TITLE

Systems biology of plant microbiome interactions

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Abstract

In natural environments plants are exposed to diverse microbiota that they interact with in complex ways. While plant-pathogen interactions have been intensely studied to understand defense mechanisms in plants, many microbes and microbial communities can have substantial beneficial effects on their plant host. Such beneficial effects include improved acquisition of nutrients, accelerated growth, resilience against pathogens, and improved resistance against abiotic stress conditions such as heat, drought, and salinity. However, the beneficial effects of bacterial strains or consortia on their host are often cultivar- and species-specific posing an obstacle to their general application. Remarkably many of the signals that trigger plant immune responses are molecularly highly similar and often identical in pathogenic and beneficial microbes. Thus, it is unclear what determines the outcome of a particular microbe-host interaction and which factors enable plants to distinguish beneficials from pathogens. To unravel the complex network of genetic, microbial, and metabolic interactions including the signaling events mediating microbe-host interactions, comprehensive quantitative systems biology approaches will be needed.

Introduction

The microbial world has caught immense attention in recent years as the decrease of sequencing costs has enabled an in-depth analysis on the composition and dynamics of host-associated microbiota. For both humans and plants, it is recognized that microbes hold an enormous potential to increase host health. In the vision of a future precision agriculture, targeted application of beneficial microbial cocktails may be a sustainable path to counteract biotic and abiotic stress conditions and ensure yield stability. However, most beneficial microbes have close pathogenic relatives and it is currently unclear how the plant immune system differentiates between pathogenic and beneficial microbes to fight infection by the former and facilitate colonization by the latter. From an evolutionary perspective it is likely that even the earliest eukaryotes were surrounded by diverse prokaryotes and that eukaryotic immune systems evolved to differentiate between beneficial and pathogenic bacteria. Therefore, a deep-rooted and complex interplay between microbes and hosts is expected that touches all aspects of eukaryote biology. Understanding of microbe-host interactions will therefore require classical as well as systems biological ‘omics’ and quantitative modeling approaches.

The plant microbiome

Plants share their habitat with a variety of microbes that include bacteria, oomycetes, fungi, archaea, and a poorly explored universe of viruses (reviewed in Agler et al., 2016; Berendsen et al., 2012; Buée et al., 2009; Swanson et al., 2009). The composition of the plant microbiota is shaped by complex multilateral interactions between the abiotic environment and its biotic inhabitants. Depending on the outcome of an interaction for the host, microbes are considered as mutualistic, commensal, or pathogenic. In this review we focus on the interplay between bacteria and to a lesser extend filamentous eukaryotes with the plant host.

Composition and dynamics of host associated microbial communities

Microbiome profiling of plants, plant organs and root associated soils has revealed a diverse and highly dynamic plant microbiome. Several studies have shown that bacterial communities are dynamically shaped by environmental factors like soil, season, daytime, as well as host-factors like species, developmental stage, and compartment. Soil and air and their properties provide the physical reservoir for the plant-associated microbiome (reviewed in Vorholt, 2012). The microbiota of aerial plant parts is more influenced by long distance transport processes, whereas for roots soil-type, soil history, nutrient and water content are influential factors (Bogino et al., 2013). Especially at the beginning of the growth season, soil also influences the plant associated microbial communities aboveground (Copeland *et al.*, 2015). A richer and functionally better characterized microbiome is found belowground. Microbial species richness is highest in bulk soil, decreases in the rhizosphere and is lowest in the endophytic compartment, indicating a strong selective gradient. In parallel, microbial cell-count increases from bulk soil towards the root surface indicating favourable conditions for the selected microbial species. Despite the great biodiversity of soils, the microbial community in the rhizosphere and endosphere of plants is dominated by four bacterial phyla: Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria (Bulgarelli et al., 2012; Bulgarelli et al., 2013; Edwards et al., 2015; Fierer et al., 2009; Lundberg et al., 2012; Schlaeppi et al., 2014; Zarraonaindia et al., 2015). Interestingly, the same phyla are also enriched within the human gut (Ley et al., 2008), suggesting that they are adapted to interact with complex eukaryotes. This interaction-potential is likely due to their ability to metabolize nutrients spared or actively made available by their host. As up to 40% of the carbon fixed by a plant can be released via roots into the rhizosphere, it is obvious that the plant takes an active role in shaping the microbial communities (Bais et al., 2006).

Within the bacterial communities, members exert strong influence on each other by antagonistic, competitive, and mutualistic interactions. Common modes of microbial interaction are nutritional competition, exchange, and even interdependence where metabolite exchange among microbes facilitates growth of some microbial species (Peterson et al., 2006). This also extends to bacterial-fungal interactions as the ability of the plant to form symbioses with arbuscular mycorrhiza (AM) fungi or nitrogen fixing rhizobia strongly affects surrounding microbial communities (Pii et al., 2016; Zgadzaj et al., 2016; Zgadzaj et al., 2019). Thus, direct cooperative or competitive interactions among the community members can influence microbiome composition and their effect on the host, and therefore determine the outcome of plant-microbiota interactions in a given condition. While the mechanisms of direct microbe-microbe interactions are not the focus of this review, they are important to keep in mind when introducing new species or communities into an agricultural field or when trying to isolate the causative beneficial species in complex microbiomes.

Given the strong selective force the root exerts on the microbial communities in the rhizosphere, the question arises whether plant genotype in form of species and cultivars affect microbiome composition. It has been described that the microbiota associated with different plant species can differ considerably (Pérez-Jaramillo et al., 2016; Wieland et al., 2001). Initial studies in maize (Peiffer et al., 2013), barley (Bulgarelli et al., 2015), and *Arabidopsis thaliana* and its relatives (Schlaeppi et al., 2014) revealed only subtle ecotype/cultivar effects on the root bacterial microbiome in a given soil. Peiffer and colleagues attributed 5-7% of microbiome variation to the host genotype. These differences were mostly of quantitative nature and they were not able to find a bacterial taxon that is diagnostic for a given host genotype (Peiffer et al., 2013). Recently, a large-scale field study of the maize rhizosphere microbiome, using 27 maize genotypes, in five different fields sampled throughout the growing season and replicated five years later, succeeded in identifying root-associated microbiota displaying reproducible plant genotype associations. They were able to identify 143 operational taxonomic units (OTUs) that were significantly correlated with plant genotype, despite the confounding effects of plant age, climate, and soil (Walters et al., 2018). Genotype effects of the plant hosts can be more dramatic for individual microbial species. Haney and colleagues screened approx. 200 naturally occurring *A. thaliana* accessions in a hydroponic system with a single-member of the rhizosphere community: the beneficial root-associated bacterium *Pseudomonas fluorescens* WCS365. Selected accessions were then planted in natural soils and two were found to inhibit the growth of some *Pseudomonadaceae* species, while leaving the majority of the microbiome intact (Haney et al., 2015). Thus, individual cultivars can influence the structure of microbial communities and sometimes in a precise manner.

These interactions are not static. The emerging ‘cry for help’ hypothesis posits that plants recruit specific microbes that are able to alleviate plant stress in a given situation (López-Ráez et al., 2011; Neal et al., 2012; Rudrappa et al., 2008). This was first noted in the recruitment of nutrient delivering AM fungi and nitrogen-fixing rhizobia when plants are grown at low phosphate or nitrogen conditions (Carbonnel and Gutjahr, 2014; Nishida and Suzaki, 2018). Recruitment appears to be more widespread, though. Upon infection by *Hyaloperonospora arabidopsidis*, *A. thaliana* accessions specifically recruited a synergistic group of three bacterial strains that helped fend off the infection and even fortified the soil to become ‘disease-suppressive’ to protect subsequent generations against the pathogen (Berendsen et al., 2018). Thus, the shaping of microbial communities by plants is not limited to individual species, but extends to small microbial communities. The use of synthetic communities (SynComs) (Vorholt et al., 2017) has started to help unravel the underlying relationships.

Understanding microbiome-host relationships using SynComs

The complexity of multi-kingdom interactions in the rhizosphere makes it challenging to unravel the mechanisms and the genetics of plant-microbe associations in a natural habitat. A powerful approach to study complexity in a controlled setting is the use of bacterial SynComs (**Table 1**). Starting from a collection of isolated microbial cultures, SynComs can be mixed and used as inoculants for a given host in a gnotobiotic system. This allows dissecting how one or few community members affect the plant and how host genes affect microbiome composition. Bodenhausen and colleagues screened a SynCom of seven strains, representing the most abundant phyla in the Arabidopsis phyllosphere, against 55 *A.*

thaliana mutants. The host alleles that displayed the strongest perturbation of the microbiota were mutants affecting cuticle formation (Bodenhausen et al., 2014), whereas immune mutants had only minor effects in this setting. A representative SynCom for the maize rhizosphere was used to investigate the functional contribution of individual members on overall community structure in maize. Removal of one community member led to a reduction of species richness, suggesting that this strain has a key role within the tested SynCom (Niu et al., 2017). An exciting study towards understanding cross-kingdom interactions was reported by Duran and colleagues studying the *A. thaliana* root microbiome (Duran et al., 2018). After profiling bacteria, fungi, and oomycetes, they established microbial cultures for all three groups to investigate their interactions. In the absence of bacteria, fungi and oomycetes had a strong detrimental effect on plant growth and survival. Both effects were neutralized upon co-inoculation of bacterial strains. Strains of the *Pseudomonadaceae* and *Comamonadaceae* families were particularly effective; however, in the absence of the respective 18 strains from these two families, other bacterial taxonomic lineages still positively affected plant survival. Thus, bacterial communities aid in maintaining the microbial balance and protect host plants against the detrimental effects of filamentous eukaryotic microbes.

Host	Microbial kingdom	Strains number	Tissue/compartment	Microbial origin	Reference
A. thaliana	Bacteria	440	Root (responses to Pi starvation)		(Herrera Paredes et al., 2018)
A. thaliana	Bacteria Fungi Oomycete	148 bacteria; 34 fungi; 8 oomycetes	Root, rhizosphere	Cologne agricultural soil (CAS)	(Duran et al., 2018)
***Saccharum sp.* (sugarcane)**	Bacteria	20	Root, rhizosphere, stalks	Greenhouse	(Armanhi et al., 2017)
***Trifolium pratense* (legume)**	Bacteria		Rhizosphere		(Hartman et al., 2017)
***Zea mays* (maize)**	Bacteria	7	Roots	Greenhouse	(Niu et al., 2017)
A. thaliana,* other *Brassicaceae	Bacteria	35	Roots	North Carolina	(Castrillo et al., 2017)
***Solanum lycopersicum* (tomato)**	Bacteria (Pseudomonas PGPR)	8	Rhizosphere	Nanjing	(Hu et al., 2016)
A. thaliana	Bacteria	218 (leaf); 188 (root and soil)	Leaf, root and rhizosphere	Cologne, Golm, Widdersdorf, Saint-Evarzec, Roscoff	(Bai et al., 2015)
A. thaliana	Bacteria	38	Roots	North Carolina	(Lebeis et al., 2015)
A. thaliana	Bacteria	7	Leaf	Madrid	(Bodenhausen et al., 2014)

Table 1. Microbial strain collections used in SynCom studies.

An analytical approach to identify potential functional relationships takes advantage of increasingly available microbiome datasets. Similar to transcriptional co-expression networks, it is possible to identify positive and negative co-occurrence correlations between microbial community members, which may reflect synergistic and antagonistic functional relationships (Faust and Raes, 2012). Such relationships can be displayed as networks and analysed using graph theory approaches. If the correlations are reflecting functional interactions, co-occurrence networks may help developing control strategies for microbial communities. Initial results indicate that positive correlations are more abundant among microbes from the same kingdom, whereas, as illustrated in the previous example, negative correlations are more common among inter-kingdom associations (Agler et al., 2016). In another study, several bacterial taxa were anti-correlated with the pathogenic wheat fungus *Rhizoctonia solani* (Poudel et al., 2016). Similar to other biological networks, hub species can be identified that have an extraordinary large number of positive and negative interactions and thus appear important for shaping communities (Agler et al., 2016; Layeghifard et al., 2017). Network approaches can thus be an important tool for understanding host associated microbiome dynamics.

Plant associated microbiomes can have beneficial effects for their hosts, however microbial composition in the rhizosphere as well as colonization efficiency are affected by environmental parameters and by the genetics and physiological state of the host. SynComs and network approaches are important research tools to dissect the shaping factors and understand the highly interdependent causalities of microbiome assembly. The plant immune system needs to differentiate between beneficial and pathogenic microbes and mount appropriate, yet diametrically opposed, colonization-enabling or defence responses.

Functions of beneficial microbes and similarities to pathogens

Among beneficial microbiota, endosymbionts that colonize the inside of root cells have been most extensively studied as they can promote plant growth and stress resistance. The best studied of these endosymbioses are AM and root nodule symbioses. AM symbiosis occurs between approximately 80% of land plants and fungi of the *Glomeromycota*, which increase plant nutrition with mineral nutrients in exchange for photosynthetically fixed organic carbon (reviewed in Keymer and Gutjahr, 2018; Roth and Paszkowski, 2017; Smith and Smith, 2011). Root nodule symbiosis with nitrogen fixing bacteria is limited to one clade of the eudicots, *i.e.* the Fabales, Fagales, Cucurbitales and Rosales, of which the legumes form root nodule symbiosis with rhizobia, the others engage with Frankia bacteria (Griesmann et al., 2018; Kistner and Parniske, 2002).

In contrast, plant-growth promoting (rhizo-) bacteria (PGPB or PGPR) are defined as ‘free living plant beneficial bacteria’ that promote plant health (Kloepper and Schroth, 1981) especially when the plant is exposed to abiotic or biotic stressors (Fahad et al., 2015). Many strains are helpful against more than one stress scenario which makes them appealing for agricultural applications in a variety of environments. For instance, *Azospirillum brasilense* NH, originally isolated from salty soil in northern Algeria, can significantly improve growth and yield of durum wheat in salt affected soils and under arid field conditions (Nabti et al., 2010). In *A. thaliana, Paraburkholderia* (formerly *Burkholderia*) *phytofirmans* induces cell wall strengthening and an increase of photosynthetic pigments, which lead to improved cold tolerance (Su et al., 2015). In addition, *P. phytofirmans* can increase host resistance against fungal and bacterial pathogens (Miotto-Vilanova et al., 2016; Timmermann et al., 2017). Equally versatile traits were reported for *Bacillus velezensis* strain NBRI-SN13, which protects rice against diverse abiotic stresses including heat, cold, and freezing (Tiwari et al., 2017). Members of the *Paenibacilleae*, e.g. *P. azotofixans*, can provide multiple benefits to their host including nitrogen fixation, phosphate solubilization, and biocontrol (Grady et al., 2016). Several molecular mechanisms have been identified that contribute to the beneficial effects, including chemically increasing accessibility and concentration of nutrients (nitrogen fixation, solubilization of phosphate or potassium, iron uptake), and modification of host physiology by signaling molecules (reviewed in Gouda et al., 2018; Olanrewaju et al., 2017).

In addition to these effects related to abiotic stressors, many PGPR increase host pathogens resistance. In contrast to pathogen-triggered systemic acquired resistance (SAR) (Chester, 1933), induced systemic resistance (ISR) (Kloepper et al., 1992) can be triggered by non-pathogenic and symbiotic microbes in the rhizosphere or by chemical inducers. Similar to SAR, ISR renders the above-ground plant tissues resistant against the attack of microbial pathogens. Inoculation of barley with *Pseudomonas* spp., e.g., increased crop resistance to the fungal pathogen *Gaeumanomyces graminis,* the causal agent of take-all-disease (Fröhlich et al., 2012). In *Medicago truncatula* the AM fungus *Rhizosphagus irregularis* enhanced resistance to *Xanthomonas campestris* and rhizobia increased resistance to *Erysiphe pisi* (Liu et al., 2007; Smigielski et al., 2019). In several cases microbial mixtures have a more pronounced and consistent effect than inoculation with single strains. A combination of *Bacillus pumilus*, *B. subtilis* and *Curtobacterium flaccumfaciens* was highly effective in enhancing resistance against different pathogens in cucumbers (Raupach and Kloepper, 1998). Drought stress resistance of maize was enhanced by a combination of *Pseudomonas putida*, *Sphingomonas* sp., *Azospirillum brasilense* and *Acinetobacter* sp. (Molina-Romero et al., 2017), and *A. thaliana* fungal pathogen resistance was enhanced by inoculation with *Xanthomonas* sp., *Stenotrophomonas* sp., and *Microbacterium* sp. (Berendsen et al., 2018).

Overall little is known about the interaction of beneficial bacterial communities with endosymbionts in the promotion or neutralization of beneficial effects. Colonization of *Lotus japonicus* by rhizobia, e.g., enables other endophytic bacteria to colonize the nodule by hitchhiking along the infection thread, a plant-derived subcellular structure that guides rhizobia into the nodule (Zgadzaj et al., 2015). These co-colonizers can be neutral or beneficial but they may also cause a carbon drain to the plant with detrimental effects on growth and yield. A few synergistic combinations of AM fungi and PGPR have been described. Growth of tomato plants was increased more strongly after co-inoculation of the AM fungi *Glomus mosseae* or *Glomus versiforme* with a PGPR (either Bacillus sp. or *Bacillus polymyxa*) than with any of the microorganisms alone. Similarly, incidence of the root-knot nematode *Meloidogyne incognita* in tomato was reduced most efficiently after co-inoculation of an AM fungi with PGPR (Liu et al., 2012).

Although many PGPR, especially commercially available strains, colonize and exert beneficial effects on different plants, their performance can be strongly species- or cultivar-specific (Chanway et al., 1988; Germida and Walley, 1996; Montalban et al., 2017). Wheat cultivars differ in their colonization by and responsiveness to beneficial strains, such as *Azospirillum brasilense* (Rothballer et al., 2003; Walker et al., 2011) or *Pseudomonas putida*. For wheat the effect of the AM fungus *Rhizophagus irregularis*, the PGPR *P. putida* and a combination of both on systemic priming of Mercato and Avalon cultivars was compared. In Mercato, the two microbes had a substantial synergistic effect on priming and callose deposition, whereas in Avalon, the callose response was equally weak after individual and combined inoculation. Avalon roots were also less colonized by both microbes (Perez-de-Luque et al., 2017).

As discussed above, plant can also recruit specific microbes to help them cope with a specific abiotic or biotic stress. Generally, the molecular determinants of triggered or constitutive cultivar-competence for PGPR colonization are incompletely understood. Besides direct genetic determinants, e.g. ability to communicate, indirect factors may play a role. For example, different nutrient requirements of cultivars may be a factor that determines whether a condition is experienced as stress and consequently if PGPR are recruited. Important questions in host-microbe research regard the underlying genetic determinants and their molecular mechanisms of recruitment and probiotic competence, e.g. to breed such competence into existing elite cultivars. To avoid undesirable consequences, this requires the ability of crops to differentiate between probiotic beneficials and closely related detrimental pathogens.

Friend or foe - closely related beneficials and pathogens

Pathogenic and beneficial lifestyles both require recognition and communication with a host, the ability to benefit from biological nutrient sources and an ability to at least partially suppress the host immune response. This is especially true for endophytes and mutualistic symbionts, which, similar to pathogens, are able to enter plant host tissue but remain there without harming and often benefitting the host. As a consequence of these similar requirements, in essentially all phyla of host-associated microbiomes, closely related species with pathogenic and beneficial lifestyles can be found (Figure 1). Frequently, relatives with opposite effects are found within the same genus, e.g. among the *Paenibacilleae*: *P. azotofixans* and *P. amylolyticus* (Grady et al., 2016), among *Bacilleae: B. velezensis* and *B. cereus* (Radhakrishnan et al., 2017), among *Pseudomonas: P. simiae* and *P. syringae* (Anderson et al., 2018) and even within the same species, e.g. *Pseudomonas aeruginosa* (Ndeddy Aka and Babalola, 2016; Steindler et al., 2009). Among the *Streptomyces* (Viaene et al., 2016), *S. lividans* can protect plants against fungal pathogens (Meschke and Schrempf, 2010), while *S. scabiei* causes rot on roots and tubers of potatoes, beets, and carrots (Hiltunen et al., 2009). Members of the *Herbasprillum rubrisubalbicans* species are usually mild pathogens in sugarcane, sorghum and rice (Valdameri et al., 2017), while *H. seropedicae* and some strains of *H. rubrisubalbicans* were reported to promote sugarcane growth (Ferreira da Silva et al., 2017). Especially for endophytes, although defined as living inside plants as commensals or mutualists (Hallmann et al., 1997; Hardoim et al., 2015), a broad spectrum of interactions can be detected spanning from beneficial to pathogenic in plant and human hosts (Berg et al., 2005; Mendes et al., 2013). In ferns, inoculation with bacterial endophytes from commonly beneficial fluorescent pseudomonads resulted in detrimental effects (Kloepper et al., 2013). The human pathogen *Clostridium botulinum* is a potent endophytic plant growth promoter in white clover, but can cause lethal botulism in cattle grazing on the affected site (Zeiller et al., 2015). A similar host-genotype dependence of interaction outcome can be observed for AM fungi, where symbiosis may lead to growth depression (Grace et al., 2009). The molecular cause for this phenomenon has not been established but it could be due to enhanced carbon drain due to suboptimal compatibility. Interestingly, in a panel of Sorghum accessions, different growth responses to AM fungi were recorded and ranged from strongly positive to negative and the outcome depended on plant and fungal genotypes; negative growth responses were correlated with expression of defense related genes (Watts-Williams et al., 2019). An interesting case is *Rhizobium radiobacter* F4, which has been isolated from its host, *Serendipita indica* (formerly

Piriformospora indica) a mutualistic root fungus that can colonize a broad range of higher plants including barley and Arabidopsis (Guo et al., 2017). The association between endobacterium and fungus seems to be essential for the fungus, as *S. indica* cannot be completely cured from its endobacterium by antibiotic treatment (Glaeser et al., 2016). *R. radiobacter* F4 is a close relative of the well-characterized plant pathogen *R. radiobacter* C58 (formerly *Agrobacterium tumefaciens)*. When the isolated F4 strain was used as an inoculum on different plants, *R. radiobacter* F4 was detected endophytically and its beneficial effects were hardly distinguishable from an inoculation with the fungus (including the endobacterium) (Glaeser et al., 2016). This qualifies F4 to be a true PGPR and suggests that *S. indica* may act as a vector for the PGPR.

Thus, beneficial and pathogenic microbes share physiological features and an evolutionary proximity to an extent that manifestation of a pathogenic phenotype may depend on small differences of the microbe and sometimes even on the host. Conversely plants must have evolved sophisticated mechanisms to distinguish a potentially beneficial microbe, which may ensure survival, from a closely related potentially fatal pathogen.

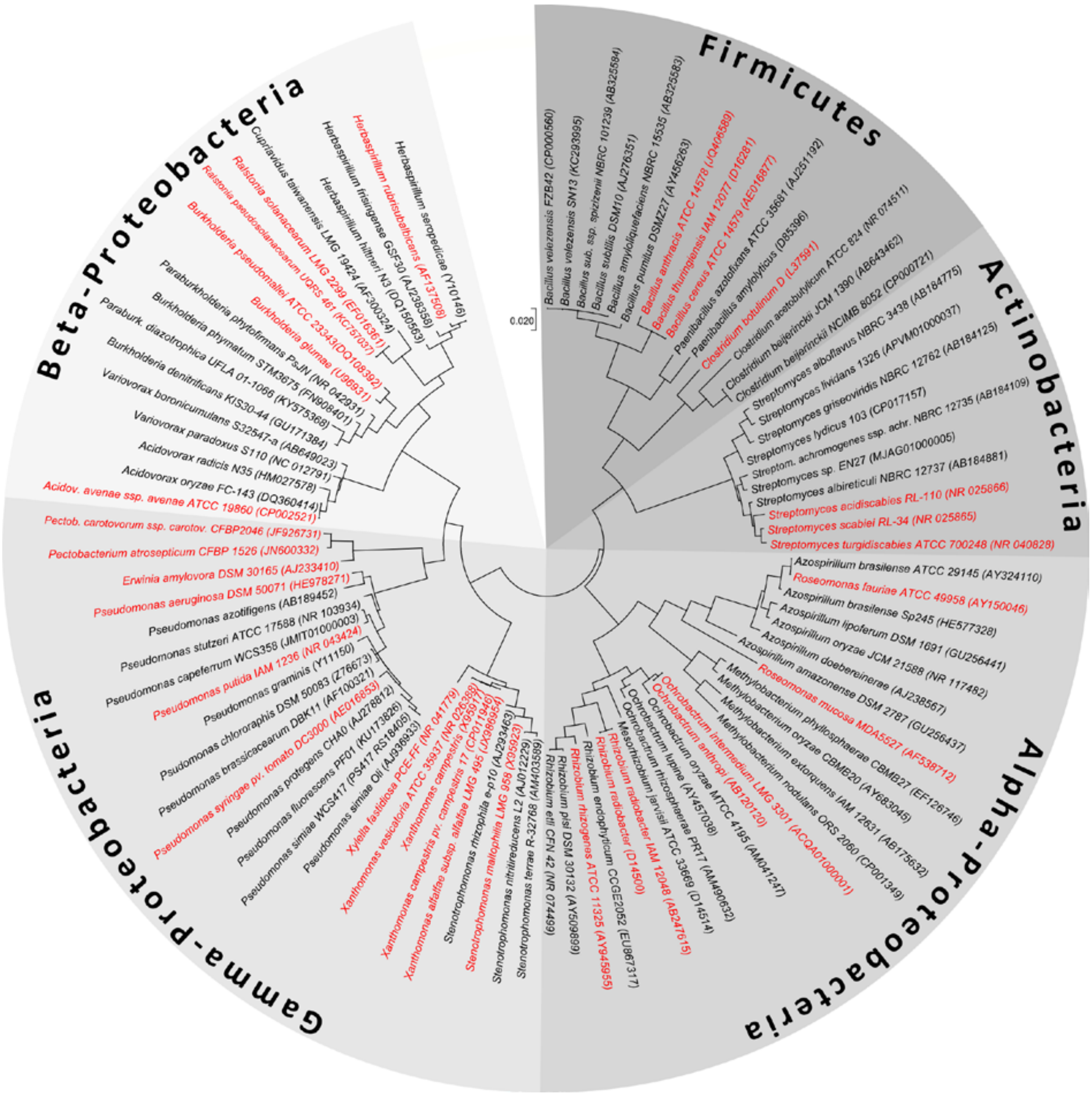

Figure 1. Phylogenetic tree of plant growth promoting (black) and pathogenic bacteria (red), and their corresponding phyla (in different shades of grey) mentioned in the text. The tree was supplemented with sequences from some widely applied PGPR and closely related plant and human pathogens for comparison. Evolutionary analyses were conducted in MEGA7 (Kumar et al., 2016) using the Maximum Likelihood method based on the Tamura-Nei model.

Systems biological approaches to molecular microbe-host interactions

Genetic and mechanistic studies of plant immunity in the context of infections have shaped the general understanding of plant pathogen interactions. However, how the differentiation between beneficials and pathogens is achieved by plant recognition and information processing systems will be a key question for plant systems biology in the coming decade.

Plant perception of microbes

Successful pathogens and endophytes must first overcome structural barriers such as cell walls (Miedes et al., 2014), waxy epidermal cuticles (Yeats and Rose, 2013) and constitutive antimicrobial products like phytoanticipins (VanEtten et al., 1994). This common requirement may partly explain the evolutionary proximity of beneficials and pathogens. Close to the cell membrane, the presence of microbes is recognized by plant surface receptors called pattern-recognition-receptors (PRR). This recognition of conserved pathogen- or microbe-associated-molecular-patterns (PAMPs/MAMPs), e.g. bacterial flagellin or EF-Tu, results in intracellular signaling that culminates in defense responses known as pathogen- or microbe-triggered immunity (PTI/MTI) (Boller and Felix, 2009; Macho and Zipfel, 2014). MTI includes production of reactive oxygen species and nitrogen oxide, stomata closure, directed callose deposition, relocation of nutrients, release of antimicrobial metabolites, initiation of plant defense hormone signaling, and transcriptional changes. A transcriptome analysis of *A. thaliana* exposed to two leaf commensals showed that these non-pathogenic microbes do activate the first layer of plant immune responses. Approximately 400 genes were induced upon commensal treatment and partly overlapped with host genes induced by the pathogen *P. syringae* (Vogel et al., 2016). The strong immune response may partially explain the induction of ISR by beneficials, however does not address, how plants recognize beneficials.
The presence or absence of PRRs could serve as host range determinants for microbial colonizers (Hacquard et al., 2017). However, the molecular patterns of beneficials and pathogens are similar if not identical, which in turn renders their differentiation by specific PRRs difficult. One of the main models to study PRR function is FLS2, which recognizes flg22 the most conserved motif in bacterial flagellin (Chinchilla et al., 2006; Zipfel et al., 2004). FLS2 requires a co-receptor, BAK1, in order to activate downstream signaling (Schulze et al., 2010; Schwessinger et al., 2011). Intriguingly, BAK1 is also a co-receptor for BRI1 (brassinosteroid insensitive 1), a leucine-rich repeat receptor kinase (LRR-RK) that perceives plant brassinosteroids (BR) and acts as an integrator between defense and growth signaling (Li et al., 2002; Nam and Li, 2002). Additional receptors recognize other parts of the protein. Tomato can perceive flgII-28 through FLS3 in an FLS2-independent manner (Fliegmann and Felix, 2016) and the rice pathogen *Acidovorax avenae* harbors a different flagellin motif, CD2-1, whose receptor remains unknown to date (Katsuragi et al., 2015). Interestingly, some strains of *A. avenae* avoid recognition by flagellin glycosylation (Hirai et al., 2011). In contrast to such masking exploited also by pathogens, some beneficials have epitopes that avoid detection by one or the other receptor (Gomez-Gomez et al., 1999).

However, besides MAMP-masking or evasion mechanisms, many beneficials are likely recognized by their flagellin and suppress full-blown immune responses by yet unknown mechanisms. Garrido-Oter and colleagues showed that most genes induced by perception of purified flg22 in Arabidopsis were downregulated in response to colonization by the commensal *Rhizobium* sp. 129E. Their analysis suggests that this commensal has the ability to interfere with MAMP-induced transcriptional responses through alternative pathways. As this rhizobium strain does neither possess Type-III-secretion system (T3SS) nor Nod factor biosynthesis genes (Garrido-Oter et al., 2018), it is likely that signaling via other heteromeric PRRs complexes plays a role.

Symbiont-plant interactions point to mechanisms underlying friend-vs-foe distinction. Upon first contact, AM fungi and rhizobia trigger transient defense-like responses that are quickly repressed (Libault et al., 2010; Liu et al., 2003). It has been suggested that Myc- and Nod-factor signaling is important for this repression (Gourion et al., 2015). Both symbiotic signals are defined by their ability to elicit nuclear calcium oscillations dependent on a signaling cascade comprising a number of conserved symbiosis proteins (Gourion et al., 2015; Singh and Parniske, 2012). Hosts perceive Nod factors by Lysine-motif (LysM) receptor like kinases (RLK) (reviewed in Gough and Cullimore, 2011) and it is suspected that similar receptors exist for Myc factors (Buendia et al., 2016). Some of these receptors appear to also mediate recognition of pathogens. OsCERK1 is a LysM-RLK important for establishment of mycorrhizal root symbiosis and resistance against rice blast fungus (Miyata et al., 2014; Zhang et al., 2015), suggesting that it acts as a “molecular switch” between symbiotic and defense responses. Although the molecular mechanism underlying this dual functionality is unknown, it is thought that specificity comes from interactions with other LysM-RLK (Gourion et al., 2015). Other examples of such dual functionality suggest that this could be a more widely used mechanism. NFP is a *Medicago truncatula* Nod factor receptor that also mediates perception and defense against the fungus *Colletotrichum trifolii* and the oomycetes *Aphanomyces euteiches* and *Phytophthora palmivora* (Gough and Jacquet, 2013; Rey et al., 2015; Rey et al., 2013).

The detailed studies of exemplary PRRs and LysM-RLK suggest that combinatorial physical interactions among receptors and co-receptors are important for signal specificity and signal integration. Plant roots in nature are in simultaneous contact with a plethora of MAMPs and a soup of different signaling molecules. Thus, it is possible, if not likely, that a tailored response is mounted to specific microbial assemblages recognized via combinatorial and quantitative perception of the diverse signaling molecules by a network of interacting receptors. Consequently, integrated global systems approaches to PRR signaling will be required. A proteome-scale interactome study by Smakowska-Luzan and colleagues constitutes an important step towards a comprehensive understanding of this crucial plant perception system. Using biochemical pull-down experiments they mapped the physical cell surface interaction network formed by 225 LRR-RKs (CSI^{LRR}) in *A. thaliana* (Smakowska-Luzan et al., 2018). CSI^{LRR} revealed a very high interconnectivity of all LRR-RKs, which clustered in several modules whose biological relevance remains to be clarified. Importantly, the authors showed that not only direct interactions, but also indirect network effects modulate the downstream signaling output and that the full network jointly provides the well-balanced responses of the plant immune system. Characterizing the integrated information processing by this LRR-RK network will be critical for understanding plant immunity.

Bacterial signaling: quorum sensing and symbiosis factors

In addition to sensing conserved microbial patterns, plants tap bacterial communication mediated by metabolites, volatiles, symbiosis signals, and quorum sensing (QS) molecules (Chowdhury et al., 2015; Jourdan et al., 2009). N-acyl homoserine lactones (AHL) are key components in bacterial communication that can also be perceived by plants. This was demonstrated for the beneficial *Acidovorax radicis* N35, where the AHL-producing wildtype was able to dampen the defense response of barley, whereas flavonoid defense was upregulated after inoculation of the non-AHL producing mutant (Han et al., 2016). Other examples demonstrate the growth promoting and priming effects of AHLs on host plants like Medicago, tomato, Arabidopsis, and barley (Mathesius et al., 2003; Schenk et al., 2014; Schuhegger et al., 2006; von Rad et al., 2008). As pathogenic bacteria similarly produce AHL (Cha et al., 1998; von Bodman et al., 2003) it is unlikely that these signaling substances alone provide sufficient information for the plant to modulate its defense responses. Possibly the combinations and concentrations of QS molecules indicate an imbalanced microbial composition. While the physiological effects of AHLs have been characterized in some detail, the pathways and mechanisms by which plants perceive these bacterial molecules remain unknown (Schikora et al., 2016). Interestingly, also lipochitooligosaccharides, i.e. Myc and Nod symbiosis factors, can promote root development, seed germination, and plant growth even in plants that do not form symbiosis (Maillet et al., 2011; Prithiviraj et al., 2003; Tanaka et al., 2015). Thus the symbiosis factor recognition and signaling system is partially independent of symbiosis competence of the host. Further research is needed to understand how the range of rhizosphere signals released by microorganisms is co-interpreted by the plant and in how far different molecules may have synergistic or antagonistic effects on plant growth and stress resistance.

Hormone signaling in microbe-host interactions

Phytohormone signaling is central to essentially all plant processes. Defense responses are canonically mediated by salicylic acid (SA), jasmonic acid (JA), and ethylene (ET). Whereas

SA mediates SAR and defense against biotrophic and hemibiotrophic pathogen attack, JA and ET mediate ISR and defense against necrotrophs and insects (Glazebrook, 2005; Pieterse et al., 2014). Other hormones predominantly control developmental processes (auxin, gibberellins (GA), BR, or cytokinins (CK)), or abiotic stress responses (abscisic acid (ABA)). Beyond these seemingly clean classifications, however, it is clear that hormone signaling is highly integrated and multiple hormones influence any process of interest (Nguyen et al., 2016; Vos et al., 2015). Accordingly, phytohormones are also significant for the bi-directional communication between plant and microbes. Strigolactones, e.g., are exuded from roots under phosphate or nitrogen starvation to attract AM fungi and their biosynthesis is downregulated upon colonization (Yoneyama et al., 2012). In contrast, GA, SA, and ET inhibit both AM and root nodule symbiosis, whereas auxin and ABA have a concentration dependent positive impact on AM development. CK and localized auxin signaling are required for nodule formation (reviewed in Gutjahr, 2014; Oldroyd et al., 2011; Pozo et al., 2015). The role of JA in symbiosis establishment is ambiguous and can be positive, negative, or neutral depending on the conditions and plant species (reviewed in Gutjahr and Paszkowski, 2009).

The hormone signaling system is actively modulated by beneficial and pathogenic bacteria. Most famously, coronatine (COR) is a toxin produced by pathogenic *P. syringae* pv. *tomato* DC3000 (*Pst*), which mimics plant JA-isoleucine (JA-Ile), but is even more active (Katsir et al., 2008). This activation of JA-dependent defense mechanisms leads to suppression of the appropriate SA-mediated defenses against the hemibiotrophic *Pst* (Wasternack and Hause, 2013). In general, pathogens manipulate plant signaling to suppress defense responses and redirecting nutrient allocation to infested tissues for sustained pathogenic colonization (Ma and Ma, 2016). Beneficial strains often have the opposite effect on SA-JA balance, which can manifest in different ways: in *A. thaliana P. fluorescens* Pf4, *P. aeruginosa* Pag (Singh et al., 2003), or *B. velezensis* LJ02 (Li et al., 2015) trigger an increase of endogenous SA levels in different plant parts, other strains decrease JA-Ile levels (Srivastava et al., 2012), and *Paraburkholderia phytofirmans* PsJN decreases expression of JA-biosynthesis and wound-induced JA accumulation (Pinedo et al., 2015). Thus, phytohormones of microbial origin mediate versatile effects depending on the individual plant-microbe combination. The SA signaling system also appears central for shaping the root microbiome although different studies report opposing results. One study reported only minor effects of SA mutants on microbiome composition (Bodenhausen et al., 2014). In contrast, Lebeis and colleagues reported that *A. thaliana* mutants deficient in synthesis or perception of SA had altered rhizosphere microbiota, whereas no such effect was observed for the corresponding JA and ET mutants (Lebeis et al., 2015).

Beyond modulating defences, which is common to pathogens and beneficials, many PGPR modulate plant development, especially root growth, by production of auxins, gibberellins, or cytokinins (reviewed in Backer et al., 2018). To dissect the underlying complexity, it will be important to complement genetics with systems biological approaches that include metabolomics, global network analysis, hormone profiling, and focused quantitative modeling of molecular processes in plants and soil. The latter is actively pursued for auxin signaling in the plant root, for which advanced models are available (Clark et al., 2014; Mironova et al., 2010). The development of such quantitative models was enabled by detailed mechanistic knowledge (Grieneisen et al., 2007; Mironova et al., 2010) and fluorescent auxin reporters that provide time-resolved data on auxin distribution (Liao et al., 2015). Both together provide the basis for quantitative time-resolved models. Generally missing are quantitative data on the molecules and receptors that translate a given auxin concentration into specific transcriptional responses, although first data on the effects of auxin concentrations on receptor pairs are available (Fendrych et al., 2016). For understanding microbe-host interactions a model of the SA signaling pathway will be powerful. The recently described SA receptors NPR1, NPR3, NPR4, (Canet et al., 2010) together mediate responses to different SA concentrations (Castello et al., 2018; Fu et al., 2012; Kuai et al., 2015). In contrast, the more distant family members BOP1 and BOP2 appear to have no function in SA signaling (Canet et al., 2012), but have been implicated in developmental programs like flowering and nodule formation in legumes (Couzigou et al., 2012; Magne et al., 2018). At the same time, the biochemical regulation of NPR1, and possibly also its paralogues, is complex and involves multiple cellular compartments, redox potential, phosphorylation, and degradation. Thus, although key elements for model development are known (Seyfferth and Tsuda, 2014), including TGA transcription factors (Li et al., 2004; Wu et al., 2012), and signaling network components (Innes, 2018), understanding of this key immune signaling system remains incomplete. The development of fluorescent SA sensors and quantitative protein level and binding data are important elements for quantitatively modeling of SA signaling.

Apart from the individual pathways all hormone signaling pathways are interconnected and very few biological responses are mediated by a single hormone. Great efforts in deciphering the crosstalk of SA, JA and ET during immunity in Arabidopsis are represented by the integrative works of Tsuda and colleagues. They divided the hormone signaling network in four sectors (SA, JA, ET and PAD4), and quantitatively assessed immunity in all possible mutants belonging to these sectors after stimulation with a panel of MAMPs and effectors. Their work showed strong interactions of the hormone network components with additive, synergistic and compensatory interactions (Tsuda et al., 2009). Later works by the same group led them to propose that the PTI signaling network is highly buffered against interference, e.g. by pathogen effectors (Hillmer et al., 2017).

Interactome network analysis

In the absence of quantitative dynamic models, molecular interaction network approaches can be powerful to identify modules, pathways, components, and system-level patterns of molecular host-microbe interactions (Marin-de la Rosa and Falter-Braun, 2015). To place host-microbe interaction data in the context of host biology, a reference protein network is required. Plant interactome analysis commenced with publication of the first experimental map of physical protein-protein interactions among several thousand Arabidopsis proteins: Arabidopsis Interactome-1 (AI-1) (Arabidopsis Interactome Mapping Consortium, 2011), which offered a first integrated organizational view of plant molecular connectivity. Complementary and more specialized maps have been produced since, which facilitate analysis of specific processes (**Table 2**). For membrane proteins a map with approx. 12,000 protein-protein interactions was acquired using the split-ubiquitin system (Jones et al., 2014). A G-protein interactome revealed a new role of G-proteins in regulation of cell wall modification, a process highly relevant for defense (Klopffleisch et al., 2011). Recently, a protein-protein interaction network for the fungus *Phomopsis longicolla*, causative for Phomopsis seed decay in soybean, was generated by interolog mapping (Yu et al., 2004), *i.e.* transferring interaction annotations among conserved protein pairs between organisms, and allowed detection of disease associated subnetworks (Li et al., 2018).

Study	Organism_1	Organism_2	Year	Reference
A. thaliana Interactome	*A. thaliana*		2011	(Arabidopsis Interactome Mapping Consortium, 2011)
Convergent targeting of hubs in a plant-pathogen interactome network	*Hyaloperonospora arabidopsidis* and *Pseudomonas syringae* effectors	*A. thaliana*	2011	(Mukhtar *et al.*, 2011)
Convergent targeting of a conserved host-microbe interface	*Golovinomyces orontii* effectors	*A. thaliana*	2014	(Wessling *et al.*, 2014)
Pathogenicity genes in *U. virens*	*Ustilaginoidea virens*		2017	(Zhang *et al.*, 2017)
Extracellular network of *A. thaliana* LRR-RKs	*A. thaliana*		2018	(Smakowska-Luzan *et al.*, 2018)
Pathogenic Protein Networks in *Phomopsis longicolla*	*Phomopsis longicolla*		2018	(Li *et al.*, 2018)

Table 2. Interactome network datasets for plant-microbe interactions studies

Pathogens and beneficial microbes can deliver hundreds of (virulence) effector proteins into the cytosol and apoplast of the host plant to modulate plant defense and physiology (Boller and Felix, 2009; Jones and Dangl, 2006). To comprehend host-microbe interactions their functions need to be understood in an integrated and time-resolved way. Initial plant-targeted pathogen effectors were characterized by small-scale studies and revealed that virulence effectors modify host protein functions to interfere with immune responses and promote disease, known as effector-triggered susceptibility (ETS) (Dou and Zhou, 2012). Recognition of pathogen effectors by a host resistance protein (R protein) can result in effector-triggered immunity (ETI) (Coll et al., 2011; Jacob et al., 2013; Jones and Dangl, 2006). In order to gain a systems-level perspective on effector functions, a large-scale interactome study (PPIN-1) mapped the interactions of virulence effectors of the bacterial pathogen *Pst* and the oomycete pathogen *H. arabidopsidis* with proteins in the AI-1 host network (Mukhtar et al., 2011); a follow-up study later added interactions of effectors from the biotrophic ascomycete *Golovinomyces orontii* (Wessling et al., 2014). The data revealed that effectors from three pathogens partially converge on common host proteins, many of which are highly connected hubs in the host network. Depending on the extent of convergence, the host proteins had genetic validation rates between 100% for the most targeted proteins, and 40% for the less intensely targeted proteins. In addition to convergence, many effectors targeted proteins across the host network, likely as consequence of the highly buffered immune signaling network (Hillmer et al., 2017). Population genetic analyses revealed evidence of positive and balancing selection in the immediate network vicinity of the highly targeted proteins. Thus, the selective pressure imposed by pathogens appears to be absorbed by the network surrounding the effector targets (Wessling et al., 2014). This finding reinforces the notion that host-microbe interactions are mediated by a highly integrated network and can only incompletely understood by analysis of isolated pathways. Studies in the *Yersinia pestis* interactome showed that pathogens appear to rearrange host networks instead of dismantling network integrity (Crua Asensio et al., 2017).

The presence of effector proteins is not limited to pathogens. Mycorrhizal fungi, endophytic fungi and nitrogen-fixing rhizobia have effector proteins that can modulate plant immune responses and symbiotic interactions (Miwa and Okazaki, 2017). Several PGPR, e.g. *P. simiae* WCS417, and many proteobacterial strains in complex microbiome datasets are predicted to have functional T3SS and effectors (Berendsen et al., 2015). For the beneficial fungus *S. indica* and rhizobial bacteria, it is known that their virulence effectors are important for productive and beneficial interactions (Akum et al., 2015; Clua et al., 2018; Rafiqi et al., 2013). T3SS-delivered effectors of *Bradyrhizobium elkanii* even permitted Nod-Factor independent nodulation of soybean (Okazaki et al., 2013). In addition to T3SS many proteobacteria have type-IV and type-VI secretion systems that can deliver bacterial protein into hosts and other microbes. *P. simiae* WCS417 has two T6SS loci (Berendsen et al., 2015) and may deliver effectors not only to its plant host, but also to other competing microbes to modulate the surrounding microbiota. Proteomic approaches can be helpful to unravel the diversity of the effector repertoire of microbes (Schumacher et al., 2014). A study comparing the genome of a beneficial soil fungus, *Colletotrichum tofieldiae*, with a closely related pathogenic counterpart, *Colletotrichum incanum*, revealed that their secretome did not substantially differ, but the beneficial fungus had 50% less effector genes and a reduced activation of pathogenicity-related genes *in planta* (Hacquard et al., 2016). Thus, microbial secretomes and the number and nature of secreted effectors may constitute an important differentiation point between beneficials and pathogens. Most likely the beneficial effector complement is important for non-pathogenic interactions. An important challenge for systems biology will be to understand the global dynamics of effectors targeting different parts of the host network, and how this dynamic relates to ETS, ETI, and what are the systems-level and dynamic differences between effector secretion by pathogens and beneficials.

Beyond proteins, RNA emerged in recent years as important communication molecules between hosts and microbes, which are delivered to the host by extracellular vesicles (EVs). Found first in mammalian cells, EVs are present in bacteria, archaea, and eukaryotes. Small RNA from the fungus *Botrytis cinerea* was shown to target host defense genes in Arabidopsis (Weiberg et al., 2013). Plants are able to silence such foreign transcripts via host-induced gene silencing (HIGS) using dsRNA, and plant EVs and multivesicular bodies accumulate around plasmodesmata during fungal infections to facilitate callose deposition at infection sites (An et al., 2006). EVs and their RNA cargo constitute another communication layer, whose significance is just emerging.

Transcriptional regulatory networks

Transcriptional profiling is widely used and results of key studies are mentioned throughout this text. While comparative transcriptomics are routine, co-expression correlation networks and causal regulatory networks are less commonly employed. Co-expression networks are based on the concept that transcript profiles of time series may be indicative of causal relationships between transcripts. The Weighted Gene Correlation Network Analysis (WGCNA) (Langfelder and Horvath, 2008) is a commonly used method to group genes by hierarchical clustering into co-expression modules. These modules are compared to signaling network connectivity, metabolic paths, or phenotypic traits. Beyond WGCNA Saelens and colleagues (Saelens et al., 2018) have systematically compared 42 different methods for clustering, decomposition, bi-clustering and iterative network inference. These techniques have been applied in *A. thaliana* and other plants like maize and wheat (Kim et al., 2018) to explore their interactions with microbes. The identified modules provide a first insight into genes sharing same functionalities (Vella et al., 2017), and can help to achieve a better understanding of processes relevant for infection or commensalism.

Metabolic exchanges and nutrient competition in the soil

Among the fundamental principles of microbiome-host interactions are metabolic exchanges. Plants provide up to 40% of complex carbons produced by photosynthesis via roots into the rhizosphere to nourish the microbiome (Whipps, 1990). Conversely, fungi and bacteria facilitate solubilization and uptake of essential nutrients like phosphorus, nitrogen, and iron to the plant (Jacoby et al., 2017; Rashid et al., 2016). Relocalization of nutrients is an important goal of plant reprogramming by pathogens via effectors and hormone signaling. Genome-scale metabolic modeling has been used to study the metabolism of an individual organism and modeling of community level reactions is progressing but challenging (reviewed by Kruger and Ratcliffe, 2015; Topfer et al., 2015). Metabolic modeling of prokaryotes is routine nowadays (Heavner and Price, 2015); on the plant side metabolic models have been generated for Arabidopsis, barley, maize, sorghum, sugarcane and canola (Botero et al., 2018). Thus, the metabolic capabilities of beneficials and pathogens can be analyzed by networks comparison. Mithani and colleagues tested the hypothesis that *P. syringae* has evolved to be metabolically specialized for a plant-pathogenic lifestyle (Mithani et al., 2011). Comparison of metabolic networks for nine Pseudomonas strains showed that the pathogenic *P. syringae* is metabolically very similar to its beneficial relative *P. fluorescens* Pf-5 and thus that metabolism may not be a key distinguishing feature. Recently, a life-stage-specific genome-scale metabolic model for the oomycete *Phytophthora infestans* was generated, which predicts biochemical reactions in diverse cellular compartments and in the pathogens stage context (Rodenburg et al., 2018). It will be important to constrain these models by measurements of metabolite levels to obtain a more precise picture of the metabolic changes induced in plant and microbe in the context of colonization.

Integrated multi-omics modeling

While there is obvious mutual benefit between plants and their microbiome and a ‘cry-for-help’ can recruit microbes to support the host, to date it is unclear how the plant integrates recognition of microbes with nutrient-related signals. Phosphorus is usually present in high concentrations, but plant-absorbable orthophosphate is scarce in soil (Raghothama, 1999). In a beautiful multi-omics, systems biology exercise Castrillo and colleagues shed light into the link between nutrition and defense. Using a combination of 16S rRNA sequencing, genome-wide expression analysis, analysis and modeling of SynComs, and functional assays they showed that the plant phosphate starvation response (PSR) has an important role in modulating the root microbiome. They demonstrated that different root-associated microbiomes were assembled by phosphate uptake-deficient and phosphatehyperaccumulating Arabidopsis mutants compared to wild-type. The transcription factors PHR1, and probably PHL1 are integrators of PSR and immune responses (Castrillo et al., 2017), as phr1 and phr1;phl1 mutant plants were more resistant to the oomycete and bacterial pathogens. The connection between PSR and plant immunity seems to be not only modulated by the surrounding microbiota but also by pathogens (Lu et al., 2014) again raising questions about the differences between beneficials and pathogens.

From systems biology to crop protection

The conceptual and molecular advances in understanding microbe-host biology are increasingly helpful in understanding crops-microbe relationships. For the emerging foliar fungal barley pathogen *Ramularia collo-cygni*, causing *Ramularia* leaf spot, McGrann and colleagues used a draft genome assembly to predict a secretome of around 1,000 proteins (McGrann et al., 2016). Based on the reduced number of plant cell wall degrading enzymes and the presence of genes related to chitin recognition avoidance, they proposed that *R. collo-cygni* first behaves as an endophyte without causing disease symptoms and then changes to a necrotrophic phase. Understanding such dynamics and the underlying molecular processes and signals will be an important aspect of systems biological analysis. In another study the host specialization of four *Rhynchosporium* species on grasses has been investigated (Penselin et al., 2016). *Rhynchosporia* are hemibiotrophic fungal pathogens that colonize the intercellular matrix of host leaves relatively slowly without symptoms. Penselin and colleagues found that six specific effector proteins from *R. commune* appeared responsible for stabilizing the biotrophic growth stage in favor of the necrotrophic destructive stage thus providing leads for treatment. In a remarkable study combining multi ‘omics’ approaches the effects of beneficial microbes towards increased biomass and higher tolerance to biotic and abiotic stresses in monocot crops was investigated. Fiorilli and colleagues studied the three-way interactions between the wheat pathogen *Xanthomonas translucens,* the protective symbiotic AM fungus, and the host using phenotyping, transcriptomic, molecular and metabolomic approaches. They proposed a two-step process for conferring *Xanthomonas* resistance to AM-treated wheat: first the activation of a broad-spectrum defense (BSD) response that takes place in roots and leaves of AM-treated plants, and secondly a switch to pathogen-specific defense (PSD) upon bacterial infection, which ultimately leads to protection against the pathogen (Fiorilli et al., 2018).

Outlook: tailored microbiomes for sustainable precision agriculture

The versatility for counteracting a number of stressors makes beneficial microbes attractive tools for sustainable intensification of agricultural production. In the emerging big data driven precision agriculture, crop health is constantly monitored remotely and targeted probiotic treatments may be applied precisely when and where indicated. For this vision it is necessary to have cultivars that are competent to optimally profit from a mix of beneficial microbes without increased pathogen susceptibility. For this, a deep understanding of microbe-host interactions, their genetic determinants and the influence on other plant growth parameters is necessary (Figure 2). The connection between plant nutritional stress responses, immune system function, and microbiome assembly revealed by Castrillo and colleagues is likely only the tip of the iceberg and many exciting mechanisms remain to be uncovered (Castrillo et al., 2017).

Equally important are microbial formulations that are able to establish themselves in the rhizosphere of crops growing in natural soils. Thus, manipulation of the soil microbiome will require an understanding of microbial community dynamics and of plant mechanisms to control the microbiome. Practical questions also regard probiotic formulation development, cultivation and synchronization of multiple species, and delivery of SynComs in the field.

Strategically, understanding host-microbe compatibility in reference organisms will allow transfer of these insights to crops and identification of the underlying genetics. Once the genetic determinants have been identified in crops, probiotic competence can become a target for breeders. Abiotic and biotic stress conditions that threaten agricultural productivity may then be counteracted by application of probiotic cocktails on the field. Due to the complexity of microbe-host interactions, systems biology will have to play an essential role in understanding of these complex inter-organismic relations.

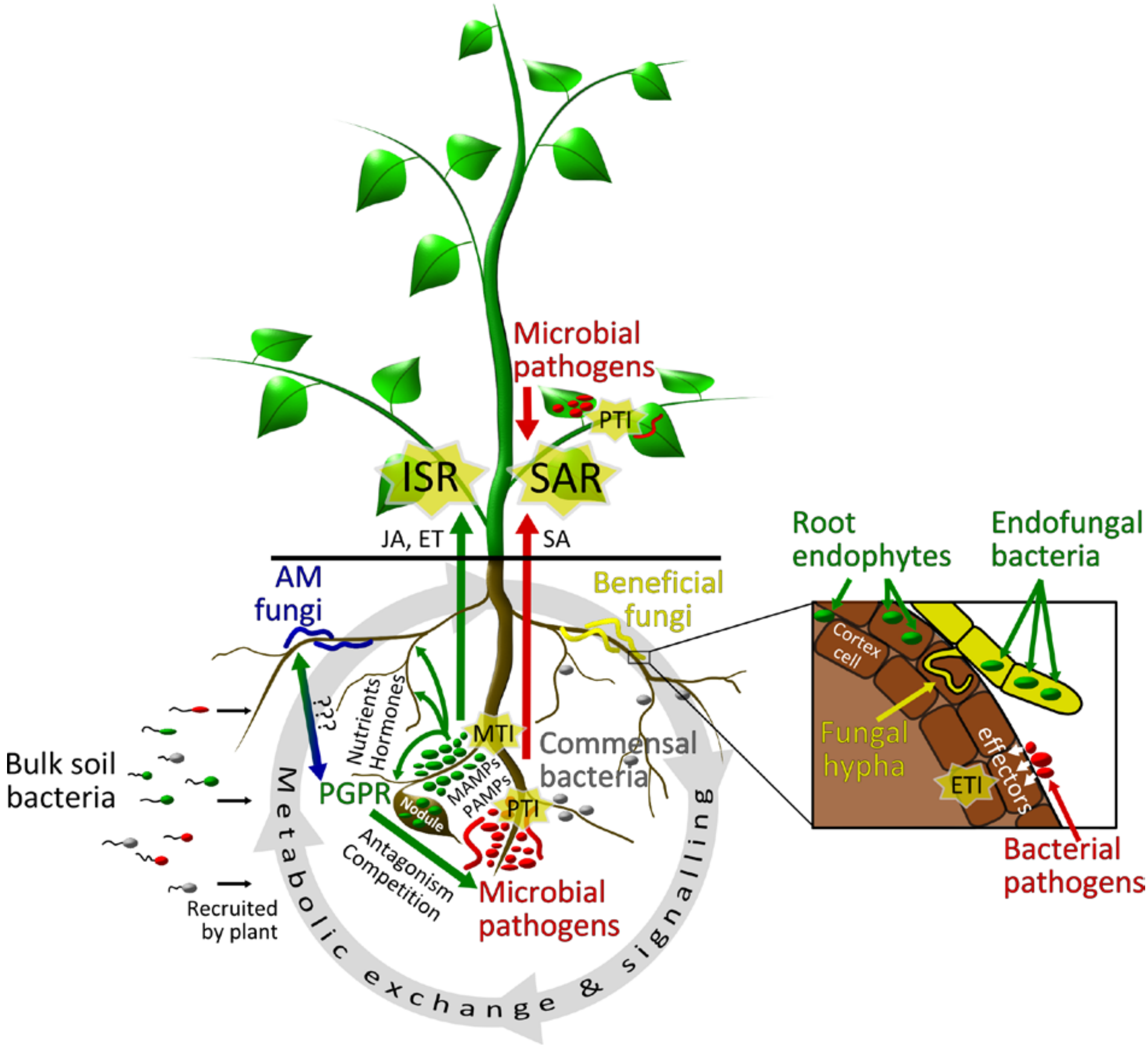

Figure 2. Schematic representation of the multiple and complex interorganismal interactions taking place in the plant rhizosphere and phyllosphere. Beneficial bacteria are depicted in green, fungal and bacterial pathogens in red, commensal bacteria in grey, arbuscular mycorrhizal fungi in blue and other beneficial fungi in yellow. Arrows in the corresponding color indicate known interactions described in the text. Inset on the right represents a magnification of the small frame in the main image.

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