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Beyond pathogens: microbiota interactions with the plant immune system

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Plant immune receptors perceive microbial molecules and initiate an array of biochemical responses that are effective against most invaders. The role of the plant immune system in detecting and controlling pathogenic microorganism has been well described. In contrast, much less is known about plant immunity in the context of the wealth of commensals that inhabit plants. Recent research indicates that, just like pathogens, commensals in the plant microbiome can suppress or evade host immune responses. Moreover, the plant immune system has an active role in microbiome assembly and controls microbial homeostasis in response to environmental variation. We propose that the plant immune system shapes the microbiome, and that the microbiome expands plant immunity and acts as an additional layer of defense against pathogenic organisms.

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Introduction

Scientists have studied the molecular aspects of plant immunity since the mid-1980s. Investigation of how plants recognize, respond, and limit the growth of invading organisms, and the strategies used by pathogens to counteract plant immunity led to a conceptual framework of the plant immune system [1]. Briefly, plants possess receptors that recognize non-self or modified-self molecules which indicate the presence of potential invaders. A first layer of pattern recognition receptors (PRRs) located in the plasma membrane perceives the presence of extracellular molecules, which are often conserved across whole classes of microbes (e.g. fungal chitin or bacterial flagellin) and are thus known as Microbe-Associated Molecular Patterns (MAMPs). Recognition of MAMPs leads to an immune response known as MAMP-triggered immunity (MTI), which is sufficient to halt the proliferation of most microbes. However, adapted pathogens have evolved effector molecules to interfere with MTI and host physiology. The clear dichotomy between extracellular MAMPS and intracellular effectors is, however, increasingly blurred [2]. In turn, plants deploy a second level of receptors to counteract adapted pathogens. These receptors belong to the family of NLR proteins (Nucleotide-binding Leucine-rich Repeat) and function as intracellular sensors that recognize the presence of specific effector proteins. Direct or indirect perception of pathogen effectors by a correspondingly specific host NLR protein activates the Effector-triggered immunity (ETI), which is a robust disease-resistance response that often includes localized host cell death and systemic defense signaling. Complex interplay between plant hormones that control defense versus growth trade-offs are a major part of the plant immune system [3].

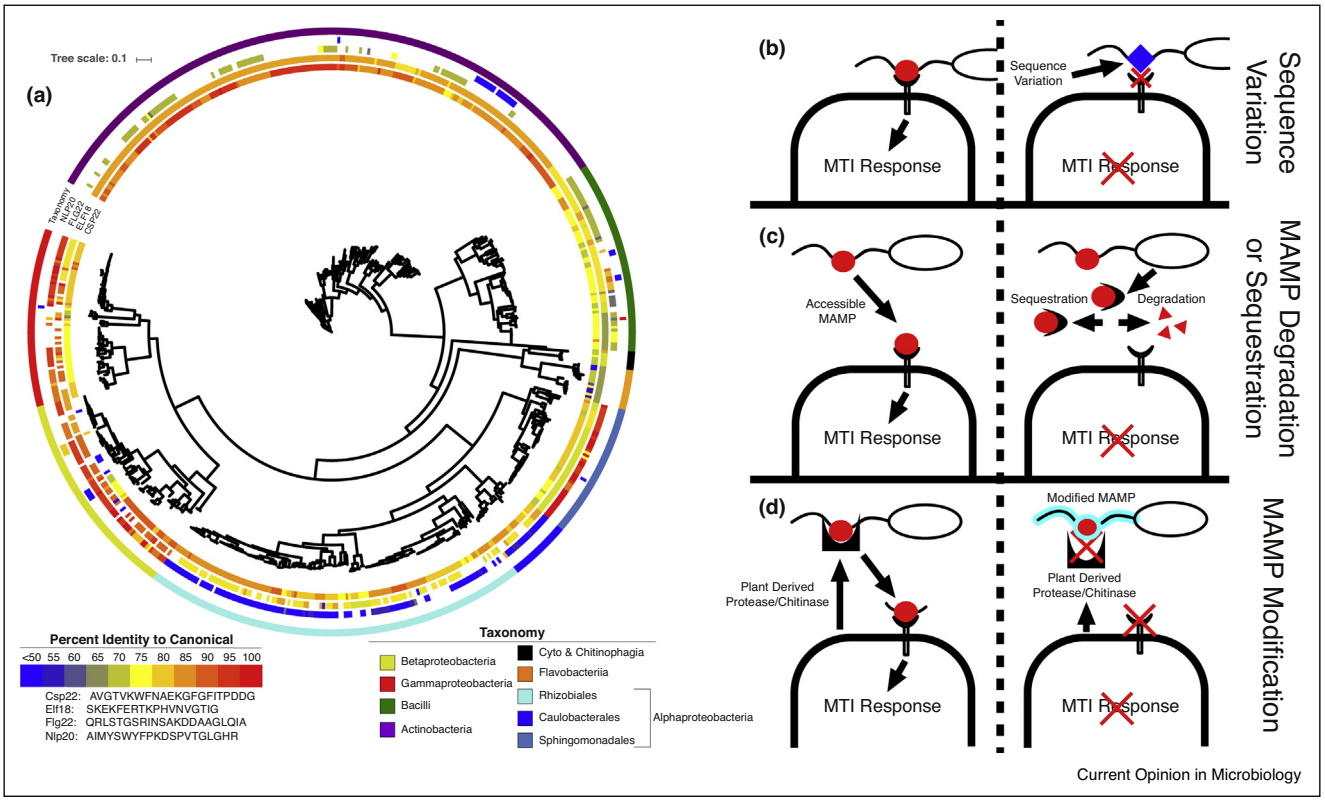
Though this model provides a good overview of the fundamental principles governing plant immunity, it is based on the interaction of plants with pathogenic microbes. However, it is clear that plants establish intimate relationships with diverse commensal microorganisms, forming complex communities in both above-ground and below-ground tissues (i.e. microbiomes), which vary across host plants and environments. In fact, most microbes with which plants interact are non-pathogenic [4], yet many of them express molecules that are potentially recognized by the plant immune system. Thus, one major question of plant microbiome research is whether and how the plant immune system distinguishes commensals from pathogens during microbiome assembly. Are the strategies used by pathogenic microbes to evade plant immunity applicable in the context of microbiomes? Can the microbiome contribute to plant immunity? How does environmental variation shape the interaction between plant immunity and the microbiome?

These are some of the key questions in an emerging field that has gained increasing attention recently [5••]. Here, we review the most recent studies and novel concepts referring to the interaction between the plant immune system and the microbiome, focusing largely on the utility of Arabidopsis and its relatives as a tractable model for these studies.

Evidence for the participation of the plant immune system in microbiome assembly

Plants host microbiomes whose composition differs from the surrounding environment [6–9], yet the mechanisms governing the recruitment of these microbes are largely unknown. The holobiont framework proposes that plants and their collective microbiome form a single entity subject to evolutionary processes [10,11], which implies that plants have adapted ways to distinguish their evolutionary partners from other microorganisms. Alternatively, the assembly of at least some of the plant microbiome may represent mere niche filling, a process influenced by plant traits but of minor adaptive importance for the plant host. Regardless of the proposed adaptive value of the plant microbiome as a whole, it is obvious that some fraction of the commensal community has adaptive value to the host. It is also commonly hypothesized that plants can distinguish between pathogenic and commensal microbes. In fact, in an analysis of closely related commensal and pathogenic *Pseudomonas* strains, the transition between lifestyles is based on the gain/loss of only a very few virulence islands [12•]. Additionally, inspection of 627 bacterial genomes derived from healthy Arabidopsis roots and leaves revealed that 608 bacteria (97%) have the potential to produce putatively immunogenic MAMPs (Figure 1a). Many of these bacteria share identical MAMP variants to known pathogens, indicating that the MTI response shown to repress the growth of pathogens [13] is potentially activated in response to commensals as well. This begs the question of how commensals avoid or suppress MTI. It is plausible that MTI can both inhibit pathogens and maintain microbiome homeostasis by gating microbes 'in' or 'out' upon intimate contact with the host. In this view, MTI functions as a general mechanism used by plants to control the assembly of their microbiota. In support, Arabidopsis multi-mutants defective in MAMP recognition and

Figure 1



Commensal MAMP profiles and potential mechanism used by microorganisms to evade the plant immune system.
(a) Bacteria isolated from healthy Arabidopsis plants harbor potentially immunogenic MAMPs while others show large divergence from the canonical, which may contribute to evasion of the plant immune system. The tree includes 627 Arabidopsis-derived isolates and was generated by pruning the 3837 microbial tree in Levy *et al.* [29•]. MAMP genes were identified using custom built profile hidden Markov models and the MAMPs were identified after aligning all MAMP genes with MUSCLE [105,106]. Percent identity was calculated using edit distance. The tree was generated with iTOL [107]. The canonical sequences are from *Micrococcus lysodeikticus* (csp22) [108], *Escherichia coli* (elf18) [109], *Pseudomonas syringae pv tabaci* (flg22) [36], and *Phytophthora parasitica* (nlp20) [110]. MAMP divergence could lead to plant immune evasion by **(b)** sequence variation, **(c)** MAMP degradation or sequestration, or **(d)** MAMP modification as detailed in the text.

downstream MTI signaling exhibit reduced defense against an avirulent mutant of a normally pathogenic *Pseudomonas syringae* strain and are unable to maintain normal leaf endophytic bacterial communities under high humidity. Inability to regulate the growth of endophytic bacterial communities led to mild chlorosis and necrosis in some leaves, resembling dysbiosis [14••]. This indicates that plants control the growth of microbial populations with their immune system in order to maintain their own health.

Strategies used by the microbiome to evade or suppress plant immunity

Plant immune receptors do not distinguish between microbial lifestyles and recognize ligands that can be present in both pathogens and commensals [15•]. Evasion or suppression of host immune responses is a hallmark of successful pathogens. Likewise, colonization by individual members of the plant microbiome, the essence of community assembly, likely requires strategies to avoid or interfere with plant immunity [16]. Recent work highlights differences and similarities between commensals and pathogens in the strategies used to suppress or evade the plant immune system.

MTI suppression is used by pathogenic microbes to bypass the plant immune system [1] but has also recently been reported for non-pathogenic microbes [17•,18–20]. The beneficial rhizobacterium *Pseudomonas simiae* WCS417 promotes plant growth and suppresses part of the transcriptional response that is triggered by the bacterial MAMP flg22 [15•,21]. Similarly, specific *Rhizobiales* strains that colonize Arabidopsis roots are able to prevent responses that are triggered by the same MAMP [22••]. Endophytes can also prevent MAMP-triggered cytosolic calcium influx in Arabidopsis [23•]. A recent study found that the plant growth-promoting bacterium *Pseudomonas capeferrum* WCS358 produces organic acids that lower the extracellular pH and interfere with the response to flg22 [24•]. Recent research also indicates that mutualistic fungi gain access to plant tissues by manipulating innate plant immunity [25]. Yet, the mechanisms involved in the suppression of immune responses by commensals and mutualists are still largely unexplored. The type III secretion system (T3SS) is a common feature among pathogenic bacteria and it can also be found in non-pathogenic strains [26–28]. Nevertheless, genes encoding this effector-delivery machinery are rare in the genomes of plant-associated commensal bacteria [29•]. This may reflect the apparently weak host specialization of most plant-associated commensals [30]. Thus, a diversity of alternative strategies to interfere with the host immune responses, particularly on the extracellular battleground of MTI, are expected to be found in plant microbiomes.

MTI evasion is another strategy used by both pathogenic and commensal microbes to colonize the plant. Microbes have evolved at least three mechanisms to evade MTI: I) MAMP divergence, II) MAMP degradation/sequestration, and III) MAMP modification.

MAMP divergence

Microbes might evade MTI by evolving MAMP variants that no longer bind to or activate the corresponding plant PRR (Figure 1b). This evasion is at face value likely to be counter-adaptive, since alteration of MAMP sequences and structures may impair the positive function of the microbial MAMP-containing molecule. For example, some flg22 variants that lose immunogenicity also lose motility [31]. Nevertheless, diverse, potentially immune evasive MAMP variants are widespread in certain bacterial taxa. This distribution is likely to be MAMP-dependent (Figure 1a): 26% of the flg22 peptide epitopes found in Arabidopsis-associated bacterial isolates have at least 50% sequence divergence from the canonical active sequence, while less than 1% of elf18 variants identified diverge from the canonical epitope by at least 50%. This suggests that flg22 recognition imposes stronger bacterial fitness defects and/or that the flg22 region is more amenable to variation than elf18, and/or that there are differential stringencies in the requirements for MAMP recognition. Consistent with the first hypothesis, the elf18 receptor EFR is not expressed in Arabidopsis roots, while FLS2 is [21,32]. The MTI response produced by MAMP sequences divergent from the respective canonical sequences is still relatively unknown. In parallel to the MAMP sequence diversity found across plant-associated bacteria, Arabidopsis and tomato lines display large variation in their response to different MAMPs and even to the same MAMP variant, indicating that MAMP recognition across plant populations is evolving [33–35]. Thus, recognition may be driven by the MAMP repertoire of local commensal and beneficial microbes, not just pathogens [15•,22••,36]. Tolerance for the former must be balanced by intolerance of the latter.

MAMP degradation/sequestration

Even if microbes express an immunogenic MAMP, they may have mechanisms to evade MTI. Microbes have evolved proteases that digest their MAMPs or proteins that sequester MAMPs to hide them from plant receptors (Figure 1b). The plant pathogen *P. syringae* DC3000 secretes a protease that, through the degradation of flagellin, decreased MTI and increased this strain's growth in Arabidopsis and tomato leaves [37]. Chitin, a conserved component of the cell wall in fungi, is another potent inducer of MTI. Several fungal pathogens have evolved chitin-binding proteins (LysM or inactive chitinases) capable of sequestering free chitin fragments to prevent the activation of plant PRRs [38–40]. Although this mechanism has been only demonstrated for pathogens thus far, LysM and presumably inactive chitinases are found throughout the fungal kingdom and, therefore, commensals may apply this method of evasion as well.

MAMP modification

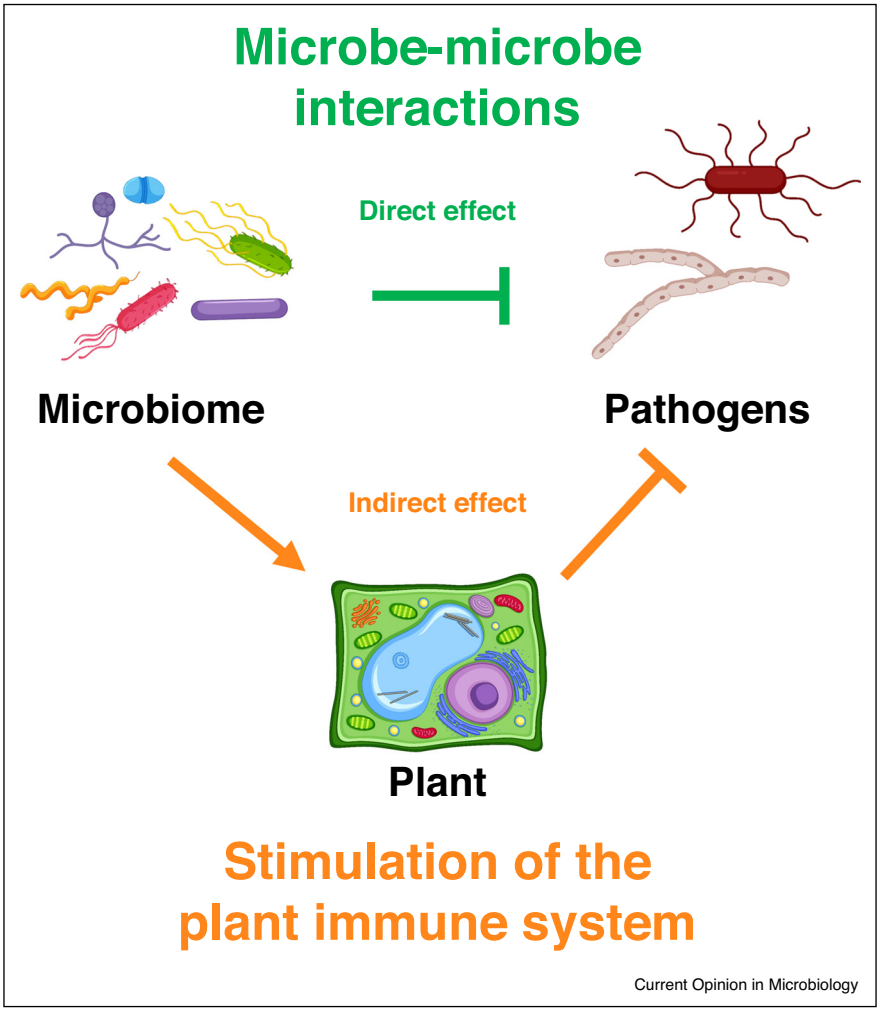
Another strategy used by microbes to prevent the elicitation of MTI is MAMP modification (Figure 1c). For example, *Nicotiana benthamiana* secretes glycosidases that strip the glycan shield from the bacterial flagellum, allowing plant proteases to release the immunogenic flg22 peptide for recognition by the FLS2 receptor [41••]. In turn, pathogens can evade flg22 recognition by either inhibiting plant glycosidases or by modifying the glycan moieties that cover their flagellum [41••]. Similarly, fungi can escape the plant immune system by deacetylating the chitin in their cell wall into chitosan, which is a weaker inducer of immunity [39]. Because both flg22 and chitin are ubiquitous in plant microbiomes, it is likely that commensals have evolved analogous MAMP modification strategies to evade MTI.

The microbiome functions as an extension of the plant immune system

Plant diseases have been traditionally studied as binary associations between a host and a pathogen. In recent years, however, it has become evident that the microbiome can expand plant defensive capabilities and often influences the outcome of plant–pathogen interactions, preventing/mitigating the establishment of diseases by largely unknown mechanisms encompassing the term 'biocontrol' [42,43•,44–49,50•,51]. Importantly, this seems to be largely determined by only two main mechanisms thus far: (I) direct microbe–microbe interactions and (II) stimulation or priming of the plant immune system (Figure 2).

Microbe–microbe interactions play an increasingly evident role in the suppression of pathogens and can

Figure 2



The microbiome expands the plant immune system.
Plant-associated microbes can function as an additional layer of defense against pathogens through at least two mechanisms. First, the microbiome can directly suppress the proliferation of pathogens by producing antimicrobial compounds or through niche competition. Second, the microbiome can indirectly promote resistance against pathogens by stimulating the plant immune system, which in turn becomes more competent to fight off diseases.

serve as a first line of defense against invading organisms in plants. For instance, a molecule secreted by the *Pseudomonas piscium* ZJU60 strain, which was isolated from infected wheat head, antagonizes the fungus *Fusarium graminearum* by inhibiting one of its histone acetyltransferases [50•]. Furthermore, a comprehensive study recently demonstrated that the ability to antagonize other microbes, including pathogens, is a common trait in bacteria isolated from the Arabidopsis leaf microbiome [52]. Genome mining further revealed a high prevalence of a wide variety of unknown biosynthetic gene clusters among inhibitory strains and allowed for the identification of two novel antibiotics [52]. These and other studies show that plant microbiomes are a rich source of pathogen antagonists that work via direct inhibition [53]. Yet, it is likely that many other factors contribute to the direct control of pathogens by the microbiome. In particular, resource competition (niche overlap) with resident microbes has been proposed as an important factor that limits pathogen invasion in plants [54•]. This is analogous to the protective role that commensal microbes play in the animal gut, where invading harmful microbes are outcompeted and their growth repressed by the already-established host microbiome [55–57]. Interestingly, Arabidopsis roots are naturally colonized by potentially harmful filamentous eukaryotes that are nevertheless controlled by multiple co-resident bacteria in the context of a multi-kingdom microbiome [58••]. Removal of protective bacteria results in disease, underscoring the importance of microbiome homeostasis and microbe–microbe interactions to plant health.

In addition to the direct inhibition of pathogens described above, commensal microbes can promote host health by stimulating the plant immune system, thus acting indirectly in the suppression of diseases. A well-known form of microbiome-mediated immunity in plants is induced systemic resistance (ISR), a defense response against foliar pathogens and pests triggered by root-associated microorganisms [59]. Required host genetic components of ISR have been uncovered [60–62] and a number of phylogenetically unrelated microbes have been shown to trigger ISR in many different plant species [59]. A hallmark of ISR is the enhanced sensitization rather than the constitutive activation of defense genes [59]. This means that ISR promotes a faster and stronger systemic immune response, but only upon stimulation. Microbiome-mediated disease resistance involving constitutive activation of the plant immune system (a state of alert) has also been reported. A *Sphingomonas melonis* strain isolated from Arabidopsis activates a subset of plant defense genes and promotes immunity against the bacterial pathogen *P. syringae* DC3000 [42,43•]. This protection is lost in the *bak1/bkk1* mutant, indicating that this commensal likely stimulates plant immunity through MAMP recognition by PRRs that rely on BAK1 as a co-receptor [43•]. These studies demonstrate that disease suppression by commensal microbes can require an intact plant immune system, highlighting the participation of the microbiome in determining the outcome of plant–pathogen interactions.

Recent studies indicate that the plant microbiome is dynamic and responds to the presence of pathogens and pests, supporting the exciting hypothesis that plants actively select protective commensals to fight off diseases under certain circumstances. Arabidopsis grown in native soil from a Dutch field promoted the proliferation of three specific ISR-inducing bacteria in the rhizosphere upon leaf infection with the downy mildew pathogen *Hyaloperonospora arabidopsidis*. Remarkably, these protective bacteria seem to have persisted in the soil and conferred enhanced protection against downy mildew to a subsequent population of plants [63•]. Infection of Arabidopsis leaves with *P. syringae* also resulted in a similar soil-borne legacy that protected a subsequent generation of plants. Supporting the active role of the host in reshaping its microbiome, infected plants displayed altered root exudation profiles that presumably selected for beneficial bacteria [64]. Changes in the microbiome composition and enrichment of potentially beneficial microorganisms have also been observed in barley roots infected with *F. graminearum* [65] and in pepper seedlings infested with whiteflies [66]. Importantly, enrichment of protective microbes in the rhizosphere is associated with the development of disease-suppressive soils, in which plants remain healthy even in the presence of pathogens [67–70]. Thus, microbiome alterations have the potential to affect subsequent generations of plants that germinate in the same soil with consequences for ecological and agricultural processes [71–73].

In sharp contrast to ISR, some root-associated bacteria can make the host plant more susceptible to foliar pathogens. *Pseudomonas* strains that promote resistance against herbivores in Arabidopsis also cause induced systemic susceptibility (ISS) against a hemibiotrophic pathogen [74]. This involves the bacterial production of spermidine, but how this molecule modulates plant immunity is still unclear [75]. Furthermore, arbuscular mycorrhiza fungi also increases the susceptibility of the legume *Astragalus adsurgens* to the foliar pathogen *Erysiphe pisi*, which causes powdery mildew [76]. These studies show that commensal microbes can have pleiotropic effects on the plant immune system, demonstrating that the efficient deployment of immunity-modulating microbes in agriculture will depend on a full understanding of the microbiome effect on plants and both pathogens and other commensals in the context of different environments.

Context-dependent immune modulation shapes the plant microbiome across environments

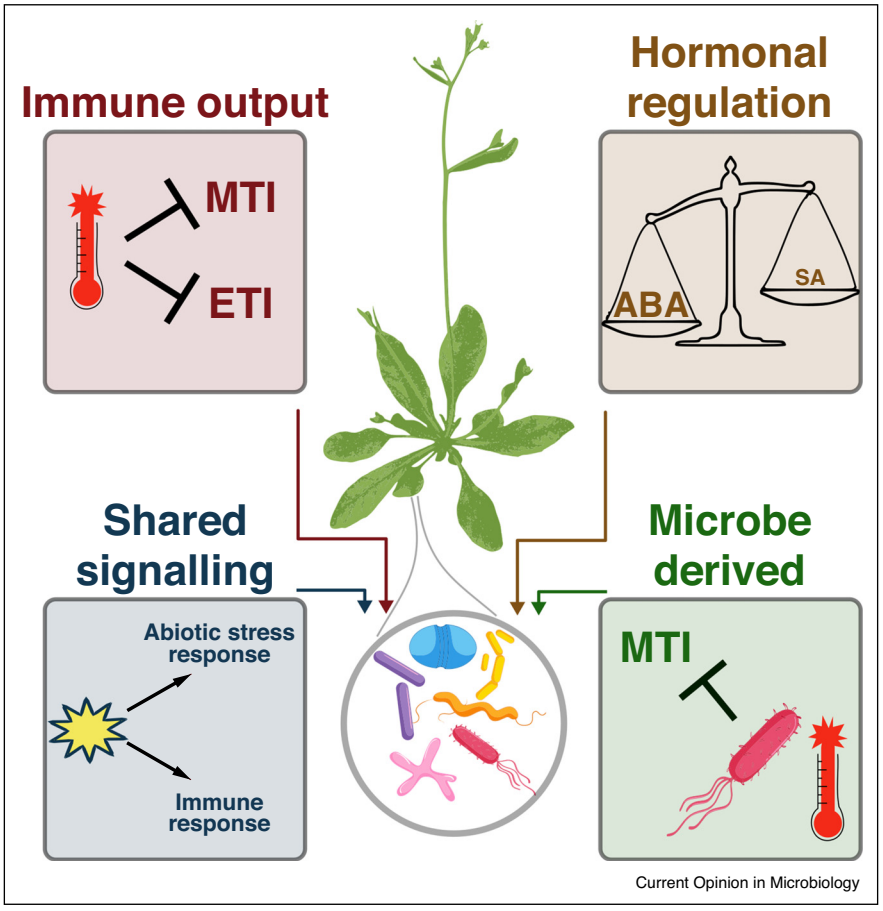
Since their colonization of terrestrial environments, plants have faced heterogeneous environments that vary

in temperature, water and nutrient availability, and chemical attributes such as salinity, pH and the presence of heavy metals. Plant responses to environmental variation are interconnected with plant immunity [77,78], driven in part by the need for plants to optimally respond to combinations of abiotic stress and pathogen invasion. However, the resultant effects of this interconnectedness on the assembly and function of the plant microbiome are only just being explored.

Environmental variation can modulate plant immunity through a number of non-exclusive mechanisms (Figure 3). First, different environments can directly modulate the expression of plant immune outputs [79,80•,81]. For example, exposure to environmental stress can modulate the expression of MTI and ETI-related genes [82–84] and under increased temperature several NLR receptors lose function [85]. Second, hormonal regulators of plant responses to abiotic stress, such as drought and nutrient availability, typically have an antagonistic effect on plant immunity through the suppression of the jasmonic acid (JA) and salicylic acid (SA) defense pathways [78,86]. Indeed, such effects are so potent that microbial pathogens hijack this interplay to facilitate their invasion [87]. Recent work demonstrates that the antagonistic effect of abiotic responses on plant immunity depends on factors such as plant age and the magnitude and temporal sequence of stressors [88•,89,90]. Lastly, shared signaling components can jointly coordinate plant responses to abiotic stress and plant immunity [91••,92••]. For example, the PRR chitin elicitor receptor kinase 1 (CERK1), is responsible for mounting a plant defense against fungal pathogens but also strongly regulates the expression of genes required for salt stress [93].

Microorganisms may also contribute to the modulation of plant immunity across environments. Translocation of bacterial effectors into the host increases at higher

Figure 3



Environmental variation, including differences in temperature, water, or nutrient availability can modulate plant immunity by a number of mechanisms.
First, different environments can modify the expression plant immune outputs including components of MAMP and effector triggered immunity. Second, crosstalk between abiotic stress hormones (such as abscisic acid) and defense hormones (e.g. salicylic acid) can modulate plant immunity. Third, shared signaling components can lead to joint plant abiotic stress and immune responses. Finally, microbes can modulate plant immunity under particular environments. All of these mechanisms of plant immune modulation have the potential to alter the plant microbiome.

temperatures, which contributes to the suppression of plant immunity [80•]. Furthermore, colonization by the fungal endophyte *Colletotrichum tofieldiae* represses plant immunity but only when host plants are grown under low phosphate conditions [94••]. Finally, members of the γ-proteobacteria eject their polar flagella under nutrient depletion, likely in an attempt to conserve energy under unfavorable conditions [95]. However, because flagellin is an important trigger of plant immunity [36], loss of flagella under particular environments may also lead to modulation of MTI with potential consequences for subsequent microbial colonization. Interestingly, persistence of the endosymbiont *Vibrio fischeri* in the light organ of the Hawaiian bobtail squid, *Euprymna scolopes*, is accompanied by the loss of flagella [96,97], suggesting that environment-dependent modulation of host immunity through MAMP modification may be a signature of associated microorganisms across plant and animal hosts.

The modulation of plant immunity under conditions of environmental or nutrient stress can reshape plant microbiota. In low phosphate conditions, plant immune-related compounds, specifically tryptophan-derived secondary metabolites, are required for the controlled recruitment of the fungal endophyte *C. tofieldiae* [94••]. Additionally, PHR1, the master transcriptional regulator of the plant phosphate starvation response, directly modulates plant immunity via targeting genes in the SA and JA pathways. This crosstalk leads to a dampening of plant immune responses and a perturbed root microbiome [92••]. A root-exuded coumarin that is produced by Arabidopsis during iron starvation or in the presence of ISR-inducing bacteria [75] exerts a selective antimicrobial effect in the rhizosphere, suppressing fungal pathogens and reshaping the microbiome to possibly select beneficial microbes [67,76]. In response to iron starvation, plants synthesize and exude coumarins into the rhizosphere, which not only help mobilize iron in soil [98] but also reshape the composition of the root microbiome through their antimicrobial activity [91••,99••]. PBS3, which modulates plant immunity under abiotic stress in an age-dependent manner, also reshapes the composition leaf bacterial communities [88•].

While growing evidence supports the idea that context-dependent immune modulation can reshape plant microbiota, the consequences, whether positive or negative, of such microbiome reshaping for plant performance remain relatively untested. Coumarins exuded by plants under iron depletion selectively inhibit the growth of pathogenic fungi while maintaining plant-growth promoting *Pseudomonas* species and other microbes [91••]. These coumarin-selected microbes may benefit plants by increasing plant tolerance to iron starvation. Similarly, plants may benefit from the alterations to their microbiota under stresses such as herbivory [66], drought [100] and pathogen attack [63•]. Though in these examples the mechanism underlying microbiome alterations was not determined. Under low phosphate conditions, recruitment of the fungal endophyte *C. tofieldiae* increased the biomass of Arabidopsis plants [94••]. However, synthetic community experiments showed that a bacterial taxon enriched in Arabidopsis roots under phosphate starvation reduced plant performance as measured by shoot phosphate accumulation [101]. A recent study demonstrated that triterpenes produced by Arabidopsis are major determinants of the root bacterial microbiome [102••]. These molecules act as antibiotics or proliferation agents depending on the bacteria taxa and selectively regulate the composition of the root microbiota. Importantly, triterpene biosynthesis can be induced in response to abiotic stresses as well as during pathogen and herbivore attack [103]. These examples highlight that microbiome alteration across environments, mediated in part by plant immune modulation, can have both positive and negative effects on plant performance.

Conclusions

Our knowledge of the plant immune system has been primarily built based on decades of study of plant–pathogen interactions. This knowledge is now being revisited, tested and structured in the context of microbiomes, revealing exciting differences and similarities. Research thus far indicates that the plant immune system mediates interactions with pathogenic and commensal microbes alike. Most MAMPs that are recognized by plant immune receptors are commonly found in pathogens and commensals, indicating that colonization of plant tissues by microorganisms involves suppression and/or evasion of the host immune system, regardless of their lifestyle. Indeed, recent work demonstrates that many commensal bacteria can suppress MTI. Future research should focus on determining the mechanisms of this suppression and its significance to microbiome assembly. Equally important is the interaction between pathogens and the community of commensals that inhabit plants. We propose that the microbiome functions as an additional layer of the plant immune system and can suppress diseases directly via microbe–microbe interactions or indirectly via stimulation of plant immunity. We predict that pathogens must have evolved strategies to overcome the immune barrier imposed by the microbiome. Finally, the plant immune system is intricately linked with environmental and nutrient responses, and altered microbial communities are often seen in the face of environmental changes [71,92••,104]. A relevant direction is to investigate how context-dependent immune modulation shifts the composition of plant microbiota and how this helps plants to thrive under stress conditions across various environments. Determining the underlying mechanisms and the resultant plant effects of the complex interplay between plant immunity and microbiota are important goals to advance the field of plant–microbe interactions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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