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Review

Coexistence ecology of pathogen-inhibiting microbes in the phytobiome

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Certain microbes have considerable potential as biocontrol agents against various pathogens, but they coexist with other microbial species in complex networks of interactions that influence their function in a host-dependent manner. These interactions and underlying mechanisms are still largely unknown. In this review we focus on *Pseudomonas,* a versatile genus of bacteria with adaptable physiological and metabolic traits, functioning as both symbionts and pathogens. We review the direct antagonism pathways *Pseudomonas* uses to inhibit different pathotypes and its role in indirectly inducing systemic defense responses in plants. We provide insights into bacterial coexistence and interactions in host plant–microbe and microbe–microbe relationships, considering pairwise and community dynamics. Understanding these interactions will help optimize synthetic communities and improve practices for sustainable agriculture.

Highlights

The mechanisms underlying microbe-driven host plant defense and growth are poorly understood.

Identification of plant and microbial conserved genetic determinants that maximize the beneficial plant–microbe association can be harnessed for disease inhibition and enhanced crop yield.

Understanding the genetic diversity (phylogenetic relatedness) and secretion systems of interacting species and their role in mediating the synergistic coexistence of microbial networks might offer key insights into how beneficial bacteria can inhibit pathogens and alleviate stress.

Integrated multi-omics approaches are crucial to understand how microbial inoculants influence soil microbial networks and plant health, as well as their ecological impact and potential for field application.

Mechanisms promoting microbial coexistence and shaping ecosystem functions

Microbes rarely exist in isolation in their natural environments; instead, they cohabit with other microbial species in complex networks [1,2]. They can either compete or coexist with these species via direct or indirect mechanisms. Interdependence and coexistence among microbes contribute to the dynamic ecosystems they inhabit. Within microbial communities, diverse interactions — ranging from symbiotic relationships to competitive dynamics — create a delicate balance that shapes the overall microbial landscape. The symbiotic coexistence of microbes in a community allows for interactions and collaborative functions that surpass the individual efficiency of any member species in isolation [3,4]. Numerous studies have addressed diverse mechanisms that operate at ecological and evolutionary scales to facilitate the coexistence of microbes in ecosystems. One way microbial species coexist is by utilizing different resources within an environment [5]. For instance, resource partitioning, driven by the use of distinct pollen-derived carbohydrate substrates, was found to facilitate the stable coexistence of closely related *Lactobacillus* species in the honeybee gut [6]. Additionally, microbes can form biofilms to create structured communities and establish microenvironments through spatial heterogeneity. For example, biofilm cultivation promoted the stable coexistence of the dairy starters *Lactococcus lactis* and *Leuconostoc mesenteroides* and reduced competitive exclusion over a hundred generations by providing separate ecological niches. Such spatial structures also drive the evolution of high-yield variants, which highlights the significance of promoting adaptive microbial communities in industrial applications [7].

In agriculture, the modern coexistence theory offers a valuable framework for deciphering the coexistence mechanisms of competing species in resource-sharing scenarios. This theory posits that the interplay between niche differences and fitness differences determines whether coexistence or exclusion dominates the ecological dynamics among species [5]. In this theory, both biotic and abiotic factors may facilitate coexistence through stabilizing or equalizing forces among species. For instance, mutualistic interactions theoretically enhance coexistence by expanding

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niche differences and equalizing fitness differences among species. However, these interactions may paradoxically lead to competitive exclusion by reducing niche differences and increasing fitness differences, contingent upon species responses to the interactions [8,9]. For example, microbes can induce mutualistic interactions through signal exchange, involving metabolic cross-feeding, and develop new niches for the coexistence of other microbes [10,11].

Moreover, microbial coexistence extends beyond signal transduction among microbial species and between the microbes and their host plant. Host plant exudates play significant roles in selecting specific microbial communities, establishing ecological niches, and promoting coexistence among diverse species [12,13]. For instance, the root-specific transcription factor MYB72 regulates the release of the coumarin scopoletin in the *Arabidopsis thaliana* rhizosphere and selectively influences microbial community assembly. This dual action involves inhibiting fungal pathogens while increasing the colonization and coexistence of beneficial rhizobacteria, such as *Pseudomonas simiae* WCS417 and *Pseudomonas capeferrum* WCS35. This orchestration ensures that the host plant actively contributes to niche establishment for its microbial partners, which results in improved growth and immunity benefits for the host plant [14]. Host-plant-associated microbes coexist in the rhizosphere and form interconnected dynamic networks in response to stress [14,15]. Understanding how microbial species interact, coexist, and influence one another is key to deciphering the consequential effects on community structure and ecosystem functions [16,17].

Inhibition of distinct pathotypes by *Pseudomonas*

Several microbial strains are employed as biocontrol agents against a variety of pathogens. However, the host and overall microbial landscape significantly influence the effectiveness of these biocontrol agents, as microbial species coexist within complex networks of both positive and negative interactions. These complex interactions and underlying mechanisms make model microbial systems valuable for studying host-beneficial microbe–pathogen interactions.

Herbivorous insects

Pseudomonas species exhibit specific toxicity against insect pests through mechanisms influenced by bacterial introduction, toxin type, and secretion system activity [18–21]. For example, Fit toxins are typically produced by *Pseudomonas protegens* and *Pseudomonas chlororaphis*. Fit is encoded by the *fitD* gene, which is flanked by genes encoding a type 1 secretion system responsible for transporting the toxin out of the cell. In *P. chlororaphis* PCL1606, insecticidal potency is enhanced by the synergy between the Fit toxin and 2-hexyl-5-propyl resorcinol (HPR) [18,20] (Figure 1). Meanwhile, *P. protegens* CHA0 exhibited strong insecticidal activity, with orfamide acting in oral infections and hydrogen cyanide hemolymph injection [21]. Moreover, the exolysin A (ExlA) toxin from *P. chlororaphis* PA23 causes cell shrinkage and cytoplasmic leakage and causes death in *Galleria mellonella* and *Drosophila melanogaster* [22]. However, in *P. protegens,* the type VI secretion system not only disrupts the insect gut microbiome by targeting members of the Enterobacteriaceae, it also transports RhsA and Ghh1 effectors to the hemocoel, which leads to bacterial colonization and insect pathogenicity [23].

Fungi and oomycetes

Certain fluorescent pseudomonads inhibit phytopathogenic fungal growth primarily by producing the natural metabolite pyrrolnitrin (PRN) and its derivatives. This metabolite disrupts the fungal respiratory electron transport chain, which suppresses ATP synthesis and the formation of essential cellular components such as DNA and proteins [24,25]. Moreover, *P. aeruginosa* LV *and P. chlororaphis* PCL1391 synthesize various phenazine derivatives – including phenazine-1-carboxamide (PCN) and phenazine-1-carboxylic acid (PCA) – that act as antifungal metabolites

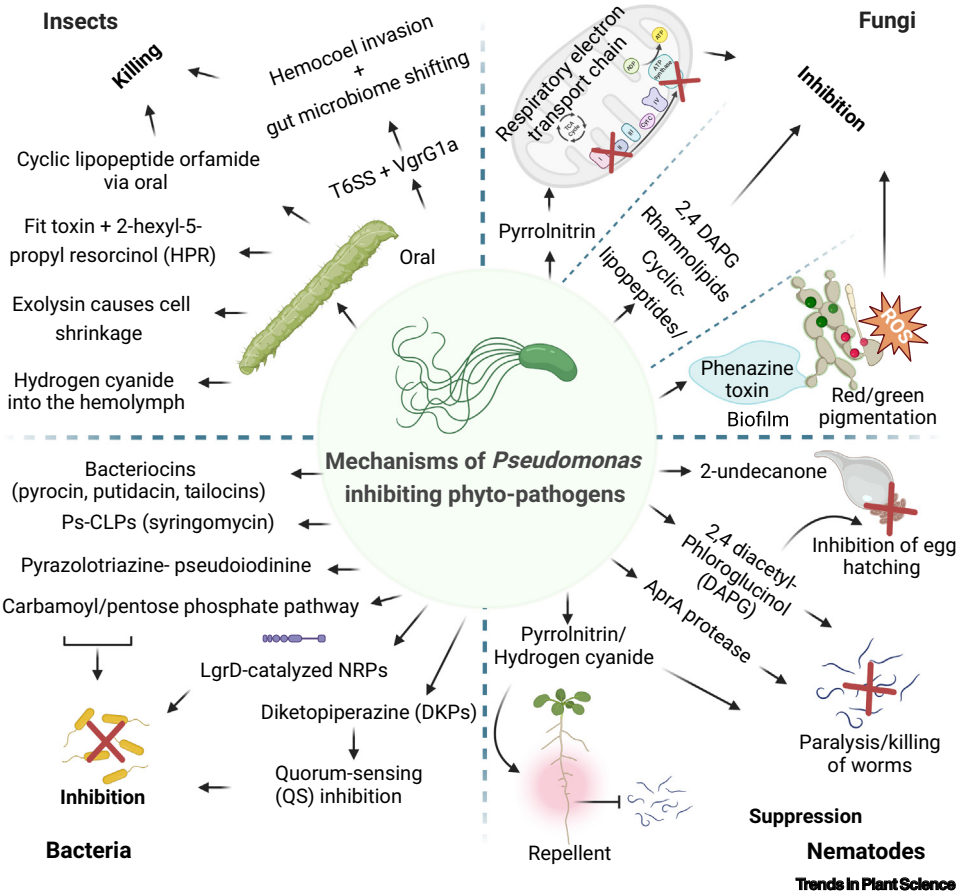

Figure 1. Various mechanisms by which *Pseudomonas* species inhibit different pathotypes, including insects, fungi, nematodes, and bacteria. These mechanisms involve the production of antimicrobial metabolites, the use of secretion systems, and the disruption of pathogen cellular processes. Abbreviations: NRP, non-ribosomal protein; ROS, reactive oxygen species. Figure created with BioRender.

against several phytopathogenic fungi, such as *Botrytis cinerea* and *Fusarium oxysporum* [26,27]. Mechanistically, phenazines contribute to biofilm formation, enhance antifungal potency in target cells, and alter the cellular redox state, which leads to the generation of reactive oxygen species (ROS) and fungal death [28,29] (Figure 1). Additionally, biosurfactants such as cyclic lipopeptides (CLPs) and rhamnolipids can inhibit phytopathogenic fungi [30]. For instance, rhamnolipid from *Pseudomonas aeruginosa* A4 inhibited mycelial growth of the phytopathogen *Aspergillus niger* F14 by 61% [31]. Meanwhile, CLPs, such as orfamide and syringomycin, are produced by non-ribosomal peptide (NRP) synthetases [32]. Interestingly, the co-production of orfamide A and sessilin-(T) by *Pseudomonas* sp. CMR12a inhibited the growth of *Rhizoctonia solani,* whereas individually they did not [33]. Similarly, syringomycin E inhibited the growth of the postharvest green mold of citrus fruits *Penicillium digitatum* [34]. The putisolvin-like CLPs produced by *P. putida 267* proved excellent biocontrol against *Phytophthora capsici* [35]. Other CLP species have been shown to inhibit the mycelial growth of *Pythium ultimum* or *Phythophtora infestans* oomycetes [36,37]. Moreover, many *Pseudomonas* strains, especially *Pseudomonas fluorescens*, produce 2,4-diacetylphloroglucinol (DAPG), a phenolic compound known to suppress fungal pathogens such as *Gaeumannomyces graminis* in wheat, *Thielaviopsis basicola* in

tobacco, *Pythium ultimum* in beet, and *Ralstonia solanacearum* in tomato [38] (Figure 1). DAPG acts as a proton ionophore that disrupts the proton gradient across the mitochondrial membrane, thereby inhibiting fungal growth [39].

Phytopathogenic bacteria

Beneficial *Pseudomonas* can also interfere with quorum sensing and inhibit biofilm formation to combat pathogenic bacteria. For instance, cyclic dipeptides (CDPs) and diketopiperazines (DKPs) from *P. aeruginosa* RKC1 effectively inhibit quorum sensing in the soft rot pathogen *Lelliottia amnigena*, impeding their cell growth [40]. Recently, *Pseudomonas mosselii* strain 923, found in rice paddy fields, was demonstrated to inhibit the growth of *Xanthomonas oryzae* pv. *oryzicola* (Xoc). This was attributed to the synthesis of antimicrobial pseudoiodinine through the psdABCDEFG cluster and the regulation of the *GacS/GacA* two-component system [41]. Meanwhile, the beneficial *Pseudomonas oryziphila* strain 1257 can potentially inhibit the Xoc RS105 strain through a non-ribosomal peptide that is catalyzed by *LgrD*, along with the carbamoyl phosphate and pentose phosphate pathways to impede the growth and movement of Xoc within rice tissues [42] (Figure 1). In addition, the most antibacterial compounds from *Pseudomonas* include CLPs and bacteriocins. For example, syringomycin Ps-CLPs have potent antimicrobial activity against *Rhodococcus* and *Micrococcus* species [43]. However, a vast majority of Ps-CLPs do not show antagonistic activities and are considered ineffective against Gram-negative bacteria; this is generally attributed to the presence of the outer membrane or peptidoglycan layer, which hinders access to the plasma membrane [44]. However, bacteriocins such as pyrocin, which are ribosomally synthesized peptides and proteins, have been well studied in Gram-negative bacteria, particularly *P. aeruginosa* [45]. Pyrocins, produced by *P. aeruginosa*, are known to inhibit the cells of other *P. aeruginosa* strains [46]. The production of putidacin (a bacteriocin) expressed in *Nicotiana benthamiana* plants conferred resistance to *P. syringae* pv. *syringae* infection, indicating that the expression of bacteriocins in commercial crops may be an effective option for disease suppression [47]. Among the newly discovered bacteriocins are tailocins that resemble the tail structures of bacteriophages. They function as antimicrobials by binding to and puncturing closely related bacterial competitors, dissipating the membrane's proton-motive force and causing bacterial death [48].

Phytoparasitic nematodes

Pseudomonas species suppress phytoparasitic nematodes by producing nematicidal metabolites and inducing systemic plant resistance [49]. For instance, *P. fluorescens* produces 2,4-DAPG, effectively reducing egg hatching and juvenile mobility in cyst nematodes [50]. Additionally, *P. putida* 1A00316 produces dimethyl disulfide and 2-undecanone, which suppress the second juvenile stage (J2) of *Meloidogyne incognita* through both direct contact and volatile fumigation [51]. Functional analysis of *P. putida* 1A00316 revealed that its nematicidal activity is due to cyclo-(l-isoleucyl-l-proline) and hydrogen cyanide but not 2,4-DAPG and pyrrolnitrin [49]. By contrast, *P. chlororaphis* strain PA23 uses pyrrolnitrin and hydrogen cyanide to exert both fast and slow killing of nematodes and repellent potency [52]. Meanwhile, *P. fluorescens* CHA0 employs an extracellular protease (AprA protease, encoded by GacA-controlled *aprA* gene or the *gacA* regulatory gene) to inhibit *M. incognita* egg hatching and induce mortality in juveniles (Figure 1) [53]. The quorum-sensing regulators LasR and RhlR in *P. aeruginosa* trigger toxin production that causes rapid paralysis in *Caenorhabditis elegans* by activating EGL-9 genes or related pathways [54].

Mechanisms of *Pseudomonas*-driven host plant defense and growth remain inadequately understood

Pseudomonas spp. play pivotal roles within the phytobiome by exerting a substantial influence on plant health through the induction of systemic resistance and the promotion of growth and yield

(Box 1). These interactions are intricate relationships between specific elicitors derived from beneficial bacteria and the host plant, which involves precise recognition and binding processes, but the bacterial pathways mediating defense, growth, and the trade-offs between them, remain poorly understood. So far, for example, *P. putida* BTP1 enhances phytoalexin accumulation and stimulates the lipoxygenase (LOX) pathway to prime tomato defense against *Botrytis cinerea* [61]. Meanwhile, *P. simiae* WCS417r enhances the capacity of tomato plants to convert the ethylene precursor 1-aminocyclopropane-1-carboxylate (ACC) to ethylene that accumulates and primes the arabidopsis defense upon *P. syringae* pv. tomato DC3000 infection [62]. In addition to ethylene, jasmonic acid (JA) is reported to induce systemic resistance (ISR) in response to beneficial *Pseudomonas* spp. For example, arabidopsis mutants lacking JA signaling, such as *jar1* and *coi1*, did not exhibit ISR upon application of *P. simiae* WCS417r [63]. However, against foliar pathogens, ISR by *P. simiae* WCS417r is strongly dependent on the root-specific *MYB72* transcription factor (Figure 2) [64]. Interestingly, upregulation of *MYB72* in the roots is associated with iron-limited conditions, indicating a complex interplay between iron availability and the elicitation of systemic resistance [65,66]. Recent studies reveal distinct mechanisms by *Pseudomonas* spp. that impact lateral root development and plant growth. *Pseudomonas* sp. CM11, for instance, activates the *PLETHORA 3,5,7* pathway, enhancing lateral root formation, root architecture, and crop yield (Figure 2) [67]. However, the ability of *P. simiae* WCS417 volatiles to promote arabidopsis growth is mediated by either auxin [68] or the ERD6-like sugar transporters *SWEET11* and *SWEET12* [69].

Insights into mechanisms underlining pathogen-inhibiting beneficial bacteria

Despite the knowledge of how beneficial microbes interact with host plants and pathogens, there is still a lack of understanding regarding their beneficial mechanisms across different genetic and complexity levels. This lack extends from the genetic determinants within the same genus to their interactions with other microbial species in both intra- and inter-species coexistence. Furthermore, the signaling pathways triggered by beneficial microbial strains in response to host plants and other microbes, including pathogens, that influence plant defense and growth and their trade-offs remain poorly understood. We highlight here that beneficial strain(s) in the phytobiome could promote a microbial shift, potentially dismantle disease complexes, or amplify synergistic cooperation among indigenous communities related to functional traits. These additional aspects and questions might contribute to bridging the knowledge gaps in plant–pathogen–microbe interactions.

Box 1. The influence of beneficial *Pseudomonas* on soil microbial networks and metabolic pathways for disease suppression remains largely unexplored

Numerous studies have investigated the impact of microbial inoculants on soil microbial community structure [55,56]. However, their influence on functional shifts within microbial networks and the associated metabolic pathways enriched in response to biotic stress or disease remains largely unexplored. A recent study demonstrated that rhizosphere microbial communities and their volatilome exhibit inoculant-specific patterns when bacterial or fungal strains are applied to tomato plants challenged by the herbivore *Spodoptera exigua*. Among the tested inoculants, *Pseudomonas azotoformans* and *Bacillus amyloliquefaciens* exhibited distinct volatilome profiles in herbivore-infested tomato plants, but both promoted the production of dimethyl disulfide and benzothiazole [57], compounds potentially involved in the suppression of different phytopathogens [58,59]. Interestingly, nonpathogenic *Pseudomonas syringae* pv. tomato DC3000 derivatives triggered the plant's 'cry for help' response and assembled a beneficial microbiome associated with distinct shifts in root exudates. For instance, Arabidopsis growth promotion was positively associated with a high abundance of *Devosia* species. This association was accompanied by negative correlations between *Devosia* abundance and myristic acid and L-malic acid, while a positive correlation was observed with 4-hydroxypyridine [60]. Although these examples highlight important interactions, further research is needed to understand how beneficial *Pseudomonas* spp. interact with soil microbial networks, metabolic pathways, and root exudates to drive disease suppression.

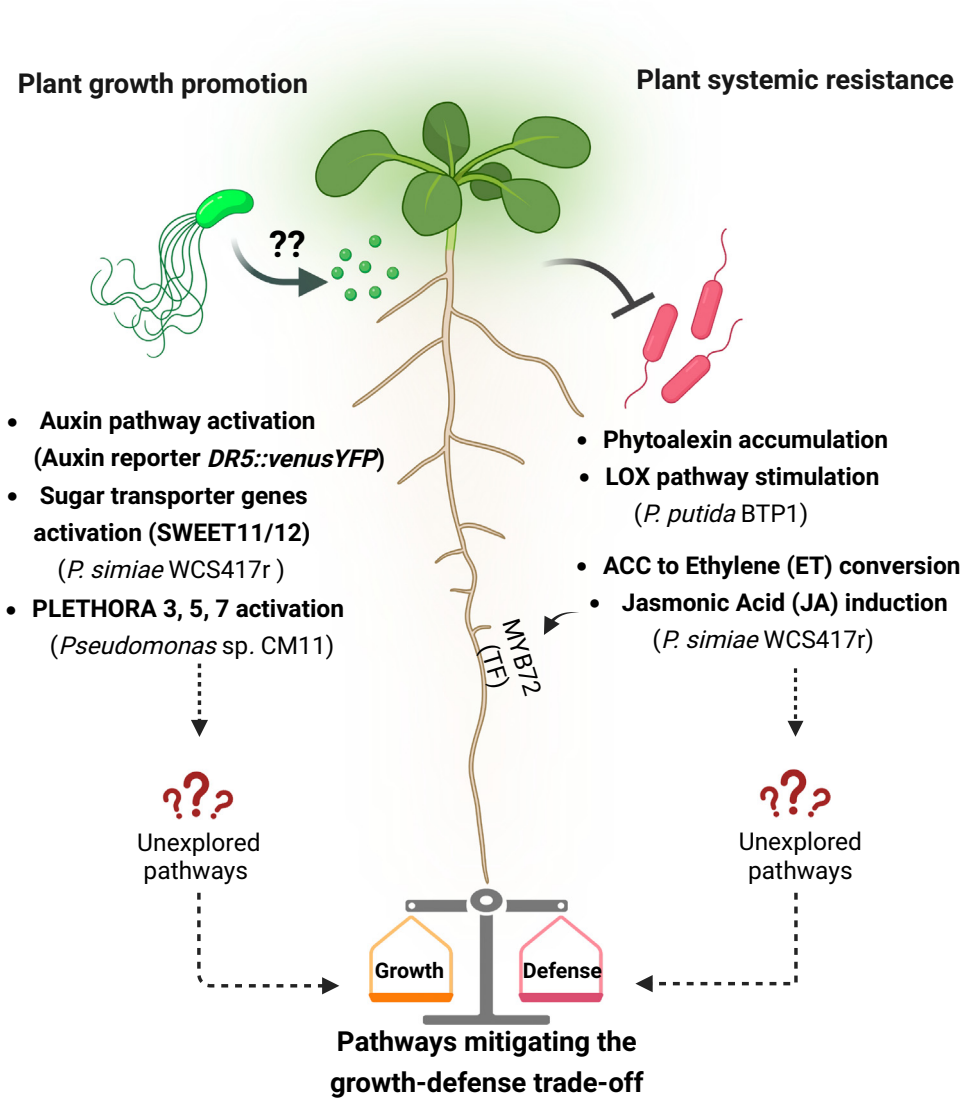

Figure 2. *Pseudomonas*-mediated enhancement of host plant defense and growth pathways. Beneficial *Pseudomonas* spp. enhance plant defenses and promote growth through multiple mechanisms. However, more research is needed on microbial-mediated pathways that address the balance between plant defense and growth and alleviate the trade-offs. Abbreviations: ACC, 1-aminocyclopropane-1-carboxylate; LOX pathway, lipoxygenase pathway. Figure created with BioRender.

Host plant–bacteria genetic determinants related to plant and bacterial functional traits

In the past two decades rapid advancements in sequencing technologies have revolutionized the ability to access whole-genome data and identify conserved genetic determinants associated with various traits through genome-wide association studies (GWAS) [70,71]. Advancements in high-throughput phenotyping technologies can handle such large datasets and provide precise and reproducible trait–phenotypic data, especially for complex traits [72,73]. However, while these studies have significantly contributed to our understanding of genetic influences on plant functional traits, they have largely ignored the identification of microbial genetic determinants

that shape functional traits when microbes coexist with the host plant. In a complementary strategy, it could be appropriate to identify genetic markers that influence plant responses and maximize microbial benefits. Only a limited number of studies have explored the complex relationship between plant genetics and the structure of the microbiome [74–76] while overlooking the identification of plant quantitative trait loci (QTLs) related to responsiveness to and harnessing of beneficial microbial traits within the phytobiome. These approaches can offer tools to elucidate evolutionary crosstalk between bacterial signals and host-plant receptors, and lead to significant implications for agriculture and the breeding of plants to improve the productivity of crops.

Plants coexist within a complex microbial network shaped by genetic heterogeneity, where intra- and inter-species variants contribute to the diversity of beneficial traits encoded in microbial genomes. These interactions support mutualistic relationships that enhance plant fitness and health. Many studies have shown the successful potential of GWAS in identifying resistance genes in crops [77,78], but breeding for plant-beneficial microbiomes may also lead to robust protection of plant growth. For example, the microbiome of a *Fusarium oxysporum*-resistant bean cultivar exhibited increased expression of genes linked to chemotaxis and antifungal compound biosynthesis, including phenazine and colicin V [79].

By contrast with plants and animals, bacteria show much less conservation of their genomes, making GWAS not the first choice for identifying genes associated with specific functions. Therefore, other tool sets and approaches are necessary for identifying the important bacterial traits. The simple and cheap metataxonomic bacterial 16S and fungal ITS rDNA analyses have become standard in microbiome research. By contrast, metagenomics offers a more powerful approach, providing a compendium of the genes and, thereby, the composition of the microbial communities in the system. However, neither approach usually distinguishes DNA from dead and live bacteria, and the costs of metagenomics are often prohibitive for deep analysis of many samples.

However, pangenomic analyses of microbial species are becoming more and more feasible as the number of sequenced microbial species grows rapidly. Although the core genomes of the microbial species can serve for GWAS, most of the traits probably are correlated with the accessory genomes that have been obtained by horizontal gene transfer. Therefore, coupling multiomics phenotypic data with pangenomic and accessory genome data of large collections of microbiomes will surely provide the most powerful way to identify the genes and understand their functions in the context of plant–microbial genetics.

Finally, classical genetic approaches coupled with high-throughput screening platforms for soil, microbial, or host plant traits will also be a major source of knowledge in the field. For example, mutagenesis approaches of selected strains can rapidly identify important traits, as shown by screening 7488 random transposon mutants in *P. fluorescens* SS101, identifying the phosphogluconate dehydratase gene (*edd*), the response regulator gene (*colR*), and the adenylsulfate reductase gene (*cysH*) as key regulators in both plant growth promotion and ISR [80] (Box 2).

Bacterial intra- and inter-species network interactions in the phytobiome

Provocation–counterattack dynamics and the role of phylogenetic relatedness in bacterial interactions

The coexistence and interaction of microbes with each other and the host plant shape microbial communities and their associated fitness functions [88,89]. Novel mechanisms that provide a deep understanding of beneficial bacteria–bacteria interactions within and across different genetic trajectories and scales of pairwise or community interactions towards pathogenic bacteria

Box 2. Integrated multi-omics are needed to explore inoculant–soil microbial network interactions

Microbial inoculants can significantly alter soil microbial communities and the functional traits of host plants [56,81]. However, their impact may vary, being either beneficial or harmful, depending on microbial interactions and environmental conditions. While inoculants are often selected based on laboratory performance, they may lack the ecological traits needed for field survival and persistence [82], making it essential to use advanced multi-omics and informatics approaches to predict their success, especially given the dynamic nature of soil microbiomes [83]. Metagenomics captures shifts in the microbial community composition and functional potential following inoculant application [84], while pangenomics reveals the genomic diversity and accessory gene variations that drive interactions among inoculant strains, soil microbes, and host plants [85]. Moreover, metaproteomics and metatranscriptomics can pinpoint active functions in both host plants and microbial communities [86], and integrating these with metabolomics or exometabolomics techniques could enable *in situ* characterization of metabolites produced within microbial cells, host plants, and the soil environment [87]. These approaches might require analytical and statistical modules that combine and deal with different datasets and facilitate the interpretation of complex datasets [88]. Together with validation under controlled and field conditions, these methods could provide a high-resolution framework to unravel complex inoculant–soil microbial networks and inform strategies for enhancing plant health.

remain largely unexplored. While bacteria often employ diffusible toxins to eliminate competing strains, some of these substances may serve as provocation signals to stimulate a robust counterattack from beneficial bacteria. This phenomenon is called provocation–counterattack (i.e., backfire) [90], where pathogens may inadvertently trigger defense responses in beneficial bacteria, which could lead to a cascade of metabolic changes aimed at neutralizing the perceived threat of the pathogen (Figure 3). However, the extent to which phylogenetic relatedness between pathogen-beneficial interacting species influences these interactions is poorly understood. To address this, one study proposed that computational modeling using the correlation of genome-wide metabolic profiles with the phylogenetic distance between the interacting bacterial species could help to predict the competitive and complementary behaviors among the interacted species [91]. In that study, the PhyloMint pipeline revealed a positive correlation between bacterial metabolic complementarity and phylogenetic distance and a negative correlation between metabolic competition and phylogenetic distance [91]. By contrast, phylogenetically close strains may share similar genetic backgrounds and metabolic pathways, increasing the likelihood of cross-recognition and response to provocation signals. As a result, beneficial bacteria may mount a more robust counterattack against pathogens by leveraging their genetic similarity to deploy defense mechanisms more efficiently. Harnessing this mechanism could help identify targeted provocation signals or compatible bacterial strains to control pathogenic bacteria and reduce the risk of microbial product infectivity when applied in field settings.

Synergistic coexistence of beneficial bacteria in microbial networks

At the community level, negative interactions frequently occur when beneficial bacteria are cocultured pairwise or within community contexts. For instance, it has been reported that *Bacillus* and *Pseudomonas* spp. consistently exhibit negative interactions and coexistence [92]. Only approximately 13% of their pairwise interactions in plants and 10% in soil are characterized as positive, mostly throughout resource sharing and cross-feeding [92]. Negative interactions may also occur when a beneficial bacterium, effective at combating a specific pathogen in the laboratory, fails to demonstrate the same efficacy in field settings. This can be attributed to the fact that microbes operate within complex ecological networks, and their responses to the host environment are influenced by interactions with other microbes and shaped by competition for nutrients, metabolic signaling, or communication mediated by volatile substances. The transition from focusing solely on individual microbes towards investigating their collective inputs and outputs has recently become more feasible [93]. Therefore, there is mounting interest in elucidating the factors that underlie the synergistic coexistence of bacteria and their role in maximizing their functional outcomes. A recent model highlights how microbes use the production and consumption of chemical mediators to enable their coexistence, which emphasizes the importance of facilitation

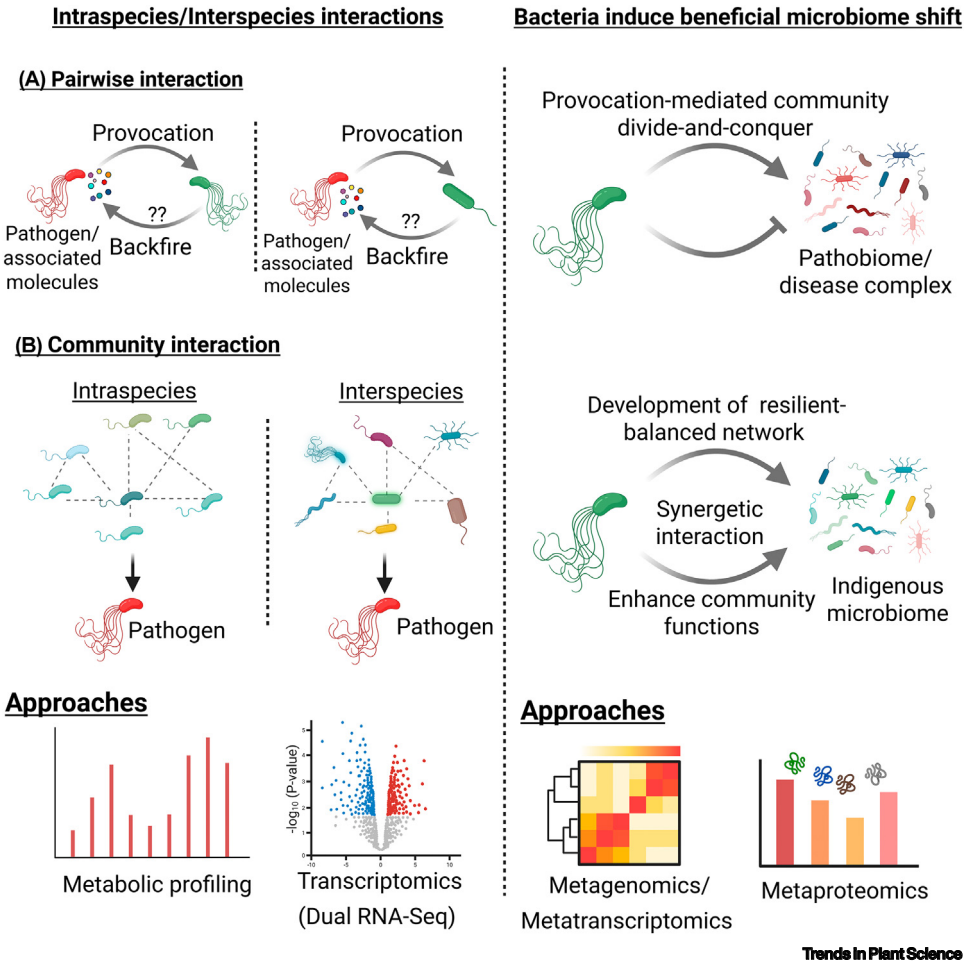

Figure 3. Proposed mechanisms of bacteria intra- and inter-species network interactions in the phytobiome. Diverse bacterial interactions within pairwise and community contexts, including provocation–counterattack responses, intra- and inter-species communication, and the potential impact of phylogenetic relatedness on interaction outcomes. Induction of shifts in the pathobiome or indigenous microbiome through the application of beneficial inoculants is also illustrated. Figure created with BioRender.

and self-restraint for community maintenance [2]. Consumption of chemical mediators can act as negative feedback on potentially dominant species and promote coexistence. Metabolic exchange and self-facilitation, such as the breakdown of complex compounds into consumable products, enhance growth rates and support coexistence [94]. However, self-restraint is crucial, as the accumulation of metabolic byproducts can become inhibitory [95]. Moreover, temporal differentiation in nutrient utilization during resource pulses may alleviate competitive interactions by minimizing niche overlap and promoting coexistence. For example, a collection of *Streptomyces* isolates exhibited temporal variation in carbon source consumption during incubation [96]. However, studies have reported that suppressing competitor bacteriocins can impact the fitness of microbial communities [97]. For example, tailocins and phage tail-like protein complexes mediate antagonism by targeting and killing closely related bacterial competitors [98,99]. Since microbial community functions rely on cooperative interactions, tailocins can disrupt this balance by selectively eliminating certain strains. This antagonism can lead to shifts in community composition, reduced diversity, and impaired network functionality. Therefore, applying tailocin inhibitors to

competitive microbial members can prevent targeted killing, enhance diversity, and promote synergistic coexistence. Moreover, understanding the role of bacterial secretion systems in mediating interactions between bacterial species could provide key insights into how beneficial bacteria can inhibit disease-causing pathogens. The type secretion systems (TSS) and outer membrane vesicles (OMVs) facilitate bacterial interactions by transporting molecules such as proteins and toxins, which enable bacterial competition, virulence, and communication, and often significantly impact the interacting partner(s) [100,101]. They can operate independently or together, and communicate through released molecules to impact the outcomes of bacterial interactions [102]. These secretion systems or vesicles deliver their effectors via bacterium–bacterium contact; however, recently, the delivery of toxic effectors via a contactless interaction through OMVs was reported [103]. Thus, correlating target patterns, such as tailocins, TSS, and OMVs among interacting species (in pairwise or triple interactions) with phenotypic data on functional traits can help us to understand and predict the network's synergistic levels and functions.

However, targeted agricultural practices – such as pre-cropping, organic amendments, repeated litter addition, and microbial inocula – can alter rhizosphere microbiomes and volatiles to enhance plant immunity against herbivores and pathogens and restore degraded ecosystems [104–106]. In particular, the interactions between microbial inocula and indigenous microbial taxa, along with the subsequent initial disturbance and shift of native microbial network members, remain poorly understood. A recent study summarized the plant microbiome potential responses or shifts induced by foreign microbial inoculants [107]. These responses might involve initial shifts, followed by long-term stabilization of a healthy plant microbiome through enhanced diversity, increased beneficial taxa, and reduced pathogens via antibiosis or dysbiosis restoration [107].

Since the network functions of a community rely on synergistic interactions among its members, one might assume that common taxa are responsible for the significant upregulation of pathways related to adjustments in the microbial network balance and enhancement of resilience functions (Figure 3). Therefore, the identification of these taxa or species could be crucial to understanding how beneficial bacterial strains can combat disease complexes, disrupt the pathobiome, and alleviate its impact through mechanisms such as dividing and conquering [90]. In terms of considering the application of these concepts to the relationships among beneficial bacterial strains introduced to the indigenous microbiome or integrated into synthetic communities, it is crucial to obtain a better understanding of the mechanisms underlying synergistic coexistence. This knowledge could be vital to harness such beneficial interactions among species against pathogens or other stresses and to reduce the potential risks associated with microbial product infectivity. Thus, elucidation of these mechanisms is essential to optimize the efficacy and safety of such microbial interventions in various contexts, ranging from agriculture to human health.

Concluding remarks

Our understanding of how beneficial bacteria interact with pathogens and host plants is still evolving, yet significant gaps remain in elucidating the underlying genetic and ecological mechanisms. The integrated application of genomic approaches to identify microbial and plant genetic markers associated with beneficial traits holds promising potential for plant breeding programs. These programs could be used to harness and optimize plant–microbe associations to enhance crop productivity. Additionally, a better understanding of the role of microbial secretion systems and phylogenetic relatedness in beneficial interactions is crucial to developing strategies to foster synergistic coexistence and design stable synthetic microbial communities. This knowledge could also clarify why certain microbial products underperform in field conditions and help to identify chemical signaling mediators or specific bacterial genera that enhance synergistic behaviors within microbial networks. These insights could guide the precise manipulation of microbial

Outstanding questions

Pairwise interactions between pathogens and beneficial bacteria:

How do pathogens interact with surrounding microbial populations within the phytobiome? How do beneficial and pathogenic bacterial species interact within pairwise and community models? What is the molecular and ecological dialog, including microbial signaling, in these interactions that potentially drives robust responses from beneficial microbes towards pathogens?

Do the beneficial bacteria respond to signals from the pathogen that lead to pathogen inhibition or trigger plant defense? What metabolites produced by beneficial or pathogenic bacteria are induced in the presence of other beneficial or pathogenic bacteria?

How does the phylogenetic relatedness of interacting species influence their ability to induce metabolites and provoke responses from each other?

Intra- and inter-species community interactions between beneficial bacteria:

To what extent does the genetic diversity of microbial communities influence their resilience and the potential for synergistic coexistence toward the inhibition of pathogens?

How does phylogenetic relatedness (intra- or inter-species interaction) influence microbial species interactions and their synergistic coexistence?

How long do the negative tension interactions last or persist within a closely related phylogenetic group (for example, *Pseudomonas* intraspecies interaction), and can such tension be mitigated after being outcompeted?

How do the presence, absence, or diversity of TSS, OMVs, or tailocins influence microbial synergistic coexistence, and how can these factors enhance the effectiveness of beneficial bacteria in pathogen inhibition?

Genetic determinants related to beneficial host plant–microbial associations:

To what extent can the combined identification of plant genetic markers and

interactions through targeted agricultural practices, to promote ecological equilibrium and sustainable management of microbial communities (see Outstanding questions).

conserved beneficial microbial traits be used to enhance crop–microbial associations, and how might this knowledge be implemented in agricultural practices and plant breeding programs?

Author contributions

A.E. and H.H. conceptualized and conceived the framework of the review and structured the outline. A.E. conducted a comprehensive literature search and synthesized findings across studies. A.E. wrote the draft of the manuscript; A.E. conceptualized and created the figures. H.H., A.E., L.A., A.H.S., and M.M.S. reviewed and revised the text and approved the final version for submission. A.E., A.H.S., and H.H. responded to the reviewers' and the editors' comments.

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Declaration of interests

The authors declare no competing interests.

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