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Molecular networks in plant–pathogen holobiont

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Plant immune receptors enable detection of a multitude of microbes including pathogens. The recognition of microbes activates various plant signaling pathways, such as those mediated by phytohormones. Over the course of coevolution with microbes, plants have expanded their repertoire of immune receptors and signaling components, resulting in highly interconnected plant immune networks. These immune networks enable plants to appropriately respond to different types of microbes and to coordinate immune responses with developmental programs and environmental stress responses. However, the interconnectivity in plant immune networks is exploited by microbial pathogens to promote pathogen fitness in plants. Analogous to plant immune networks, virulence-related pathways in bacterial pathogens are also interconnected. Accumulating evidence implies that some plant-derived compounds target bacterial virulence networks. Thus, the plant immune and bacterial virulence networks intimately interact with each other. Here, we highlight recent insights into the structures of the plant immune and bacterial virulence networks and the interactions between them. We propose that small molecules derived from plants and/or bacterial pathogens connect the two molecular networks, forming supernetworks in the plant–bacterial pathogen holobiont.

Keywords: bacterial virulence; microbiota; plant immunity

Biological systems in an organism are often represented as networks that consist of complex interactions between biological elements, such as genes, proteins, and metabolites. These molecular networks provide the organism with a variety of regulatory functions. In an ecological context, organisms do not live in isolation but with intimate interactions with other organisms. This collective assemblage of different organisms is called "holobiont" [1], in which molecular networks of an organism can be connected to those of other organisms, resulting in the formation of a "supernetwork".

The plant innate immune system relies on an expanded repertoire of immune receptors on the cell surface or inside the cell to detect molecular signatures associated with microbial invasions [2,3]. Perception of microbe- and damage-associated molecular patterns (MAMPs and DAMPs) and effector molecules by the plant immune receptors activates pattern-triggered immunity (PTI) and effector-triggered immunity (ETI), respectively [2,3]. PTI and ETI activate various immune signaling pathways such as those mediated by phytohormones and restrict microbial invasion and proliferation [2,4,5]. Plants have evolved complex interactions between immune receptors and between immune signaling components. These immune receptors and signaling networks are collectively defined as

Abbreviations
ABA, abscisic acid; AHLs, Acyl-homoserine lactones; ECDs, extracellular domains; ET, ethylene; ETI, effector-triggered immunity; HR, hypersensitive response; IAA, indole-3-acetic acid; PRRs, pattern recognition receptors; PTI, pattern-triggered immunity; QS, quorum sensing; ROS, reactive oxygen species; SA, salicylic acid.

plant immune networks in this review (Fig. 1). The plant immune networks are further connected with components in other physiological processes to optimize plant responses in a given condition. For instance, phytohormone signaling networks coordinate plant immunity with developmental programs and abiotic stress responses [5–9].

During the course of coevolution with host plants, pathogens have evolved diverse virulence mechanisms to manipulate components of the plant immune networks [10]. A remarkable example is that many pathogens deploy effector proteins or produce phytohormones or their mimics to exploit existing antagonistic interactions in the phytohormone signaling networks, thereby dampening plant immunity [11,12]. Thus, the interconnectivity in the plant immune networks provides not only versatile regulation in plants but also vulnerability to pathogen exploitation.

Bacterial pathogens are well studied with respect to virulence mechanisms. In addition to proteinaceous type III effectors (T3Es) delivered into the host cell by the type III secretion system (T3SS), many other virulence-related molecules and processes have been characterized, including siderophores, exopolysaccharides, quorum sensing, and production of phytohormones and their mimics [13–17]. Moreover, bacterial cells globally regulate expression of these virulence factors, which may coordinate diverse tasks in host plants [18] These coordinated regulations of virulence factors can be regarded as bacterial virulence networks (Fig. 1). Analogous to the bacterial virulence molecules that interfere with plant immunity, some plant-derived compounds are shown to affect the components of bacterial virulence networks [19].

In the past decade, significant progress has been made in the systems analysis of molecular networks underlying plant–pathogen interactions with a primary focus on the plant side during the interactions [20–22]. In this review, we highlight recent biological and functional insights into the plant immune networks whose highly interconnected property provides a great regulatory potential for the benefit of the plant but is also exploited by pathogens. Then, we discuss relatively understudied research topics in plant–pathogen interactions, namely, the bacterial pathogen virulence networks and their potential manipulation by plant immunity. Finally, we propose that small molecules produced by plants and bacteria likely connect the molecular networks of plants and bacteria, which results in a supernetwork of the plant and bacterial

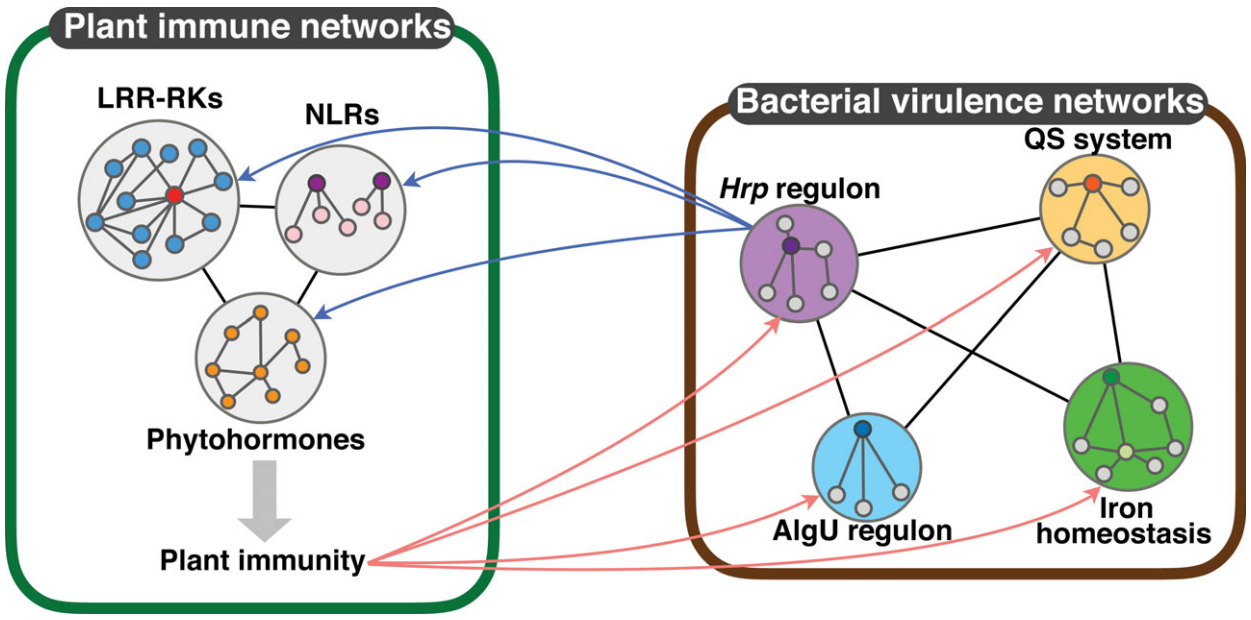

Fig. 1. Possible structures of the plant immune and bacterial virulence networks and their interactions. Blue arrows: Bacterial type III effectors and toxins regulated by the *hrp* regulon target the plant immune networks. Red arrows: Plant immunity targets components in the bacterial virulence networks with unknown mechanisms. The plant immune networks include leucine-rich repeat receptor kinases (LRR-RKs) networks, nucleotide-binding domain and leucine-rich repeat-containing proteins (NLRs) networks, and phytohormone networks. The bacterial virulence networks include *Hrp* regulon, AlgU regulon, quorum sensing (QS) system, and iron homeostasis system. The subnetworks in the plant immune or bacterial virulence networks are interconnected (black lines).

holobiont. We do not intend to present a comprehensive review of this body of knowledge, but rather aim at introducing important concepts using key examples to stimulate future researches.

Immune receptor networks

LRR-RK and NLR networks

Pattern-triggered immunity is activated through recognition of microbe-derived ligands, called MAMPs, or plant-derived ligands, known as DAMPs, by cell surface-localized pattern recognition receptors (PRRs), a major class of which are leucine-rich repeat receptor kinases (LRR-RKs) [2]. For instance, FLS2 recognizes the MAMP flg22 derived from bacterial flagellin, while PEPR1 and PEPR2 sense Pep peptides, which are DAMPs processed from endogenous PROPEP proteins in *Arabidopsis thaliana* [2]. Upon ligand binding, these LRR-RKs recruit another LRR-RK, BAK1, for transducing the signal to the cytosol [23]. Although it has been often reported that LRR-RKs interact with each other through their extracellular domains (ECDs) [24], a comprehensive analysis on LRR-RK interactions is confounded by a massive expansion of this class of receptor proteins in plants [25]. By employing a high-throughput *in vitro* interaction assay, Smakowska-Luzan *et al*. tested 40,000 interactions between 200 ECDs in *A*. *thaliana* to construct an LRR-RK interaction network (CSI^{LRR}) [26]. CSI^{LRR} helped to identify multiple LRR-RKs that modulate immune responses. The LRR-RK FIR interacts with both FLS2 and BAK1 and promotes flg22-induced FLS2-BAK1 complex formation, reactive oxygen species (ROS) production, defense gene expression, and the growth inhibition of the bacterial pathogen *Pseudomonas syringae* [26]. In CSI^{LRR}, BAK1 and APEX are hub LRR-RKs whose removal could strongly affect network connectivity [26]. BAK1 is an integral signaling partner for multiple PRRs, including FLS2, PEPR1, and PEPR2 [23]. APEX interacts with PEPR1 and PEPR2 in the presence and absence of the Pep2 peptide ligand, and contributes to Pep2-induced immune responses [26]. As opposed to BAK1, the APEX protein does not interact with FLS2. Interestingly, however, genetic removal of APEX enhanced flg22-induced FLS2-BAK1 complex formation, ROS production, MAP kinase (MAPK) activation, and defense gene expression [26]. Thus, even without a direct physical interaction with FLS2, APEX affects the FLS2 functions through CSI^{LRR}. This suggests that CSI^{LRR} may monitor the integrity of APEX and accordingly modulate plant immune responses by an unknown mechanism. Interestingly, it was shown that PEPR1 is functional in the absence of BAK1 as it can form complexes with most members of SERK proteins, including BAK1 [27]. This study further showed that genetic or pathogen elimination of BAK1 enhances PEPR1/PEPR2-mediated cell death and immune responses, thereby compensating for the loss of BAK1-dependent PRR signaling. It will be of a key future challenge to explore and define such regulatory functions of CSI^{LRR}.

Effector-triggered immunity is a potent form of plant innate immunity that is often accompanied by hypersensitive response (HR) cell death and is mediated by nucleotide-binding domain and leucine-rich repeat-containing proteins (NLRs) [4]. Typically, NLRs are intracellular immune receptors that either directly detect pathogen effectors or indirectly sense the virulence actions of pathogens [3,4]. Emerging evidence points to complex NLR networks, in which "sensor" NLRs recognize pathogen effectors and "helper" NLRs act downstream of effector recognition [28–30]. In *A*. *thaliana*, the helper NLRs, ADR1, ADR1-L1, and ADR-L2, contribute redundantly to ETI mediated by three different sensor NLRs that detect bacterial or oomycete effectors [28]. Similarly, *Nicotiana benthamiana* NRC2, NRC3, and NRC4 are helper NLRs that function to elicit HR cell death following recognition of bacterial, oomycete, nematode, or viral effectors by nine different sensor NLRs, and in most cases, the redundant functions of NRC2, NRC3, and NRC4 are evident [30]. Phylogenetic analysis of plant NLRs revealed that the ADR1 and NRC families are distantly related [30]. Moreover, the NRC family is present in asterids including *N*. *benthamiana*, but absent in rosids including *A*. *thaliana* [30–32]. These findings suggest that the ADR1 and NRC families have independently evolved as helper NLRs, on which signals from various sensor NLRs converge. In this way, sensor NLRs could gain a new recognition spectrum without losing the inter-relationship with cognate helper NLRs for signal transduction. Thus, the network structure consisting of pathogen-detecting sensor NLRs and downstream functionally redundant helper NLRs could allow plants to evolve sensor NLRs against a large variety of effectors from fast-evolving pathogens and, at the same time, to maintain robust NLR signaling mediated by helper NLRs.

The plant receptor networks as targets of pathogens

Pathogens have evolved effector molecules that target components of CSI^{LRR} to dampen PTI. Not surprisingly, BAK1, a hub of the network, is targeted by

multiple effectors: AvrPto, AvrPtoB, HopF1, and HopB1 [33–35]. Intriguingly, HopB1 protease specifically cleaves immune-activated BAK1, thus conferring virulence without perturbing other BAK1 functions, such as those in plant growth [35]. AvrPtoB also targets the MAMP receptors FLS2 and CERK1 [36–38]. HopAO1 targets another MAMP receptor, EFR [39]. Therefore, although CSI^{LRR} enables plants to finely control PTI responses, it can be exploited by pathogens as the manipulation of a PRR could affect other parts of CSI^{LRR} due to the highly interconnected network structure.

Although ETI confers potent and robust immunity against biotrophic pathogens, which feed on living host tissues, ETI is exploited by some necrotrophic pathogens that actively kill host tissues and feed on the remains. In oats, an immune component TRX-h5 is guarded by the NLR LOV1 [40,41]. *Cochliobolus victoriae*, a necrotrophic fungus and the causal agent of Victoria blight, hijacks this defense system by producing an effector molecule, victorin, which binds to TRX-h5 and consequently triggers LOV1-mediated HR cell death, conferring disease susceptibility to *C. victoriae* in oats [40,41]. Another necrotrophic fungus, *Parastagonospora nodorum*, produces SnToxA, which indirectly activates the wheat NLR Tsn1 to cause HR cell death and susceptibility [42]. *P. nodorum* also produces SnTox1, which directly binds to Snn1, a wall-associated kinase class receptor kinase, to trigger cell death for inducing susceptibility [42]. Thus, plant immune signaling triggering cell death is exploited by necrotrophic pathogens that benefit from host cell death. However, it was shown that prior ETI activation in one half of a leaf has no effect on promoting the growth of the necrotrophic fungus *Alternaria brassicicola* in the other leaf half [43]. Furthermore, ETI-associated cell death and defense responses are tightly regulated in a spatiotemporal manner [44,45]. Therefore, it may be possible that spatiotemporal regulation of ETI responses including cell death provides certain tolerance against exploitation by necrotrophic pathogens.

Immune signaling networks

Phytohormone networks

Phytohormones are small signal molecules that are produced in plants in response to internal and external stimuli, such as developmental cues and pathogen invasion, and regulate plant responses to the stimuli [46]. Land plants have expanded the repertoire of phytohormones, which likely contributed to plant adaptation to the more variable terrestrial environments [5]. Consistently, an evolutionary and comparative genomic analysis of species representing all the major plant lineages revealed that signaling mediated by the major immunity-related phytohormones jasmonate (JA) and salicylic acid (SA) likely originated in the last common ancestor of land plants [47]. JA and SA signaling can interact either antagonistically or synergistically, depending on the context, and these interactions are modulated by other phytohormones, such as ethylene (ET), abscisic acid (ABA), and auxin, collectively forming a phytohormone signaling network [5]. The properties of the phytohormone signaling network were difficult to study due to complex interactions among network components. An approach to dissect such a complex network is to remove network components to the level where the network fully loses its functional output and then assign functions to individual network components and their interactions by studying how the network output is recovered during stepwise reconstruction of the network using combinatorial genetic perturbations [20]. To this end, all possible combinations (from single to quadruple) of *A. thaliana* mutants deficient in signaling mediated by JA, ET, SA, and PAD4 were generated, enabling experimental stepwise reconstitution of the four signaling sectors and their interactions in the network [20,48]. PAD4 contributes to SA accumulation and also mediates an SA-independent immunity [49]. This SA-independent signaling mechanism is defined as the PAD4 sector hereafter. Quantitative measurements of expression of marker genes for each signaling sector, as well as the growth of *P. syringae* pv. *tomato* DC3000 (*Pto*) and pv. *maculicola* ES4326 in all possible combinations of plant genotypes treated with three different MAMPs enabled construction of a highly predictive regression model that describes signal flow in the JA/ET/SA/PAD4 signaling network during PTI [50]. The model showed that the ET sector represses the JA and PAD4 sectors, the latter of which explains a mechanism for ET-mediated SA suppression, as PAD4 is required for SA accumulation in PTI [51]. Loss of either ET or JA sectors increased network fragility, indicating that the inhibitory effect of the ET sector on the JA sector is important for robustness of the network output [50]. The model also revealed that dominant activation of the SA sector over the JA sector by the bacterial MAMP flg22 is associated with strong growth restriction of *P. syringae* strains, whereas stronger activation of the JA sector than the SA sector by the fungal MAMP chitosan is associated with weak bacterial resistance [50]. In nature, plants are simultaneously exposed to bacteria, fungi, and

other microorganisms. Hence, it is conceivable that plants distinguish different mixtures of MAMPs from different classes of microbes and activate the immune signaling sectors with different strengths, resulting in PTI tailored to particular assemblage of microbial communities that the plant encounters.

The network reconstitution approach was also used to dissect complex regulation of *A. thaliana* transcriptome responses to flg22 by the JA/ET/PAD4/SA signaling network [52]. Statistical modeling of the contributions of the individual signaling sectors and their interactions to expression changes of over 5000 flg22-responsive genes revealed that these genes are not merely dependent on single signaling sectors, but rather on multisector interactions. Consequently, the transcriptional responses of most of the flg22-responsive genes are highly buffered (i.e., single mutations do not affect flg22 responsiveness) and thus likely resilient to perturbation of the network components by, for example, pathogen effectors and environmental factors. The combination of network reconstitution and statistical modeling also unveiled transcriptional regulatory logic that could not be detected in conventional genetic studies. For instance, the SA-dependent genes defined by a conventional genetic means (genes showing no transcriptional responses in an SA-deficient mutant *sid2*) were not simply regulated by the SA signaling sector alone, but were regulated by the ET, PAD4, and SA signaling sectors and their interactions [52]. Moreover, simultaneous perturbation of the JA, ET, PAD4, and SA signaling sectors in a quadruple mutant led to identification of a signaling mechanism that modulates HR cell death during ETI [53]. In the quadruple mutant, the ETI-triggering effector AvrRpt2 failed to elicit HR cell death when delivered by *P. syringae*, but, surprisingly, was capable of doing so when expressed directly in plants by means of a transgene. A difference in the two experimental conditions, that is, PTI activation by MAMPs, was shown to inhibit ETI signaling-mediated HR cell death in a manner independent of the JA/ET/PAD4/SA signaling network. The molecular identity of this ETI signaling and its inhibition mechanism by PTI remain elusive, but the latter could be explained by the GYF domain protein PSIG1 that is phosphorylated upon MAMP perception and is required for suppressing HR cell death during ETI in an SA- and ROS-independent manner [54].

Both JA and SA accumulation increases during PTI and ETI [50–52,55], suggesting the importance of JA-SA crosstalk for orchestrating plant immune responses. Nevertheless, our understanding of the biological significance of JA-SA crosstalk was mostly limited to their antagonistic interactions explaining prioritization of JA- or SA-mediated immunity, each of which is effective to suppress the growth of pathogens with different lifestyles over the other [43,56]. This is likely because most studies on JA-SA crosstalk have been performed with exogenous application of these hormones or through analysis of single null mutants [57]. The PTI signaling network model mentioned above generated a surprising hypothesis that JA, together with PAD4, accounts for activation of SA signaling during PTI [50]. A follow-up study validated this prediction by demonstrating the mechanism by which JA controls flg22-induced SA accumulation [58]. JA exerts a repressive effect through MYC transcription factors on expression of *PAD4* that positively contributes to expression of *EDS5*, a gene essential for SA accumulation [58]. Paradoxically, JA activates *EDS5* directly through the same MYC transcription factors [58]. The former inhibitory effect of JA on SA is functionally dominant when PAD4 can fulfill its function, thereby mitigating SA accumulation to minimize its negative impact on plant growth [58]. However, the latter positive effect of JA on SA comes to play an important role in supporting robust SA accumulation and immunity when PAD4 is perturbed by, for example, high temperature [58]. Thus, this "incoherent feed-forward loop" consisting of JA, PAD4, and EDS5 coordinates SA-mediated immunity with plant growth and high-temperature response during PTI [58]. Another excellent example of the biological significance of JA-SA crosstalk was recently proposed [44]. During ETI, a concentration gradient of SA is formed around the pathogen infection site that eventually undergoes HR cell death [59]. Intravital time-lapse imaging of the promoter activities of the SA maker gene *PR1* and the JA marker gene *VSP1* during *Pto* AvrRpt2-triggered ETI showed that JA signaling is activated in a spatial domain surrounding the HR area at an early stage, which is followed by activation of SA signaling in the region between the HR- and JA-active domains [44,45]. This temporally dynamic and spatially separated activation of JA and SA signaling during ETI could be interpreted as a plant strategy to locally confine the SA-active cells via JA-SA antagonism and to create JA-active cells for preventing secondary infection by necrotrophic pathogens that are sensitive to JA-mediated immunity [43,45,56]. Thus, this study clearly highlights the importance of spatiotemporal analysis to understand the functionality of phytohormone signaling networks. Taken together, highly interconnected phytohormone signaling networks enable plants to integrate multiple inputs from microbes and environments and accordingly regulate immune responses at the transcriptional level with temporal and spatial coordination.

Phytohormone networks as targets of pathogens

Bacterial and fungal pathogens have evolved to target the phytohormone network to subvert plant immunity, often by exploiting the interconnected feature of the phytohormone signaling networks [11,12]. Hormone crosstalk suppressing SA (e.g., JA-SA, ABA-SA, and auxin-SA) is often exploited by biotrophic bacterial pathogens that are sensitive to SA-mediated immunity. Here, we highlight two types of exploitation/targeting of phytohormone crosstalk in plant–bacteria interactions. The first is the manipulation of phytohormone signaling pathways by using effector proteins. AvrB, HopX1, HopZ1a, and HopBB1 employ different mechanisms to degrade JAZ proteins, the repressors of JA-mediated transcriptional reprogramming, thereby activating JA signaling to dampen SA-mediated immunity [60–63]. AvrPtoB and AvrRpt2 enhance the accumulation of ABA and auxin, respectively, and promote virulence [64,65]. The second strategy is the production of phytohormones or their mimics. The phytotoxin coronatine (COR) produced by certain strains of *P. syringae* functions as an analog of JA-isoleucine (JA-Ile), an active endogenous JA, and contributes to suppressing stomatal and apoplastic immunity by reducing SA accumulation and/or by inactivating MAPKs [66,67]. Production of COR or COR-like compounds is known in other bacterial pathogens, suggesting that producing JA-Ile mimicking compounds may be a widespread strategy for bacterial pathogens to confer fitness advantages in plant hosts [68]. Several plant pathogens produce the auxin indole-3-acetic acid (IAA) to affect host auxin signaling [16]. Disruption of *aldA* and *aldB*, encoding IAA biosynthesis enzymes, leads to reduced bacterial virulence in the plant host in an SA-dependent manner [69], suggesting that hijacking auxin signaling is a virulence mechanism that suppresses SA-mediated immunity. Notably, some bacteria are known to produce SA although the physiological significance of this during interaction with plants remains elusive [70,71].

Which of these strategies (signaling manipulation by proteinaceous effectors or phytohormones) is more advantageous for pathogens? Effector proteins that target phytohormone signaling pathways can potentially be recognized by plant NLRs and trigger ETI. Indeed, AvrRpt2, AvrB, AvrPtoB, and HopZ1a are known to trigger ETI in certain plant genotypes [62,72–75]. On the other hand, phytohormones or their mimics produced by bacteria would have no or less risk of triggering ETI as they can hardly be recognized as foreign molecules. Thus, it could be argued that the production of phytohormones (mimics) is more advantageous. However, a comparative genome analysis of 287 *P. syringae* strains showed that COR is not the dominating JA-activating molecule over other JA-manipulating effectors [63]. Although more comprehensive analysis including COR-like molecules would be helpful, these data imply that there are additional factors that determine the value of these virulence molecules. It was proposed that, while COR and HopX1a fully activate JA responses, HopBB1 targets only a subset of the JAZ proteins and activates a subset of JA-mediated responses, potentially minimizing pleiotropic negative effects on the hosts, which could lead to the benefit of the pathogens [63]. Since biosynthesis of COR requires a series of chemical reactions and enzyme-encoding genes, one can speculate that COR production may be costly for bacteria compared with T3Es as a single T3E can provide an added value [76].

Effector-triggered immunity can effectively suppress pathogen growth despite the existence of many virulence T3Es and toxins that interfere with the plant immune networks. An emerging idea for explaining this is that ETI can counteract virulence actions of pathogen effectors. For instance, ETI triggered by AvrRpt2 induces S-nitrosylation and inactivation of the bacterial effector HopAI1 that suppresses MAPKs, important components of plant immunity [77], thereby restoring plant immunity [78]. Also, AvrRpt2-triggered ETI cancels COR-triggered gene regulation that causes MAPK inactivation [67]. Understanding the precise mechanisms of pathogen virulence and its suppression by plant immunity is key to engineer the plant immune networks. In a pioneering work, based on the crystal structure of the receptor-ligand complexes, the JA receptor COI1 was engineered to avoid binding to COR while maintaining the binding with JA-Ile [79]. Transgenic plants expressing the modified COI1 receptor in *coi1* background showed insensitivity against COR while maintaining the functions of endogenous JA [79].

The virulence networks of plant–bacterial pathogens

Bacterial genes and processes that are important for virulence in plants have been characterized in different bacterial species. These include T3SSs, T3Es, quorum sensing, and iron homeostasis. However, how these processes are regulated *in planta* is poorly understood. In addition, the regulatory mechanisms of pathogen virulence pathways appear to be different even between closely related bacterial strains, which makes it difficult to distil a general concept. Nevertheless, in this section, we highlight relatively well-studied

bacterial virulence factors and their regulations *in planta* and discuss the possible feature of the bacterial virulence networks.

T3SSs and T3Es are the best studied bacterial factors in plant pathogens that are crucial for virulence and for structuring host range [80–83]. Genes related to T3SS and T3Es are involved in so-called the *hrp* regulon and are regulated in a synchronized manner, e.g., they are induced upon infection to the host or in growth media mimicking plant environments [80]. HrpL, an ECF sigma factor, is the primary regulator of this regulatory pathway in many plant–bacterial pathogens [80]. *hrpL* mutants of *P. syringae* show impaired virulence in tomato and *A. thaliana* [84,85]. HrpL also regulates several non-T3E genes, some of which are important for pathogen virulence. These include *iaaL*, an IAA-amino acid conjugate synthase, *matE*, a putative MATE family transporter, and *corR*, a COR regulator, all of which are important for the virulence of *Pto* [84,86,87].

Quorum sensing (QS) is a cell–cell communication process with which bacteria orchestrate their responses as a community and is important for bacterial virulence [88]. QS is mediated by signaling molecules called autoinducers that are produced and secreted into the environment and are perceived by specific receptors. Acyl-homoserine lactones (AHLs) are the most common autoinducer in gram-negative bacteria [88]. In *P. syringae* pv. *syringae* (*Pss*), a mutant lacking both the AHL synthase and AHL receptor showed reduced virulence in bean leaves [15]. The QS system was shown to regulate many genes related to virulence, such as plant cell wall degrading enzymes and T3SS in *Pectobacterium atrosepticum* during infection in potato [89]. Bacteria likely employ QS systems to respond to host signals in addition to their own signals. Typically, genes encoding an AHL synthase and AHL receptor are linked on the genome, but some receptor genes lack their paired AHL synthase genes; these are called orphan or solo receptors [90]. A subgroup of the orphan receptors, found in plant-associated bacteria, responds to plant-derived compounds and regulates virulence-related genes [91,92]. For instance, an orphan receptor of *Xanthomonas oryzae* pv. *oryzae*, OryR, is important for responding to rice-derived compounds and positively regulating the expression of genes important for virulence [93–95].

Iron is an essential element for most organisms, including plants and bacteria and iron homeostasis is known to be important for bacterial virulence in plant and animal hosts [13,96]. Fur is the primary regulator of iron homeostasis in many bacteria, which typically functions as a transcriptional repressor of its target genes in the presence of Fe^{2+} and this negative regulation is released under an iron-deficient condition [97]. Among the Fur-regulated genes is *pvdS*, encoding an ECF sigma factor, which regulates genes related to the production of a siderophore, pyoverdine, and other genes [98,99]. Siderophores have been shown to be important for virulence of *P. syringae* pv. *tabaci* in tobacco [100], but are dispensable for virulence of *Pto* in tomato and *A. thaliana* [101].

Another ECF sigma factor, AlgU, is known to be important for the virulence of bacterial pathogens [102]. AlgU controls alginate biosynthesis and other processes and *algU* mutants of *Pto*, *P. syringae* pv. *glycinea* (*Psg*) PG4180, and *Pss* B728a showed reduced virulence in plants [102–104]. Despite the important role of alginate in the virulence of *P. aeruginosa* and *Pss* [105,106], alginate production was shown to be dispensable for the virulence of *Pto* and *Psg* PG4180 [102,103], suggesting that other processes controlled by AlgU are important for bacterial virulence. Indeed, RNA-seq analysis of *in vitro*-cultured *Pto* showed that, in addition to alginate biosynthesis, AlgU regulates genes related to osmotic and oxidative stress responses and T3SS, which might explain the role of AlgU in bacterial virulence [102]. Moreover, a microarray analysis of the *algU* mutant of *Pss* B728 showed that AlgU impacts a large number of genes *in planta* [104].

In some plant bacterial pathogens, T3SS and QS systems are influenced by AlgU and/or iron availability. The *hrp* regulon of *Pto* is positively regulated by AlgU and external iron [102,107]. Fur positively regulates *psyI* and *psyR*, which encode an AHL synthase and receptor, respectively, in *P. syringae* pv. *tabaci* [108]. A PvdS-binding site was found in the upstream region of *psyI* in *Pto* [99], although the functional relevance of this remains elusive. In addition, Dulla *et al.* [109] showed that iron availability affects QS processes in *Pss*. Thus, bacterial virulence signaling pathways appear to be interconnected to form the bacterial virulence networks. Similar to plant immune networks, this interconnected feature would provide regulatory potential that benefits bacterial pathogens inside and outside the host. This deserves further research.

Impacts of plants on bacterial virulence networks

Plant-derived compounds affect bacterial virulence-related processes

The role of plant-derived compounds during plant–bacterial interactions is well studied in the legume–rhizobium symbiosis. Phenolic compounds, especially

flavonoids, secreted by legume plants are recognized by rhizobia in a species-specific manner, thereby inducing rhizobial genes important for establishing symbiotic interactions [110]. However, how plant-derived compounds affect bacterial pathogens in plants is scarcely understood.

Despite our poor understanding of how plants disrupt or exploit the bacterial virulence networks, accumulating evidence suggests that plant-derived compounds can affect bacterial physiology. The QS signaling of multiple bacterial species was shown to be affected by plant-derived compounds *in vitro* [19,111–118]. For instance, SA and γ-aminobutyric acid activate the quorum-quenching system, *attKLM* operon, in *Agrobacterium tumefaciens* and suppress QS responses [19]. Also, flavonoids derived from citrus inhibit the QS system, biofilm formation, and T3SS expression of *Vibrio harveyi* [118]. Rosmarinic acid was shown to directly bind to a QS receptor RhlR of *P. aeruginosa* and act as an AHL mimic [119]. These examples illustrate the possibility that plants modulate bacterial QS processes as an immune mechanism.

Evidence supports that phytohormones not only regulate plant responses but also directly affect bacterial physiology. SA was shown to suppress the expression of virulence genes in *A. tumefaciens* and *P. aeruginosa* [19,120]. Lebeis *et al*. showed that SA directly affects *in vitro* growth of some bacterial strains isolated from *A. thaliana* plants grown in a wild soil [121]. Importantly, the accumulation of SA in the apoplast was shown to increase upon pathogen infection [122]. These results suggest that SA can affect metabolism of bacterial pathogens directly as well as through well-described SA-mediated plant immune signaling [123]. In addition, a plant-derived auxin, IAA, negatively affects expression of virulence genes in *A. tumefaciens* and the T3SS in *Pseudomonas savastanoi in vitro* [19,124]. On the other hand, plant-produced IAA in plants and the exogenous application of IAA *in vitro* positively regulate the expression of virulence genes in *Dickeya dadantii* 3937 [125] and genes encoding components of the type VI secretion system of *P. savastanoi* [124], respectively. Although it is evident that phytohormones can affect bacterial metabolism and behaviors, how bacteria perceive phytohormones and if phytohormone perception is important for bacterial virulence are poorly understood.

The *hrp* regulon is also responsive to plant-derived compounds [80]. For instance, the *hrp* genes are induced when bacteria contact plant cells [80]. Also, plant apoplastic extracts can induce the *hrp* genes [126]. Several organic acids produced by plants were shown to induce the *hrp* genes of *Pto in vitro* as well as *in planta* [127]. Plant-derived flavonoids suppress the expression of *hrp* genes and flagella [128]. Furthermore, the *A. thaliana* mutant of *att1*, a cytochrome P450 monooxygenase catalyzing fatty acid hydroxylation, showed higher expression of T3SS genes of *P. syringae* pv. *phaseolicola* (*Pph*) compared with wild-type plants [129], implying that plant-derived fatty acids may suppress the expression of T3SS. Collectively, various plant-derived compounds might function as signaling cues for bacterial pathogens to induce the virulence pathways and also function as defense molecules for plants to suppress bacterial virulence.

How does plant immunity affect bacterial signaling networks?

It has been shown that PTI, but not ETI, suppresses the translocation of T3Es into plant cells [130–132]. Consistently, PTI, but not ETI, suppresses the expression of T3SS genes in *Pto* [130,132,133]. PTI also suppresses the expression of genes related to biosynthesis of COR, siderophore, and alginic acid [133]. Yet, the mechanism of how plant immunity affects bacterial gene expression is mostly enigmatic. It was shown in *A. thaliana* that the immune-related MAPK, MPK6, suppresses the production of organic acids that induce T3SS expression and T3E translocation, thereby inhibiting bacterial growth [127]. These organic acids are most likely secreted into the plant apoplast, an important growth niche for bacterial pathogens, and changing apoplastic conditions may be a major plant immune strategy to control bacterial pathogens. During ETI triggered by the infection of *Pph*, the leaf apoplast of *Phaseolus vulgaris* showed many changes including increased pH and accumulation of GABA and metal cations, some of which may be responsible for pathogen growth inhibition [134]. Limiting or over-supplying metals is known to be a defense strategy in animals [96]. Thus, it is possible that plants change the content of metals in the apoplast for inhibiting bacterial growth [13]. A transcriptome study of *Pto* in *A. thaliana* leaves revealed that bacterial genes suppressed in an iron-rich *in vitro* condition were also suppressed by PTI and ETI, suggesting plant immunity causes iron-rich-like responses in the bacterial pathogen [133]. However, the apoplastic iron content remained unchanged during PTI or ETI activation [133]. Thus, plants might regulate bacterial iron homeostasis by means other than directly changing iron content in the apoplast (e.g., producing iron mimics).

Other factors are also changed in the apoplast during plant immunity. Sugar transporters in *A. thaliana* are activated during PTI and sequester apoplastic sugar to inhibit the activity of the T3SS and bacterial growth [135]. Plant immunity might also control pathogen virulence by keeping water content in the apoplast low, as *Pto* creates an aqueous apoplast for virulence [136]. The temperature of the apoplastic space in relation to plant immunity is one of the unexplored research topics. The activation of plant immunity causes stomatal closure [137] and stomatal closure is known to lead to higher leaf temperature [138]. Thus, it may be possible that apoplastic temperature rises during plant immune activation and affects bacterial virulence as analogous to the fever response of vertebrates, a hallmark of infection and inflammatory response [139]. Understanding how these changes in the apoplast caused by plant immunity affect bacterial metabolisms *in planta* is understudied and an important future research area.

In planta bacterial transcriptome

An effective approach to understanding the impact of plant immunity on bacterial signaling networks is to profile bacterial transcriptome responses *in planta*. *In planta* bacterial transcriptome studies using microarray have been conducted in root nodules and xylem, in which bacterial cells are relatively highly abundant and are compartmentalized in specific organs [140–143]. However, it is very challenging to profile transcriptomes of bacteria colonizing in the apoplast because bacteria are in low abundance and difficult to isolate without affecting their gene expression. Yu *et al.* pioneered the transcriptome analysis of the bacterial pathogen, *Pss* B728a, in the apoplast of bean leaves as well as leaf surface by using microarray [144]. Later, the same group performed microarray analysis of bacterial mutants and highlighted the contribution of sigma factors in regulating the bacterial transcriptome *in planta* [104]. *In planta* transcriptome analysis was also reported in *D. dadantii* infecting *A. thaliana* using microarray [145]. Recently, RNA sequencing (RNA-seq) approaches were applied to profile *in planta* transcriptomes of *Xanthomonas axonopodis* infecting bean [146], and *Pto* infecting *A. thaliana* [133,147]. RNA-seq profiling of wild-type and mutant strains of *Pto* in a variety of *A. thaliana* immune compromised mutants revealed the global impact of PTI and ETI and phytohormone signaling pathways on bacterial gene expression [133]. In susceptible plants, the bacterial pathogen-induced genes related to T3SS, T3Es, COR, siderophores, and alginate at an early stage of infection; and these genes were suppressed in PTI-activated plants [133]. On the other hand, ETI suppressed only a subset of these PTI target genes, namely siderophore-related genes, although both PTI and ETI can effectively suppress pathogen growth, suggesting different modes of action for PTI and ETI [133]. Notably, bacterial genes related to protein translation (ribosomal proteins) were induced in susceptible plants and suppressed by PTI, but not by ETI [133]. In nature, plants are colonized by a multitude of microbes including bacteria collectively called the plant microbiota, which is important for plant health [148], and plant immunity is known to affect microbial community composition and microbial load in plants [121,136,149]. Targeting of such a fundamental process for life (i.e., not specific for pathogens) by PTI may suggest a role in affecting metabolisms of microbiota members. Profiling *in planta* transcriptome of a variety of plant-associated bacteria would reveal mechanisms by which plants control metabolisms of bacterial community colonizing in plants. For this, it is important to develop high-throughput methods for *in planta* bacterial transcriptome as current approaches are limited in throughput because they are still labor-intensive or costly.

Toward the holistic understanding of interactions between plants and bacteria

As discussed, both plants and bacterial pathogens have evolved their own molecular signaling networks. The molecular networks of plants and bacterial pathogens appear to be interconnected to form supernetworks, as bacterial pathogens interfere with plant immune networks by multiple means and plant immunity also affects components of the bacterial virulence networks (Fig. 1). Here, we discuss small molecules produced by plants and bacteria that potentially play a role in assembling the supernetworks between the two organisms.

Bacteria produce a variety of phytohormones (mimics), such as IAA, SA, ET, ABA, cytokinin, gibberellin, and COR [16,68,71,150,151]; some of these phytohormones (mimics) produced by bacteria have been shown to affect plant physiology including plant immunity [16,68]. On the other hand, bacteria also use phytohormones to regulate their own responses. For instance, IAA is used as a QS signal in some bacteria [152], suggesting that plant-derived IAA has a potential to affect bacterial physiology, including virulence via the QS system. The ability of both plants and bacteria to produce and perceive phytohormones raises the possibility that phytohormones are key molecules that connect the plant immune and bacterial virulence

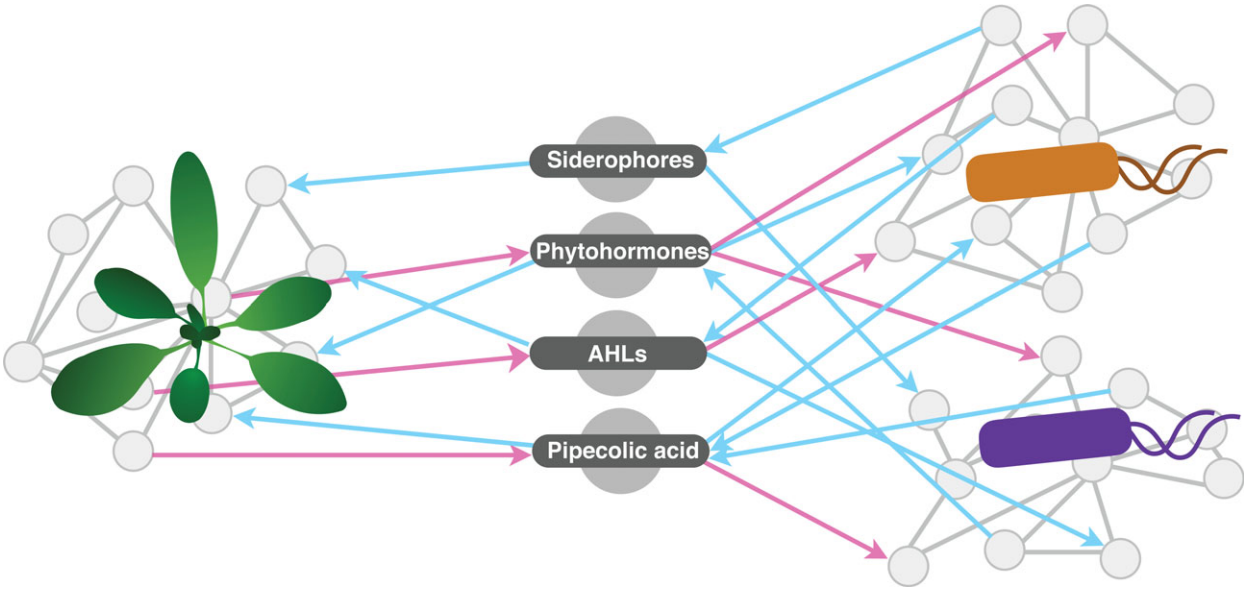

Fig. 2. A conceptual model illustrating the plant–bacterial supernetwork. In the supernetwork, the molecular networks of plant immunity and bacterial virulence are connected by small molecules shared between plants and bacteria. Red and blue arrows indicate signals derived from plants and bacteria, respectively. AHLs, Acyl-homoserine lactones.

networks. Moreover, plants can perceive siderophores [153] and AHLs [154–156] produced by bacteria to trigger defense responses, suggesting that the role of these small molecules is not restricted within or between bacterial species but that they might be used for direct interactions between plants and bacteria. Intriguingly, a number of bacterial strains produce pipecolic acid and appear to release a large amount of this chemical into the soil [157]. Pipecolic acid is also produced by plants and plays an important role in mediating systemic acquired resistance, which is effective against a broad range of pathogens [158]. Therefore, bacteria-derived pipecolic acid may have a significant effect on inducing systemic acquired resistance, thereby protecting plants from potential pathogens. Reciprocally, plant-derived pipecolic acid may affect bacterial networks. Indeed, it is known that a number of bacterial strains assimilate pipecolic acid [157]. Collectively, small molecules that play important roles in the signaling networks within plants and/or bacteria can potentially connect these two networks, assembling supernetworks and potentially driving the evolution of the plant–bacterial pathogen holobiont (Fig. 2).

The concept of supernetwork is not specific to the interaction between plants and pathogenic bacteria. For instance, in legume–rhizobium symbiosis, regulation of symbiosis-related genes of the hosts and bacteria are tightly connected by the exchange of small molecules produced by both sides [110]. Plants would form molecular supernetworks also with various commensal bacteria in the plant microbiota, in which inter- and intrakingdom communications occur via diverse signals [159]. Recent development of *in planta* bacterial transcriptome analysis using RNA-seq, together with transcriptome analysis of plants, will open a new avenue for dual '-omics' analyses of various combinations of plant and bacterial genotypes/species during interactions. Currently, *in planta* bacterial transcriptome analysis is mostly limited to studies of binary interactions between plants and single bacterial species. Establishment of *in planta* metatranscriptome analysis of bacterial communities would pave the way for comparing the structure of molecular supernetworks between plants and various microbiota members including pathogens, mutualists, and commensals under more ecologically relevant conditions. Understanding the commonalities and differences of molecular supernetworks in different plant–bacterial interactions is an important future research area for unlocking the complex molecular interactions between plants and microbiota, which will provide untapped engineering potential in plant breeding.

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