, 84, 128). As is discussed below, there is increasing evidence that these epigenetic processes can influence genetic mutations and the rate at which new defense genes evolve. In addition to these internal strategies, plants are capable of orchestrating multitrophic ecological interactions for their protection (138). These external strategies involve above- and belowground recruitment of beneficial insects and microbes. Recruitment of beneficial microbes can lead to the formation of disease-suppressive microbiomes that offer long-term protection to individual plants and their progeny (11, 58).

In this review, we provide a broad overview of short- and long-term plant strategies by which plants cope with biotic stress (**Figure 1**). We discuss the relative importance of these strategies and their underlying mechanisms. Although most of this knowledge is based on the model plant *Arabidopsis thaliana* (hereafter referred to as *Arabidopsis*), we draw comparisons with non-model perennial species and discuss the importance of studying defense strategies in a broader range of commercially and ecologically relevant plant species.

INTERNAL STRATEGIES

The Innate Immune System

Preexisting constitutive defense structures, such as secondary cell walls, trichomes, and thorns, provide the first layer of protection against attackers. Although these structures are efficient against nonadapted opportunistic aggressors, they can also be costly and are typically ineffective against more specialized attackers. Consequently, plants have evolved a regulatory system for more efficient exploitation of defense resources: the plant innate immune system (33, 62). This genetically controlled system regulates the perception of attack and subsequent activation of inducible defenses and is subject to an evolutionary arms race with virulence strategies of pathogens and herbivores (4, 62). We briefly review the two major pillars of the plant innate immune system: pattern-triggered immunity (PTI) and effector-triggered immunity (ETI), both of which provide instant protection over relatively short timespans ranging from hours to days.

Pattern-triggered immunity. PTI protects plants against most potential attackers and involves multiple defense layers that are induced after recognition of specific molecular patterns (62, 127). This recognition is mediated by pattern recognition receptors (PRRs), which are receptor kinases and receptor-like proteins that are receptor-like proteins that are localized to the surface of plant cells (17, 161). PRRs detect attackers via molecular patterns. Some PRRs detect pathogen-/microbe-/herbivore-associated molecular patterns (PAMPs, MAMPs, and HAMPs), which indicate the presence of chemical signatures that are not from the host plant itself (non-self) (7, 162).

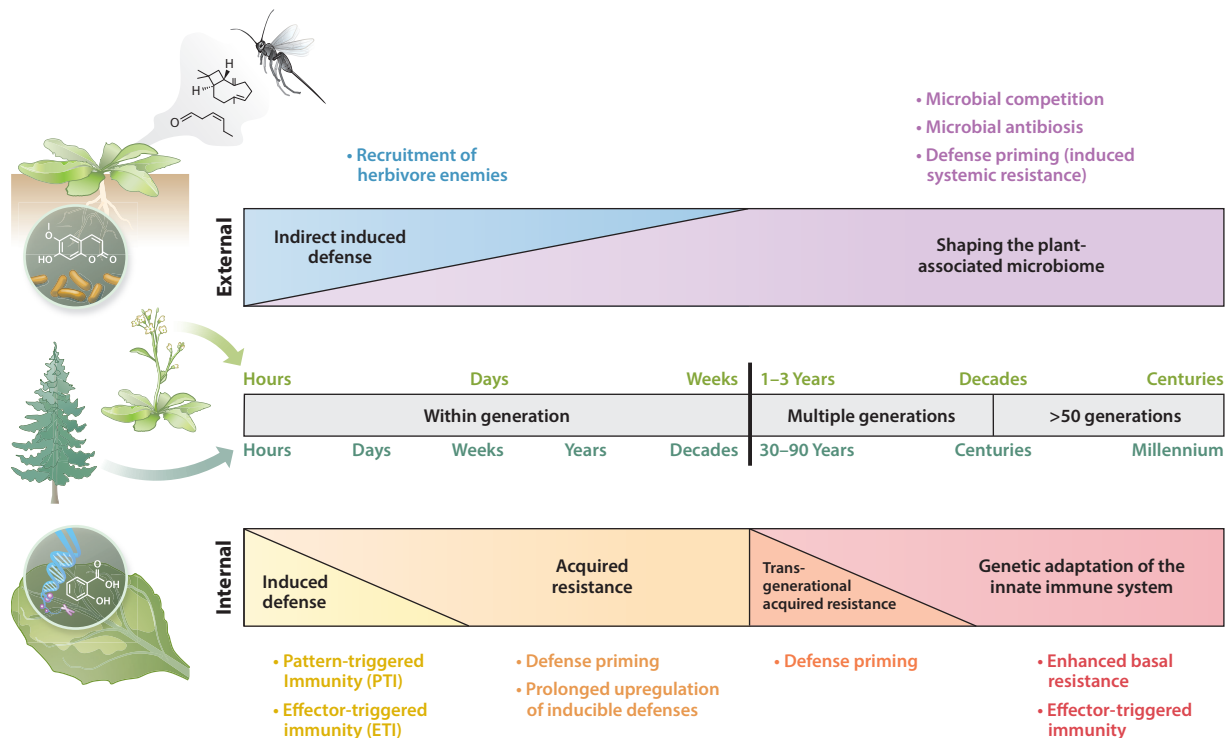


Figure 1

Short- and long-term strategies by which plants adapt to stress from pests and diseases. Shown at the bottom are internal strategies, which are controlled by plant immunological pathways involving physiological, molecular, and (epi)genetic mechanisms. Shown at the top are external strategies, which involve ecological interactions with plant-beneficial organisms. Mechanisms underpinning the internal and external strategies are shown below or above, respectively, the colored triangles. All strategies are aligned against a timescale (*middle*), which varies depending on generation time and habitat of the plant.

PRRs also detect damage-associated molecular patterns (DAMPs), which indicate the presence of host-derived chemical signatures from damaged cells (damaged-self) (17, 53).

Regulation of PTI is controlled by a complex signaling web that varies between plant species and the molecular patterns perceived (14, 35). Despite this variation, there are common signaling components. For instance, perception of PTI-eliciting molecular patterns induces fluxes of defense hormones, which regulate defenses that are effective against different groups of attackers (109). Jasmonic acid (JA)-dependent defenses are generally more effective against necrotrophic pathogens and herbivores, whereas salicylic acid (SA)-dependent defenses are mostly effective against biotrophic pathogens (50). Defenses contributing to PTI include cell wall reinforcements (87), production of pathogenesis-related (PR) proteins (143), and accumulation of secondary metabolites such as terpenes and tryptophan-derived metabolites (108).

A subset of specialized attackers has evolved strategies to suppress PTI. Virulent pathogens can suppress PTI via effector proteins, metabolites, and/or small RNAs (sRNAs), which can be injected into host cells (135, 150). This effector-triggered susceptibility can give rise to an evolutionary arms race with the host plant (62).

Effector-triggered immunity. To counter immune-suppressing effectors from (hemi)biotrophic pathogens, plants have evolved resistance genes (*R* genes). Most *R* genes encode nucleotide binding

site-leucine-rich repeat (NLR) receptor proteins, which directly or indirectly detect pathogen effector activity (1, 36, 70, 127). Activation of NLR receptors elicits ETI, which often leads to a form of programmed cell death at locally infected tissues, the hypersensitive response (HR). The HR is very effective against biotrophic pathogens that rely on living plant cells for their growth (36, 50) but can also come with costs. For instance, the HR can facilitate infection by necrotrophic pathogens (67, 82). Another limitation of ETI is its narrow range of effectiveness. Each R protein recognizes a limited number of effectors, thereby providing protection against one or a small number of pathogen isolates. This reliance on single *R* genes allows pathogens to rapidly overcome ETI, as a single mutation can give rise to a virulent pathotype (62).

Attackers capable of suppressing ETI and/or PTI are still faced with a residual level of basal resistance when infecting a susceptible host. This resistance contributes to slowing disease progression. Like PTI, basal resistance is effective against a broad spectrum of attackers. The next section describes how plants can augment the effectiveness of their basal defense arsenal via AR.

Acquired Resistance

Enhanced resistance to pests and/or pathogens following exposure to specific stimuli is known as induced or acquired resistance (AR). AR is an example of phenotypic plasticity because it allows plants with the same genotype to have different resistance phenotypes. The classic example is systemic AR (SAR). This whole-plant resistance response to localized pathogen attack was first reported in tobacco in 1961 (118). It soon became apparent that SAR is a long-lasting resistance response, which can still be detected at 42 days after induction (19). Over subsequent decades, a range of biotic and abiotic stimuli have been reported to elicit AR in taxonomically distant plant species and against a wide spectrum of pests and pathogens. For instance, colonization of roots by beneficial rhizobacteria or mycorrhizal fungi can result in induced systemic resistance (ISR) and mycorrhiza-induced resistance (MIR), respectively (25, 110). Furthermore, a multitude of natural and synthetic chemicals have been reported to elicit AR (148).

AR is generally based on two nonexclusive mechanisms: prolonged upregulation of inducible defenses and defense priming (Figure 2). Following exposure to a resistance-inducing stimulus, inducible defenses can remain upregulated, providing AR against subsequent attack (Figure 2a).

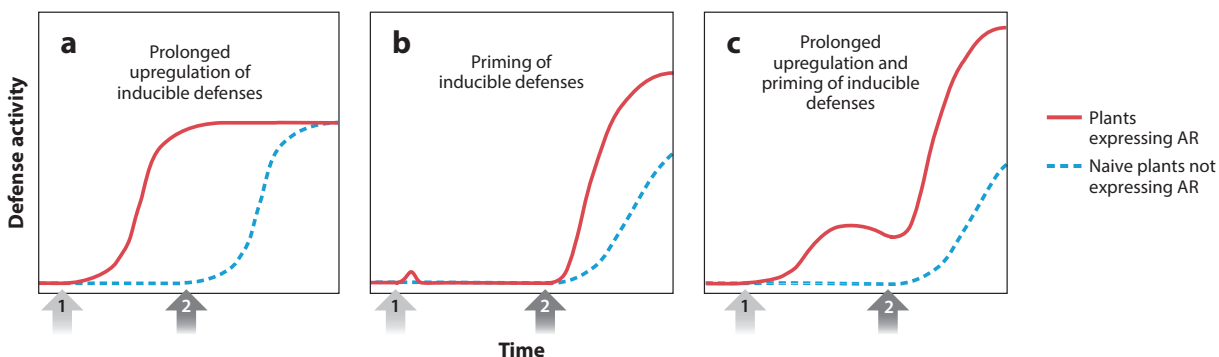


Figure 2

Mechanisms of acquired resistance (AR). Graphical models show levels of plant defense activity against time for the different mechanisms of AR. (a) Prolonged upregulation of inducible defenses. (b) Priming of inducible defenses. (c) Combination of prolonged upregulation and priming of inducible defenses. Light gray arrows (1) represent different AR-eliciting treatments (e.g., localized attack by a pathogen, β -aminobutyric acid). Dark gray arrows (2) represent defense elicitation by pest or pathogen. Red lines represent plants expressing AR. Blue dashed lines represent naive plants that do not express AR.

ACQUIRED RESISTANCE: A COSTLY BUSINESS?

Acquired resistance (AR) is often associated with costs. For instance, allocation costs can arise from the redirection of resources from growth or reproduction to defense (99). Allocation costs can result in severe reductions in growth and seed production, particularly when AR is based on a prolonged upregulation of inducible defenses (142). Defense priming also comes with allocation costs, which can make it unfavorable under stress-free conditions (43, 142, 147). Opportunity costs occur when the allocation of resources to defense occurs at a sensitive life stage, resulting in reduced ability to thrive at later developmental stages (40). The loss of interactions with beneficial symbionts (39, 52) and increased susceptibility to other attackers due to signaling cross-talk (67, 84, 109) are examples of ecological costs. In some cases, priming can incur loss-of-specificity costs, whereby the primed defense state mediates an augmented defense response to an inappropriate stimulus (9, 61). However, despite these examples of costs, the benefits of protection often outweigh the costs, making AR a valuable strategy helping plants to survive in hostile environments (43).

Alternatively, the resistance-inducing stimulus may prime the plant immune system, providing resistance through faster and/or stronger upregulation of inducible defenses after subsequent pathogen/herbivore attack (**Figure 2b**). The optimal strategy depends on the cost–benefit balance of the resistance in a given environment (22) (see the sidebar titled Acquired Resistance: A Costly Business?). Here, we outline both mechanisms in more detail and explain how their cost–benefit balance depends on plant life-history strategies.

Prolonged upregulation of inducible defenses. Examples of stress-inducible defenses that can remain upregulated for prolonged periods of time (**Figure 2a**) include benzoxazinoids and glucosinolates in Poaceae and Brassicaceae, respectively. Although these defense metabolites are produced constitutively, they can accumulate to higher levels at the site of herbivore feeding. For instance, leaf benzoxazinoid concentrations can remain elevated for seven days after feeding by moth larvae, resulting in increased resistance to secondary attack at the same location (86). Furthermore, glucosinolates can remain locally upregulated in Brassicaceae roots for eight weeks after herbivore attack (15). The formation of anatomical defense features in response to pathogen infection can also be regarded as a prolonged upregulation of inducible defenses. Methyl jasmonate (MeJA) application results in increased trichome density in newly formed leaves of tomato (*Solanum lycopersicum*) for up to 21 days after treatment (16). Furthermore, in spruce (*Picea* spp.), treatment with MeJA, wounding, and fungal infection induces traumatic resin ducts (48, 89), which enhance resistance by increasing the reservoir of antiherbivory resin and remain functional for several years (48).

Although prolonged upregulation of inducible defenses provides resistance, it can also be costly to maintain. The fitness cost of a given investment may vary between short-lived annuals and long-lived perennials. For *Arabidopsis*, a two-week upregulation of chemical defenses and trichome density could equate to 25% of the plant's lifespan and thus be relatively costly, whereas this type of investment would be less costly for large long-lived tree species over a lifespan of tens to hundreds of years. Nevertheless, keeping costly defenses upregulated for much of a plant's lifespan is maladaptive for any plant species. This is why plants have evolved an alternative AR strategy that is based on a more cost-efficient mechanism: priming of inducible defenses (43, 91).

Priming of inducible defenses. Priming enables a faster, stronger, and/or more sustained upregulation of inducible defenses after pathogen attack (**Figure 2b**) (31, 32, 91, 105). A variety of cues can elicit priming, including natural and synthetic chemicals, localized pathogen attack,

EPIGENETICS: WHAT'S IN A NAME?

Waddington (146) introduced the term epigenetics in 1942 to describe phenotype-altering interactions between genes and their products that cannot be explained by genetic inheritance. Since then, epigenetics has commonly been used to describe nongenetic changes that are transmittable through meiotic and/or mitotic divisions and that influence phenotypes at cellular and/or whole-organism levels. Advances in molecular biology have provided mechanisms to Waddington's definition but have also created ambiguity. First, small RNAs (sRNAs) that modify gene expression via (post)transcriptional mechanisms are commonly referred to as an epigenetic mechanism but can equally be considered a genetic mechanism because sRNAs are encoded by the organism's genotype. Second, histone modifications, sRNA production, and DNA methylation typically co-occur, making it difficult to separate cause and effect. Third, the heritability of nongenetic changes remains unclear. Although histone modifications can be stable over mitosis, they are not necessarily stable over meiosis. There is, however, ample evidence that changes in DNA methylation can be inherited faithfully over meiosis, making methylation the prime candidate for germline transmission of metastable epigenetic traits. Despite ongoing debate about the exact definition of epigenetics, there is a consensus that the combined effects of histone modifications, sRNAs, and DNA (de)methylation are responsible for most epigenetic phenomena, providing organisms with increased phenotypic plasticity.

herbivore-induced plant volatiles, and beneficial microbes (23, 63, 132–134, 141). Different mechanisms of priming have been proposed (21, 30–32). For example, inactive mitogen-activated protein kinases (MAPKs), which accumulate in plants after priming treatment with the SA homolog benzothiadiazole (BTH), facilitate augmented induction of SA-dependent defenses upon subsequent challenge (9). Priming can also be based on increased accumulation of glucosylated phytohormones (105). Increased concentrations of SA glucosides have been reported in primed tobacco and *Arabidopsis* following localized pathogen attack (74, 104, 126). Additionally, the resistance-inducing effects of the chemical priming agent β -aminobutyric acid (BABA) are reduced in *Arabidopsis* plants impaired in SA glucoside biosynthesis (104).

Over recent years, increasing evidence has suggested that defense gene priming involves regulation by epigenetic mechanisms (see the sidebar titled Epigenetics: What's in a Name?) (30, 32, 105). Biochemical modifications to DNA and DNA-associated proteins that control the density of chromatin have the potential to mediate long-term changes in defense gene responsiveness without major physiological costs (21, 30). In the following sections, we discuss these epigenetic mechanisms and review the evidence for epigenetic inheritance of priming.

Epigenetic mechanisms of defense priming. Genomic DNA in the nucleus is tightly wrapped around histone protein octamers called nucleosomes, which form the basic unit of eukaryotic chromatin. The density of chromatin regulates to what extent the DNA is available for the transcriptional machinery. For this reason, tightly packed chromatin (heterochromatin) is often associated with silenced genetic areas, whereas lightly packed chromatin (euchromatin) is more associated with transcriptionally active areas (10). Chromatin density is controlled by methylation and acetylation of histone tail residues and the presence of specific histone variants inside nucleosomes (37). Jaskiewicz and coworkers (61) were the first to report that SAR-related priming of *WRKY* gene promoters in *Arabidopsis* is associated with increased methylation and acetylation at lysine residues 4 and 9 of histone H3 (H3K4me3 and H3K9ac, respectively). These marks typically indicate reduced chromatin density. Similar results were reported by López and associates (80) in BTH-primed wild-type plants and constitutively primed mutants of *Arabidopsis*. Recently, Schillheim and coworkers (121) used formaldehyde-assisted isolation of regulatory elements

Heterochromatin:

tightly packed chromatin, associated with transcriptional repression

Euchromatin: lightly packed chromatin, associated with active transcription

(FAIRE)-quantitative PCR to more directly demonstrate that chemical priming of the *WRKY6* gene promoter is associated with chromatin decondensation. Together, these studies suggest that histone modifications and related changes in chromatin density *cis*-regulate priming of defense genes.

In addition to histone modifications, there is increasing evidence that DNA methylation regulates priming. Unmethylated DNA is often associated with euchromatin, whereas methylated DNA is more likely to be associated with heterochromatin (111). DNA methylation in plants mostly occurs at the fifth carbon of cytosine in three DNA sequence contexts: CG, CHG, and CHH (where H indicates any base except guanine). Maintenance of DNA methylation in these contexts is achieved by different DNA methyltransferases. In *Arabidopsis*, METHYLTRANSFERASE1 (MET1) and the CHROMOMETHYLASE-class methyltransferase (CMT) 3 are largely responsible for the maintenance of CG and CHG methylation, respectively (77, 120). Asymmetric CHH DNA methylation is maintained by RNA-directed DNA methylation (RdDM) and CMT2, a methyltransferase that is dependent on the activity of the chromatin remodeler DECREASED DNA METHYLATION1 (DDM1) (92, 156). The three types of DNA methylation are not evenly distributed across the genome. CG methylation is found mostly at gene bodies and heterochromatic transposable elements (TEs) (see the sidebar titled A Whistle-Stop Tour of Transposable Elements), whereas CHG and CHH methylation mostly occurs at intergenic regions and TEs in both heterochromatic and euchromatic regions (29). It should be noted, however, that these methylation patterns are based on *Arabidopsis* and the distribution of DNA methylation varies across different plant species and families (100).

The first evidence for the involvement of DNA methylation in defense gene priming came from López and associates (80), who demonstrated that SA-dependent *WRKY* and *PR* genes are constitutively primed in RdDM-deficient *Arabidopsis* mutants. Since then, various studies have confirmed that DNA methylation is inversely correlated with basal resistance to biotrophic pathogens and responsiveness/expression of SA-dependent genes (81, 84, 155). Furthermore, independent groups have reported that infection of *Arabidopsis* with *Pseudomonas syringae* alters genome-wide DNA methylation (44, 106, 128).

The exact mechanisms by which DNA methylation controls defense gene expression are complex. For instance, transcriptome analysis of downy mildew-infected *Arabidopsis* identified numerous defense-related genes that are transcriptionally primed in the CHH-hypomethylated RdDM mutant *mpe1-11* and/or repressed in the hypermethylated DNA demethylase mutant *ros1-4* (81).

Hypomethylated:
decreased in amount
of DNA methylation

Hypermethylated:
increased in amount of
DNA methylation

A WHISTLE-STOP TOUR OF TRANSPOSABLE ELEMENTS

Transposable elements (TEs, or transposons) can be broadly classified into DNA transposons and RNA transposons. DNA transposons (class 2 TEs) move within a genome via single- or double-stranded DNA intermediates and are characterized by terminal inverted repeats. The six superfamilies of DNA elements transpose via either a classic cut-and-paste mechanism of excision followed by reinsertion (*Ac/Ds/hAT*, *MuDR/Mutator/Mu/MULE*, *En/Spm/dSpm/CACTA*, *Tc1/Mariner/Stowaway*, and *PIF/Harbinger/Tourist* superfamilies) or rolling circle replication (*Helitron* superfamily). The more prevalent RNA transposons (class 1 TEs) replicate via a copy-and-paste mechanism involving an RNA intermediate. RNA transposons are grouped by the presence of long-terminal repeats (LTRs), such as retrotransposons of the *Copia* and *Gypsy* superfamilies, or absence of LTRs, as in the long and short interspersed nuclear elements (LINEs and SINEs). Both DNA and RNA transposons can be classified as autonomous elements, which encode all required proteins to replicate and transpose, or nonautonomous elements, which require proteins encoded by the same subfamily or family of autonomous elements for transposition. For more comprehensive reviews describing the TE superfamilies, we refer the reader to References 152 and 160.

Pericentromeric:

related to chromosome regions that flank the centromere

Trans-regulation:

expression of a gene is controlled by distant regulatory element(s)

Cis-regulation:

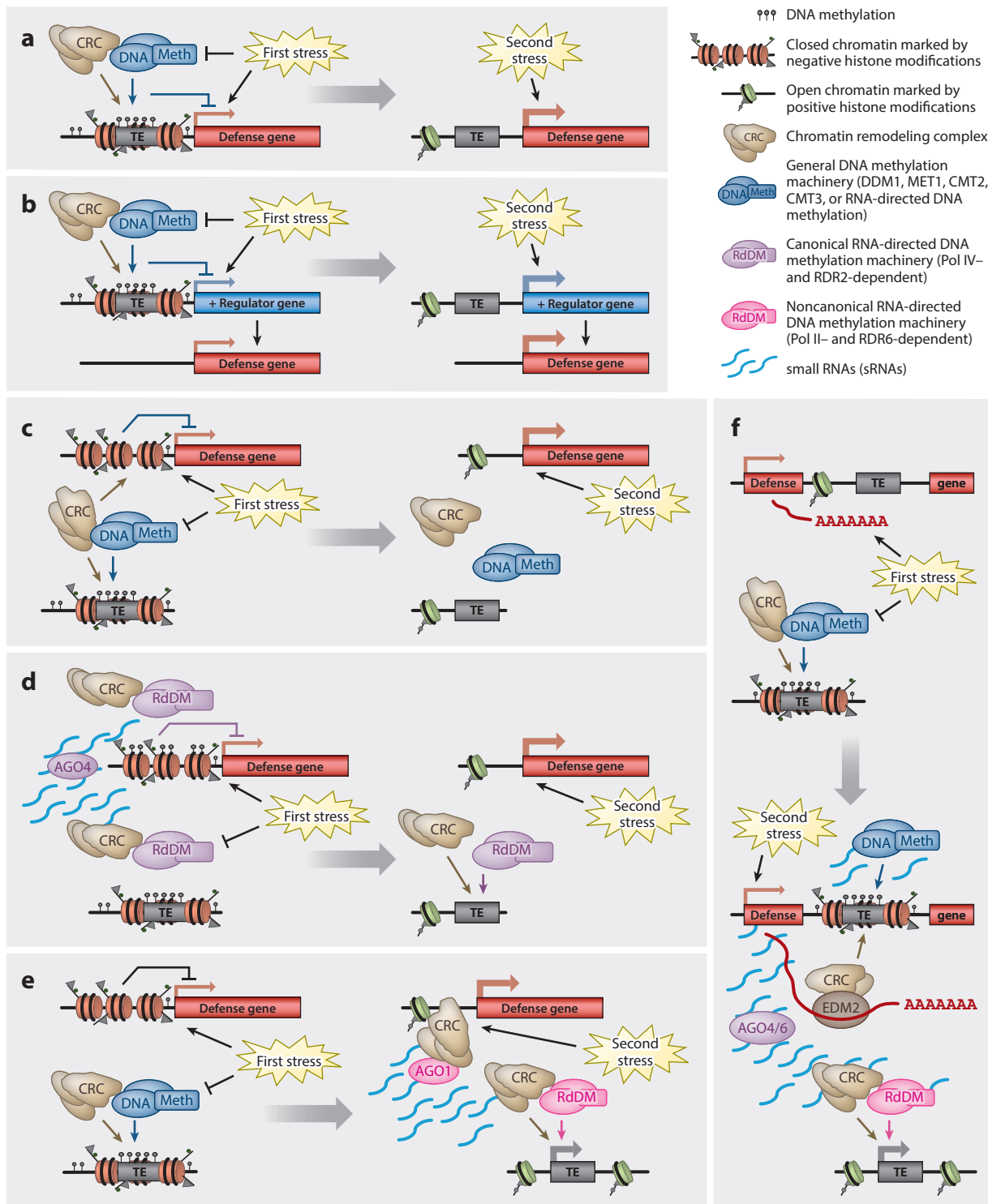
expression of a gene is controlled by a nearby regulatory element(s)

Interestingly, the majority of these defense genes were not targeted by NRPE1- and/or ROS1-dependent DNA (de)methylation, suggesting that their responsiveness is *trans*-regulated by DNA methylation (81). More recently, Cambiagno and coworkers (24) reported that *P. syringae* infection of *Arabidopsis* results in both the transient expression of pericentromeric TEs and the accumulation of RdDM-related sRNAs that map to both TEs and defense genes. Although the TEs were resiled over time, the complementary defense genes remained active (24). Cambiagno and coworkers proposed that this antagonistic response is caused by sRNA competition, whereby sRNAs are allocated away from the defense-related genes toward the TEs (24). Apart from this competition model, TE-derived sRNAs could also positively regulate the priming of distant defense genes. Recent evidence has shown that sRNAs can *trans*-activate defense-related genes through interaction with ARGONAUTE 1 (AGO1) and the SWI/SNF chromatin remodeling complex (79). Further support for *trans*-regulation of defense gene priming came from a recent study of *Arabidopsis* epigenetic recombinant inbred lines (epiRILs), which identified four hypomethylated epigenetic quantitative trait loci (epiQTLs) that control quantitative resistance against downy mildew (49). Transcriptome analysis revealed that the most resistant epiRILs were constitutively primed to activate defense-related genes. However, a comprehensive comparison of gene transcription and DNA methylation failed to identify defense-regulatory genes within the pericentromeric epiQTLs that were simultaneously primed and hypomethylated, or that were located near hypomethylated TEs, suggesting that the hypomethylated epiQTLs *trans*-regulate genome-wide priming of defense genes.

We hypothesize that stress-induced DNA hypomethylation at TEs provides a blueprint for genome-wide defense gene priming. In addition to *cis*-regulation of defense genes by nearby TEs (**Figure 3a**), DNA methylation at pericentromeric TEs can regulate the responsiveness of distant defense genes via *trans*-acting mechanisms. Methylated TEs could control the induction of nearby regulatory genes (e.g., transcription factors), which in turn mediate augmented induction of downstream defense genes during secondary stress exposure (**Figure 3b**). Alternatively, disease-induced hypomethylation of pericentromeric TEs could affect the formation of long-range heterochromatic interactions, removing the repression of distant defense genes (**Figure 3c**). Finally, TE-derived sRNAs complementary to distant defense genes could *trans*-regulate defense gene priming. This can be achieved by disease-induced suppression of RNA polymerase IV-dependent RdDM gene silencing (**Figure 3d**) (155). Alternatively, RNA polymerase II-derived 21/22-nt sRNAs from disease-induced TEs could augment distant defense gene induction via their association with AGO1 and the SWI/SNF complex (**Figure 3e**) (79), or they could augment full-length transcription of distant defense genes with intronic TEs by alternative polyadenylation (**Figure 3f**) (136).

Transgenerational Acquired Resistance

The first indication that plants are capable of rapid transgenerational adaptation to biotic stress came from the finding that caterpillar-infested wild radish produces progeny that are more resistant to the same herbivore (2). In following years, other studies reported that isogenic progeny from herbivore-, wounding-, or JA-treated plants develop different morphological traits, such as leaf trichome density, specific leaf area, petal area, and seed production (56, 66, 144). Furthermore, independent groups have shown that progeny from plants exposed to pathogens, herbivores, and/or chemical priming agents express transgenerational acquired resistance (TAR), which is associated with priming of defense-related genes (64, 84, 114, 123). Because patterns of DNA methylation can remain stable over meiosis (101), subsequent research has focused on the role of DNA methylation in TAR. In *Arabidopsis*, mutations in DNA methylation machinery mimic



(Caption appears on following page)

Figure 3 (Figure appears on preceding page)

Mechanistic models of the regulation of defense gene priming by DNA methylation at transposable elements (TEs). (a) *Cis*-regulation by nearby TEs. Primary exposure to biotic stress induces defense gene expression and simultaneous DNA demethylation and chromatin decondensation at a nearby TE in the defense gene promoter. The open chromatin structure enables augmented defense gene induction after secondary stress exposure. (b) *Trans*-regulation of defense genes through intermediate regulatory genes. Primary stress induces a transient increase in the expression of a defense regulatory gene (e.g., transcription factor encoding gene), which controls the induction of defense genes located elsewhere in the genome. Simultaneous DNA demethylation and chromatin decondensation at a TE in the promoter of the regulatory gene enable augmented induction of this gene after secondary stress exposure. This in turn enables augmented defense gene induction. (c) *Trans*-regulation by long-range chromatin interactions. Primary stress induces DNA demethylation at a heterochromatic TE that forms a long-range heterochromatic connection with a distant defense gene promoter. The resultant chromatin decondensation at the TE disrupts the long-range heterochromatic interaction, enabling augmented induction of the distant defense gene after secondary stress exposure. (d) *Trans*-regulation by small RNAs (sRNAs) from canonical RNA-directed DNA methylation (RdDM). Primary stress represses RNA polymerase IV (Pol IV)-, RNA-DEPENDENT RNA POLYMERASE 2 (RDR2)-, and ARGONAUTE 4 (AGO4)-dependent RdDM, reducing the production of 24-nt-long sRNAs from a TE containing complementary DNA sequences with distant defense gene promoters. This allows for augmented induction of the distant defense gene after secondary stress exposure, as the gene is no longer repressed by RdDM. (e) *Trans*-regulation by sRNAs from noncanonical RdDM. Primary stress results in transcriptional reactivation of functional TEs that contain complementary DNA sequences to distant defense gene promoters. Subsequent resilencing of the TEs by Pol II- and RDR6-dependent RdDM results in the production of 21/22-nt-long sRNAs that are loaded onto AGO1 and interact with the SWI/SNF chromatin remodeling complex at distant defense gene promoters. The increased recruitment of Pol II and associated chromatin remodeling to the distant defense gene promoters enables augmented induction after secondary stress exposure. (f) Combination of *cis*- and *trans*-regulation by local and distal TEs, respectively. The defense gene contains an intronic TE with an alternative polyadenylation site. Initially, when the intronic TE is in a demethylated and euchromatic state, the alternative polyadenylation site is in use, resulting in the majority of the defense gene transcripts being truncated and nonfunctional. Primary stress leads to demethylation and transcription of a distant TE that is partially complementary to the intronic TE. The sRNAs derived from the stress-inducible TE induce noncanonical RdDM at both TEs. The resulting heterochromatinization at the intronic TE prevents the use of the alternative polyadenylation site in an EDM2/EDM3/IBM2-dependent manner, allowing for full-length transcription of the functional defense gene upon secondary stress exposure.

TAR in terms of resistance and priming of defense genes (81, 84, 85), pointing to a mechanism by which disease-induced DNA hypomethylation is transmitted to following generations to control TAR. This hypothesis is supported by Furci et al. (49), who identified hypomethylated DNA regions that control quantitative disease resistance and that are stable over multiple generations. Furthermore, mutation of the DNA demethylase gene *ROS1* not only affects basal resistance to biotrophic pathogens (155) but also prevents TAR in progeny from diseased plants (81). Hence, DNA demethylation is essential for the elicitation, transmission, and/or expression of TAR. Another recent study revealed that TAR in *Arabidopsis* is associated with global shifts in DNA methylation at CG contexts in gene bodies, which were more pronounced after three generations than one generation of disease stress (128). However, the genes carrying these differentially methylated cytosines (DMCs) were not enriched for defense-related functions and there was little overlap in DMCs between independent experiments. Because the role of gene body methylation in gene expression remains unclear (13), it was concluded that the observed changes in DNA methylation mark TAR but do not necessarily cause TAR (128).

Although the exact mechanisms underpinning TAR require further study, there is little doubt about the epigenetic nature of the phenomenon (see the sidebar titled Epigenetics: What's in a Name?). First, TAR can still be apparent in isogenic progeny after multiple stress-free generations, indicating that TAR is transmittable through the germline and not a consequence of a physiological maternal effect (84, 114, 128). Second, TAR requires active DNA demethylation at and around TEs by *ROS1* (81). Third, TAR is reversible and its transgenerational durability seems to depend on the level of parental stress. For instance, TAR triggered by localized infection with avirulent *P. syringae* disappears after one stress-free generation (123). By contrast, TAR is still apparent after two stress-free generations when elicited by repeated inoculations with a

virulent strain of the same pathogen (128). The reversibility of TAR also suggests that it is associated with ecological costs (see the sidebar titled Acquired Resistance: A Costly Business?). Indeed, Luna et al. (84) reported that TAR-expressing progeny from *P. syringae*-inoculated *Arabidopsis* are more susceptible to the necrotrophic fungus *Alternaria brassicicola*. Further research is needed to clarify the ecological drivers of TAR and determine to what extent TAR provides a selective advantage to plants in a changing environment.

Genetic Adaptation of the Innate Immune System

TEs are increasingly considered as important regulators of gene transcription and evolution (45, 78). As outlined above, several studies have reported that disease and associated defense activation induces TE hypomethylation (24, 44, 106, 155), which in turn can influence transcription of defense genes via *cis*- or *trans*-acting mechanisms (Figure 3). Furthermore, this hypomethylation can lead to transcriptional activation and mobilization of TEs, which, in turn, can generate genetic variation (45). Indeed, a recent study used a hypomethylated epiRIL population of *Arabidopsis* to increase occurrences of TE reactivation and found that the histone variant H2A.Z guides preferential integration of reactivated TEs within environmentally responsive genes (113). Thus, stress-induced epigenetic variation at TEs may accelerate genetic adaptation to biotic stress (122). In the following section, we review the evidence that stress-inducible TEs have been domesticated to act as regulatory elements of defense gene expression. On the basis of the high incidence of TEs within *R*-gene clusters (112), we furthermore propose a model by which disease-induced TE hypomethylation accelerates *R*-gene duplication and mutation, thereby providing plants with increased genetic diversity to resist pathogens.

Regulation of defense genes by domesticated transposable elements. Hayashi & Yoshida (51) demonstrated that *Renovator*, a long-terminal repeat (LTR) retrotransposon, acts as a regulatory promoter element of the rice blast resistance gene *Pit*. Because the 5' and 3' LTRs of *Renovator* had not accumulated mutations, it was concluded that this transposition had occurred relatively recently (51). Similarly, the rice blast resistance locus *Pigm*, which controls broad-spectrum resistance without major yield penalties, is under *cis*-regulation by two promoter-localized TEs (38). In *Arabidopsis*, it was shown that a solitary LTR (soloLTR), which is derived from the PTI-inducible retrotransposon *ATCOPLA93*, controls pathogen-induced expression of the nearby *RECOGNITION OF PERONOSPORA PARASITICA 4 (RPP4)* resistance gene (157). TEs can also exert *cis*-regulatory effects from within genes. For example, the ratio of coding to noncoding transcripts of the *Arabidopsis RPP7* *R* gene is influenced by a *COPLA*-type retrotransposon in the gene's first intron (136). Together, these examples illustrate how stress-inducible TEs, which are derived from recent transpositions, have acquired a role in regulating the expression of nearby defense genes. It is noteworthy that TEs with a transcriptional enhancer element can exert regulatory activity on defense genes from more than tens of kilobases away (149), possibly via the *trans*-regulatory mechanisms outlined in Figure 3. On the basis of the evidence presented in this section, we conclude that prolonged periods of disease can expand the regulatory potential of the plant immune system through increased transposition and domestication of TEs in defense gene regulation.

Accelerated evolution of *R* genes under prolonged biotic stress. *R* genes are primarily known for their role in gene-for-gene resistance (ETI). As such, they are subject to a coevolutionary arms race with effector genes from biotrophic pathogens (62). Because microbes have shorter generation times than plants, one could wonder how *R* genes keep pace in this evolutionary arms race. This dichotomy can be explained by the emerging evidence that *R* genes evolve faster than other plant genes.

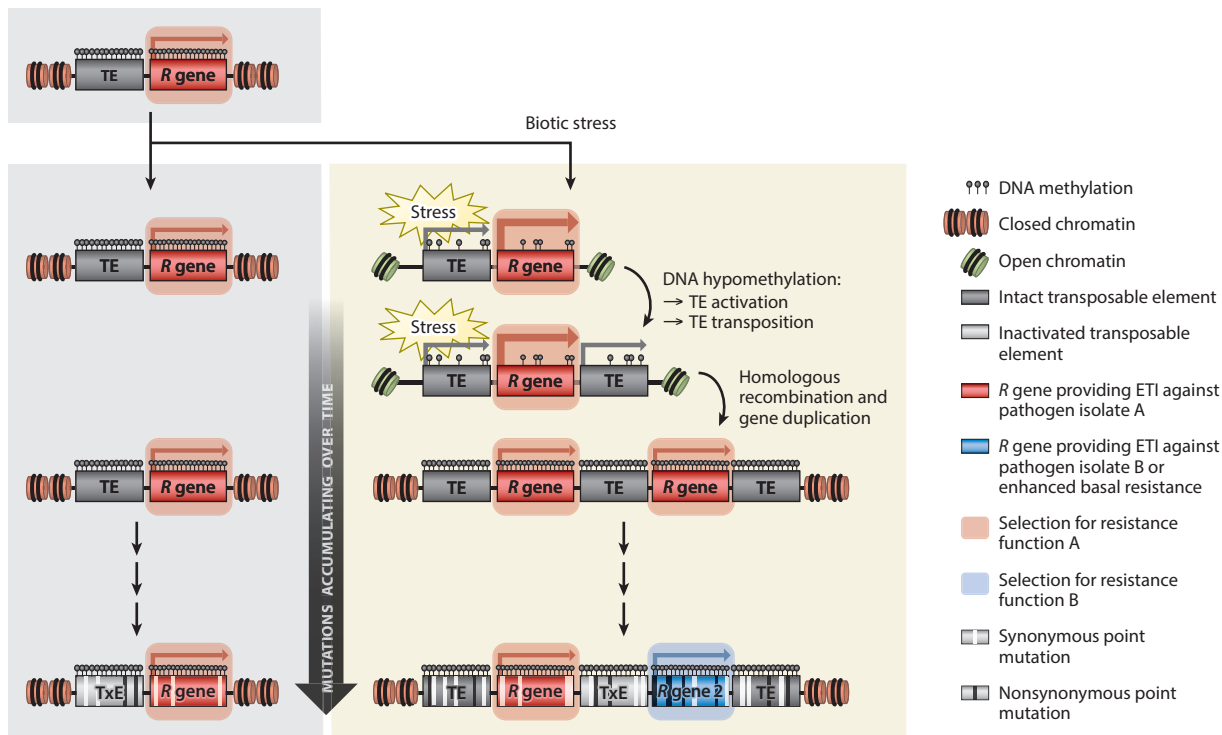


Figure 4

Model of accelerated evolution of resistance (*R*) genes under prolonged biotic stress. Stress induces localized hypomethylation at the site of a class 1 transposable element (TE), which is located near an *R* gene that controls effector-triggered immunity (ETI) against pathogen isolate A. The resulting euchromatinization induces transcription and transposition of the TE, causing duplication of the TE within the *R*-gene cluster. Prolonged exposure to biotic stress increases homologous recombination rates. Nonallelic homologous recombination between repetitive regions of the TEs flanking the *R* gene causes gene duplication within the cluster. In the absence of stress exposure, the TEs are resiled by DNA methylation, which spreads to the neighboring *R* genes, causing increased G:C→A:T mutation rates. Because only one *R*-gene copy is required to provide resistance against pathogen isolate A, the other copy can accumulate mutations over multiple generations and eventually acquire a new resistance function, such as ETI against pathogen isolate B or enhanced basal resistance through constitutive priming of salicylic acid-dependent defense.

R genes are often assembled in gene clusters (158), and some *R* genes, like *Rp1* genes in grasses, show unusually high variation in copy numbers within the same species (42, 125). This enhanced duplication rate can in part be attributed to the high incidence of retrotransposons within *R*-gene clusters (65, 122), as retrotransposons can increase gene duplication through nonallelic homologous recombination (116). Furthermore, because TE transposition rates, homologous recombination, and G:C→A:T point mutations are influenced by chromatin density and DNA methylation (102, 137, 153), it is tempting to speculate that there is a causal link between disease, epigenetic change, and *R*-gene evolution. Indeed, Siedl & Thomma (122) recently suggested that plants and pathogenic microbes contain rapidly coevolving genomic regions that are enriched with both TEs and genes, which regulate disease resistance and virulence, respectively.

The evidence reviewed above points to a model by which prolonged exposure to biotic stress accelerates *R*-gene evolution (Figure 4). Disease-induced hypomethylation within *R*-gene clusters leads to transcriptional reactivation and transposition of the associated TEs. The resulting proliferation of repetitive TE sequences facilitates tandem *R*-gene duplication through nonallelic

homologous recombination (103, 116, 124). Functional redundancy allows for subsequent diversification of duplicated *R* genes via nonsynonymous mutations (103). Considering that methylated cytosines are subject to higher G:C→A:T mutation rates (102, 124), the occurrence of nonsynonymous mutations will be enhanced by the spreading of DNA methylation from nearby TEs. Because exposure to biotic stress is also known to increase homologous recombination frequency (18, 64, 69, 83, 94), the *R*-gene diversification rate could be enhanced further by homologous recombination between highly similar sequences within *R* genes (47, 93). Collectively, this cascade of (epi)genetic changes in response to biotic stress enables plants to diversify their *R*-gene arsenal and expand associated immune functions (**Figure 4**).

It is important to note that the contribution of *R* genes to resistance extends beyond ETI. Previous studies have shown that genetic variation in basal resistance is linked to polymorphisms in *R* genes. Genetic analysis of basal resistance against *P. syringae* across *Arabidopsis* accessions linked variation in gene responsiveness to SA to a highly polymorphic *R*-gene cluster on chromosome 4 (3). This work confirmed previous reports that mutations in the *SUPPRESSOR OF npr1-1*, *CONSTITUTIVE 1 (SNCI)* gene within this *R*-gene cluster influence SA-dependent basal resistance (76, 159). Furthermore, the *Arabidopsis bal* mutant, which shows enhanced expression of multiple *R* genes within the *SNCI* *R*-gene cluster, has a higher level of SA-dependent basal resistance (130). Obtained from a backcross with the hypomethylated *ddm1-2* mutant, the *bal* mutant phenotype was initially assumed to have an epigenetic basis. However, subsequent research revealed that *bal* is caused by genetic duplication within the *SNCI* *R*-gene cluster (154). Strikingly, a screen for suppressor/revertant mutations of the *bal* phenotype revealed a 20-fold higher frequency than expected from average mutation rates (130), all of which was caused by missense mutations in the duplicated *SNCI* gene (154). The example of the *bal* mutant provides experimental evidence in support of our model of *R*-gene evolution (**Figure 4**) because it demonstrates that DNA hypomethylation can lead to *R*-gene duplication, followed by diversification through hypermutation (154).

EXTERNAL STRATEGIES

Plants constantly interact with beneficial organisms, such as insect pollinators, animal seed dispersers, nitrogen-fixing bacteria, and nutrient-providing fungi (20, 90). These organisms can assist plants in their battle against pests and pathogens. In this section, we explore how plants enhance their survival by enlisting beneficial organisms for their defense. This includes both short-term strategies, such as recruitment of natural enemies of attacking herbivores, and long-term strategies, such as shaping rhizosphere and soil microbiomes (**Figure 5**).

Indirect Induced Defense

In response to feeding or egg deposition by herbivores, plants often emit herbivore-induced plant volatiles (HIPVs) (27, 96, 115, 140). HIPVs can mediate tritrophic interactions by attracting predators and/or parasitoids of the attacking herbivore (**Figure 5**) (41, 115, 138, 140). The recruitment of natural enemies of plant attackers by HIPVs is commonly referred to as indirect induced defense because plants are not directly antagonizing their attackers (96). Indirect induced defense is controlled by the plant innate immune system, as HIPVs are induced by defense-eliciting molecular patterns (DAMPs and HAMPs). Accordingly, this plant defense strategy operates over relatively short timescales (138).

Many early reports about indirect induced defense involved maize. In response to feeding by caterpillars, maize releases a rich blend of volatiles that can recruit parasitoid wasps (139, 140)

Rhizosphere:

the narrow region of root-surrounding soil that is influenced by root exudation chemicals and associated microorganisms

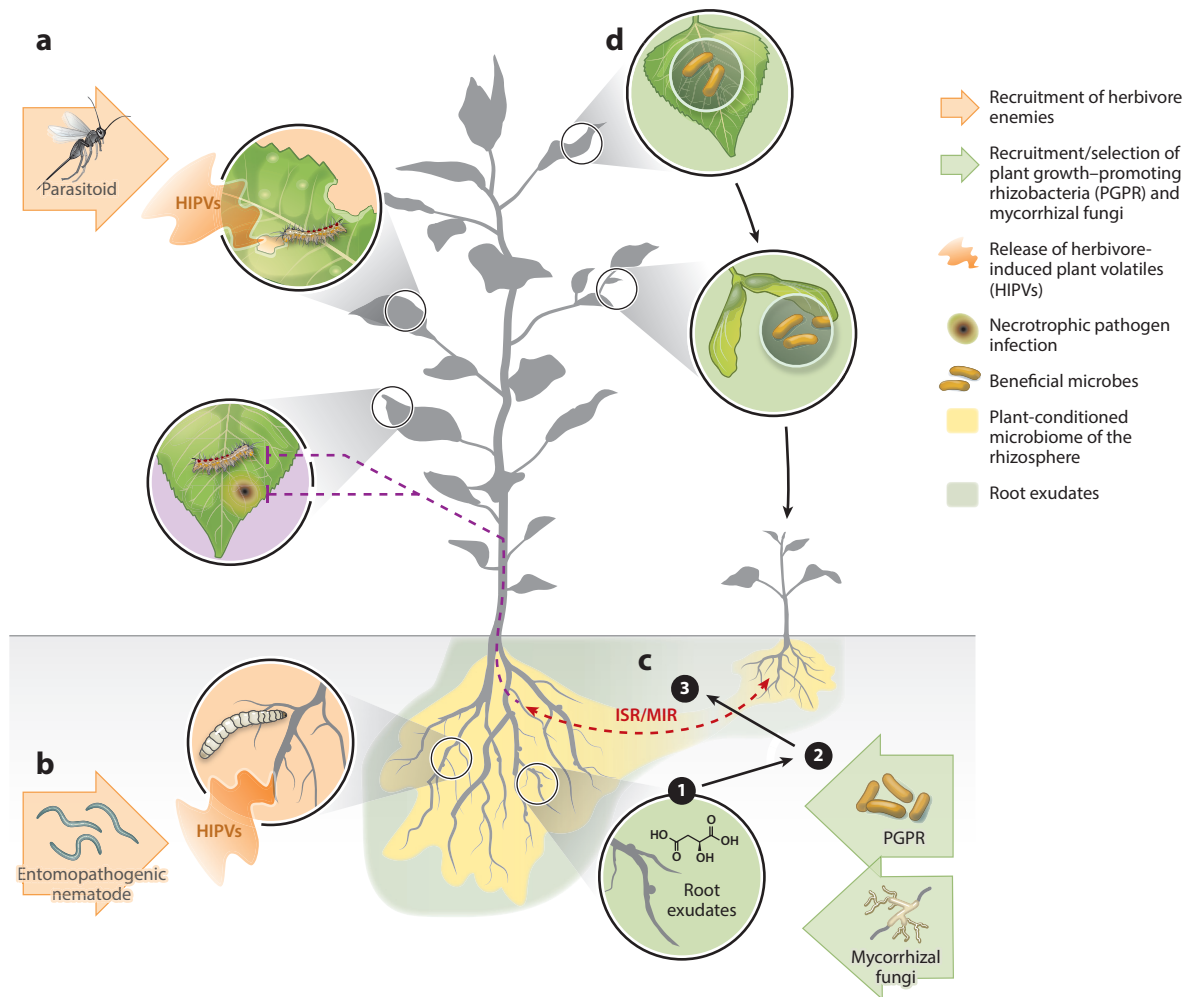


Figure 5

External strategies by which plants resist pests and diseases. Volatile-based strategies that involve tritrophic interactions are shown on the left in orange shading. In response to egg deposition and/or feeding by herbivores, plants release herbivore-induced plant volatiles (HIPVs) that can recruit herbivore enemies, such as (a) parasitoid wasps and (b) entomopathogenic nematodes. These beneficial organisms kill the herbivore and so reduce damage to the host plant. Strategies involving recruitment of disease-suppressing microbial communities are shown to the right in green shading. (c) Plants can change their rhizosphere microbiome upon exposure to disease or herbivory. ❶ Biotic stress changes the quantity and composition of root exudates, resulting in ❷ increased recruitment of beneficial microbes. ❸ The recruited microbes can antagonize soilborne pathogens and/or trigger an acquired resistance (AR; ISR/MIR) response in the host plant (red dashed line), leading to augmented defense expression upon pathogen/herbivore attack (purple dashed line and purple shading). The conditioned microbiome (yellow shading) can spread to and protect neighboring plants including nearby progeny (as indicated by the small plant). (d) Plants may also shape their phyllosphere microbiome and transfer the associated microbes to their progeny via seeds. Abbreviations: ISR, induced systemic resistance; MIR, mycorrhiza-induced resistance.

(Figure 5a). Maize can also recruit natural enemies of belowground herbivores (Figure 5b). In selected maize varieties, feeding by larvae of the western corn rootworm induces emission of the sesquiterpene (*E*)- β -caryophyllene, which can attract entomopathogenic nematodes that infect western corn rootworm larvae (115). Although most studies of indirect induced defense have

focused on angiosperm crop species, there are examples of this defense strategy from across the plant kingdom, including long-living tree species. Following egg deposition in Scots pine needles by the common pine sawfly, there is a systemic increase in emission of the sesquiterpene (*E*)- β -farnesene, which in turn recruits a hymenopteran egg parasitoid (55, 97, 98). Furthermore, black poplar foliage responds to feeding by gypsy moth larvae by releasing HIPVs that recruit endoparasitic wasps (28). Thus, the exploitation of HIPVs in indirect induced defense appears to be conserved across the plant kingdom, indicating that it is an early evolutionary trait (96). However, debate continues surrounding whether HIPVs have evolved specifically to recruit herbivore enemies or to serve other functions, such as acting as airborne signals in plant–plant communication (138). In addition to herbivore enemies, plants can also recruit beneficial microorganisms from their environment. In the next section, we describe how plants recruit these microbes to help their survival in a hostile world (**Figure 5**).

Phyllosphere: the aboveground surfaces of a plant that are influenced by secreted surface chemicals and associated microorganisms

Shaping the Plant-Associated Microbiome

The rhizosphere, phyllosphere, and spermosphere of plants are heavily colonized by commensal and mutualistic microbes (75, 145). These plant-associated microbiomes can help suppress biotic stress via different mechanisms, including antibiosis, nutrient competition, and induction of AR. Consequently, changes in the plant-associated microbiome can improve the long-term survival of plants and even their progeny.

Rhizosphere. Plants control their rhizosphere microbiome through root exudates (34, 107, 119), which change the chemical composition of the rhizosphere to attract and support beneficial microbes, such as plant growth–promoting rhizobacteria (PGPR) and mycorrhizal fungi (**Figure 5**) (59, 129). Pests and diseases are known to alter root exudation composition, which can result in changes in soil- and root-associated microbiomes (11, 46, 68). Although the exact mechanisms driving these stress-induced changes remain unclear, key defense signaling chemicals, including SA, JA, and benzoxazinoids, have been shown to influence microbial communities in the rhizosphere (26, 58, 73). Microbes recruited to roots of pathogen- or herbivore-infested plants can contribute to defense via both direct mechanisms, such as biocidal activity against the attackers (46, 68), and indirect mechanisms, such as competition for nutrients or induction of AR (11, 151) (**Figure 5**).

Stress-induced changes in root exudation can also benefit the progeny of the attacked plant. This transgenerational effect acts through soil conditioning, during which plant-beneficial microbiota are vertically transmitted from parent to offspring via the soil (**Figure 5**). For instance, a recent study by Berendsen and coworkers (11) demonstrated that soil conditioned by downy mildew-infected *Arabidopsis* developed growth- and resistance-inducing activity, whereas soil from healthy *Arabidopsis* did not. Such soil legacy effects are also thought to contribute to the development of disease-suppressive soils in agriculture. A classic example comes from the take-all decline phenomenon, where years of continuous monoculture of barley or wheat under disease pressure by the take-all fungus (*Gaeumannomyces graminis* var. *tritici*) leads to the development of disease-suppressive soil (72). This activity has been attributed to changes in bacterial communities, including fluorescent *Pseudomonas* spp. that control soilborne pathogens through production of antifungal metabolites (72).

It should be noted that most plant–soil feedback experiments report negative effects of sequential monocultures because of the buildup of soilborne diseases (54, 71). Hence, the deleterious effect of vertical transmission of soil pathogens usually exceeds the beneficial effect from the transmission of biocontrol microbes. However, although this trend is apparent for grasses and

forbs, this is not the case for trees (71). This highlights that defense strategies of long-lived plant species may differ substantially from those employed by the more commonly studied annuals.

Phyllosphere. In the context of disease suppression, microbial communities in the phyllosphere have received less attention than those in the rhizosphere (145). There is, nevertheless, growing evidence that phyllosphere communities can contribute to disease suppression in plants (12, 60, 117). There is further circumstantial evidence that plants are capable of shaping their phyllosphere microbiome after biotic stress exposure. For instance, it has been shown that pathogen infection alters bacterial phyllosphere communities (131). Furthermore, genetic studies have linked microbial community structure on *Arabidopsis* and maize leaves to plant defense-related loci (6, 57). If plants indeed shape their phyllosphere microbiome to aid in their defense, one could speculate that vertical transmission of disease-suppressing microbes may also occur. Although plausible pathways exist, for example, via seeds (Figure 5) or leaf litter (145), further studies are needed to confirm vertical transmission of disease-suppressing phyllosphere microbes.

CONCLUSIONS

We have outlined internal and external strategies by which plants adapt to biotic stress (Figure 1). Because of the diversity in life forms and life histories, the timescale and cost–benefit balance of these strategies vary across the plant kingdom. Over the lifetime of a tree, biotic stress conditions likely vary considerably. One could therefore argue that epigenetic inheritance of TAR may be of little benefit to a tree, particularly if the resistance is acquired early in life. Conversely, for annual angiosperms like *Arabidopsis*, there is less time between generations, making it more likely that biotic stress affecting the parent will also pose a threat to its progeny. Therefore, TAR may be more beneficial in annual angiosperms. Regardless of whether this hypothesis is right or wrong, comparisons between species are essential to determine to what extent knowledge from short-lived annuals is transferable across the plant kingdom. There is an urgent need for such comparative studies to prepare global agriculture and forestry for global change.

With ever-increasing global interconnectedness and our rapidly changing climate, the distribution of pests and pathogens is expanding (8). Reliance on a limited number of crop and tree species for food and wood products makes our production systems vulnerable to these shifts in pest and pathogen ranges, as is dramatically illustrated by the recent spread of ash dieback disease across Europe. Diversification of species used in our production systems is essential. Understanding the strategies by which different plants adapt to biotic stress will aid with the selection of new crop and tree varieties.

Apart from the burden of low genetic diversity, agriculture and forestry remain heavily reliant on pesticides. Because of stringent regulations on pesticide usage, the evolution of pesticide resistance, and public concerns about environmental sustainability and chemical residues, this reliance will need to change. It is widely believed that an integrated approach to plant protection can improve the environmental sustainability of the global bioeconomy. The plant defense strategies outlined in this review seem promising for exploitation in such an integrated approach. However, more research is needed to understand the underpinning mechanisms, ecoevolutionary drivers, and complementarity of these strategies. For instance, if agriculture places greater priority on improving soil quality for pest and disease management, research should focus on identifying the root exudation and rhizosphere chemicals that recruit and shape disease-suppressing microbial communities. This information will help to direct the selection of new crop varieties and/or intercropping species that excel in exploiting the soil microbiome for protection (5). To maximize the benefits of AR, plant varieties should be selected that maintain defense priming over time

frames that are useful in agriculture or forestry. Expanding our knowledge about the effects of priming on disease epidemiology in monocultures and mixed plant populations will also help us take full advantage of AR. On a molecular level, more research on the epigenetic mechanisms of defense priming is needed to fully exploit long-lasting (T)AR in pest and disease management. For instance, a better understanding of the epigenetic underpinnings of TAR can aid the generation and selection of epiRILs that are constitutively primed for defense. In *Arabidopsis*, this approach allows the selection of lines that express quantitative disease resistance without affecting plant growth (49). Whether this approach is suitable for crops depends on a variety of factors, including the stability of the resistance and potential nontarget effects. Finally, the introduction of new technologies and practices to improve agricultural sustainability requires consideration of consumer opinions. This is particularly relevant in the context of ongoing public resistance to genetically modified crops in Europe (88).

In summary, our understanding of how plants resist pests and diseases has drastically increased over recent decades, largely due to the adoption of model plant species. Moving forward, we need to increase our understanding of how a diverse range of species survive in a hostile world if we are to establish resource production systems that will remain resilient on our ever-changing planet.

SUMMARY POINTS

1. To resist pests and diseases, plants employ internal and external strategies that are based on plant immunological pathways and can involve interactions with beneficial organisms. These strategies occur over varying timescales ranging from innate immune responses within seconds to (epi)genetic and symbiotic adaptations that occur over multiple plant generations.
2. The two pillars of the plant innate immune system, PTI and ETI, provide instant protection against the majority of potential pests and pathogens.
3. AR can provide relatively long-term protection against biotic stress and is based on two nonexclusive mechanisms: prolonged upregulation of inducible defenses and defense priming. In some cases, priming can be transmitted to following generations.
4. Exposure to biotic stress reduces DNA methylation at TEs, which can prime defense genes via *cis*- and *trans*-regulatory mechanisms.
5. Biotic stress can accelerate *R*-gene evolution through epigenetic and genetic mechanisms. Stress-induced DNA hypomethylation and transcriptional activation of TEs within *R*-gene clusters can enhance gene duplication, facilitating *R*-gene diversification through homologous recombination and point mutation at methylated cytosines.
6. Attack by pests and/or pathogens induces the release of plant metabolites that recruit and support beneficial organisms, which can help plants and their progeny resist pests and diseases.

FUTURE ISSUES

1. To elucidate the mechanisms by which DNA hypomethylation at TEs primes defense gene expression and provides (T)AR, integrated studies of biotic stress-induced changes

in DNA methylome, chromatin structure, chromatin interactions, and noncoding RNAs are needed. These genome-wide studies should be carried out over multiple plant generations to determine the extent to which biotic stress influences (epi)genetic control and genetic diversity of defense genes over longer timescales.

2. Further research is needed to address questions about the ecological and evolutionary context of plant defense strategies. How does defense priming impact disease epidemiology in natural and agricultural ecosystems? Are the intensity, durability, and costs of TAR proportional to the stress encountered in the parent generation? Can TAR-controlling epialleles be selected for and increase plant fitness in hostile environments? Are there costs associated with soil legacy effects?
3. Integrated studies of the plant exudome and associated microbiome are needed to identify which semiochemicals shape disease-suppressing microbial communities above- and belowground.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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